Third Party Observations of International Patent Cooperation Treaty Applications Relating to Pharmaceutical Products

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Table of Contents

Abbreviations and Acronyms

DHHS	US Department of Health and Human Services
EPO	European Patent Office
FDA	United States Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papilloma virus
IB	International Bureau of WIPO
INN	international non-proprietary name
INSTI	integrase strand transfer inhibitor
IPER	International Preliminary Examination Report
IP	Intellectual Property
IPRP	International Preliminary Report of Patentability
ISA	International Searching Authority
ISR	International Search Report
MB	megabyte
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NATAP	National AIDS Treatment Advocacy Project
NIH	United States National Institutes of Health
NRTI	nucleoside reverse transcriptase inhibitor
PCT	Patent Cooperation Treaty
PDF	portable document format
PhD	Doctor of Philosophy
TAG	Treatment Action Group
TB	tuberculosis
TPAC	third party additional comments
TPO	third party observation
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
USPTO	United States Patent and Trademark Office
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WOSA	Written Opinion of the International Searching Authority
XDR	extensively resistant

About this Report

In October 2018, the Third World Network initiated a project to determine if the Third Party Observation (TPO) procedure of the Patent Cooperation Treaty (PCT) could assist in providing access to additional prior art documents for over-burdened patent offices in developing countries that tend to be over-reliant on the PCT's search and preliminary examination services.*

The TPOs filed under the project, and as reported here, followed the procedure under the PCT wherein third parties are allowed to submit to the International Bureau (IB) of WIPO observations with regard to international patent applications filed through the PCT. The TPOs submitted under this project make reference to prior art that may challenge the novelty and/or inventive step of claims made in the patent applications. Before this, observations or oppositions on patent applications could be filed by third parties only once the patent application entered a national or regional patent system. These TPOs are accessible to individual nations in addition to the International Search Report (ISR). This is of import as, unlike earlier, most patent applications are now filed through the PCT system.

The objectives of the TPO project are threefold:

i. to ensure that access to affordable medicines is not compromised by unwarranted patent barriers;
ii. to use the PCT's TPO system to provide key prior art documents through the international system;
iii. to document the challenges and experiences of using the TPO system to determine if it can help in deciding appropriately on the patentability of a claimed invention and/or prevent evergreening.

The TPO project runs across several years. The initial phase of the project focused on understanding the TPO system under the PCT, establishing a method for screening patent applications that may impact public health and access to medicines, and starting the process of filing TPOs.

This report highlights the progress in the first year of the TPO project and analyses the TPOs filed in the initial phase as well as first year of the project from 1 March 2019 to 31 March 2020. It is hoped that the TPOs filed will draw the attention of national and regional patent officers to the prior art documents referred to, during the patent examination process and help in improving pharmaceutical patent quality.

The report reflects the progress of the project, and provides analysis of the TPOs filed, findings on the nature of claims filed by patent applicants, and observations on both the TPO process and the manner in which the international search and examination system functions.

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* See https://www.wipo.int/export/sites/www/pct/en/epct/pdf/epct_observations.pdf and https://www.wipo.int/pct/en/faqs/third_party_observations.html

Executive Summary

Since July 2012, the Patent Cooperation Treaty (PCT) administered by the World Intellectual Property Organization (WIPO) has established a system of Third Party Observation (TPO) that permits third parties to submit to the International Bureau (IB) of WIPO observations referring to prior art which they believe may be relevant to the question of whether the invention claimed in an international patent application is novel and/or involves an inventive step. An effective TPO system could have a significant impact on the quality of patents granted across the world. Most national patent systems rely on the PCT mechanism in terms of not only applications coming in but also the International Search Report (ISR) and the Written Opinion of the International Searching Authority (WOSA). The TPO system can complement the ISR in helping to identify prior art, provide additional analysis and determine whether the subject of the application is truly novel or inventive.

In October 2018, the Third World Network initiated a Project to trial its use with respect to selected HIV, TB and HCV patent applications, motivated to limit patent evergreening that hinders access to medicines, and to document the experience with the aim of improving the working of the TPO system. A total of 2,584 patent applications published between May 2018 and June 2019 were identified through specially designed search strings and then screened for TPO filing. Sixty-five TPOs were filed up to April 2020, i.e., on 2.5% of total applications screened. All the TPOs filed by the project team have been accepted by the IB of WIPO.

Establishment of the TPO system was an important step forward towards improving the quality of patents granted across the world. The Project's experience in using the TPO system over the course of almost one and a half years reveals that there is significant room for improving the effectiveness of the TPO system and the user experience as well as related processes. In summary, the Project's findings are:

- *On the TPO filing system*: Lack of information on the patent applications makes it difficult to identify which patent applications may be of public health importance. Hence the particular importance of disclosing the international non-proprietary name on patent applications. Further flaws in the design of the TPO system frustrate its effective use. The system only allows brief explanations, imposing various limits including the number of prior art documents that may be referred to and the grounds on which the patent may be challenged. There are also many technical difficulties for users of the TPO system.

- *On the International Search Reports (ISR)*: ISRs are not all of the same quality, nor do they employ the same approach to searches and use of prior art documents. Most of the ISRs were published by the European Patent Office (EPO) and United States Patent and Trademark Office (USPTO), each using different approaches. In several ISRs, especially those relating to secondary applications, the focus is on prior art related to the specific compound or those that are structurally similar, and not on prior art documents demonstrating knowledge of general science, common knowledge or state of the art. In several cases, the ISRs appear to have not cited crucial prior art documents. Often the ISRs do not cite textbooks and other periodical documents that disclose the information that would be obvious to a person skilled in the art to make the product claimed in the application. Only in a few instances was the ISR issued by the office of a country other than the country of origin of the applicant.

- *On the patent applications*: TPOs filed confirm what several studies have shown and health groups have argued for some time now: that evergreening patent applications are a common feature of pharmaceutical patent filing strategies, that there is a routine use of Markush structures when claiming basic molecules (usually leading to multiple selection patents resulting in a long line of patents and patent applications emanating from the original Markush patent), and the significant presence of method of treatment claims in patent applications. Markush claims try to create exclusive rights on nearly all possible developments,

and if granted have the potential to hamper research. They also create significant pressure on the patent office reviewing such applications that can cover a multitude of compounds. An interesting observation is that while originator companies continue filing multiple patent applications on the same molecule for years if not decades, it appears that multiple companies other than the originator company also file such evergreening patents on these molecules. The majority of the applications selected for TPOs were from the US and under the US Bayh-Dole Act, patent applicants are required to disclose federal government funding in their applications. However, the Project found that patent applicants tend not to reveal in the patent applications the public funding they have received for inventions claimed.

- *Reach of TPOs*: Under PCT rules, information on patent applications (filed through the PCT) is transmitted to patent offices only if they have specifically requested it. Those that have not specifically requested transmission of TPOs will have to proactively seek out the TPOs. Thus far, very few patent offices have opted to receive the TPOs.

Based on the above-mentioned findings, several recommendations are made for improvement of the TPO system as well as related processes:

World Intellectual Property Organization

- ***Disclose international non-proprietary name (INN) on front page of patent applications:*** There is a need to improve information on the front page of the patent application, to increase transparency and facilitate screening and identification of relevant patent applications which are important from a public health perspective.

- ***Audit of pharmaceutical patent applications:*** An audit of pharmaceutical applications filed through the PCT would highlight the extent of the problem of secondary claims or broad Markush claims that impact research and development and access, and measures to address this should be discussed at the relevant WIPO Committees as well as the WIPO General Assembly with the participation of health and public interest groups.

- ***Review and remove restrictions on TPO filings:*** Procedural requirements and restrictions, such as on the size of documents, limits on documents, and character limits, make filing of TPOs very difficult. As a process designed to improve the quality of patents, the TPO filing mechanism needs to be simplified to encourage proper and effective use. TPO filers should also have the opportunity to comment on patent applicants' response to the filed TPO.

- ***Expand the grounds on which TPOs can be filed:*** The grounds for challenging patent applications through TPOs should be expanded beyond novelty and inventive step. In particular, the large number of patent applications claiming Markush structures should be challenged for lack of disclosure, as should overbroad or non-specific claims. With the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) allowing, and most countries including in their legislation an exemption of methods of treatment from patenting, this should also be permitted as a ground for challenge.

- ***Conduct audits of international searches:*** The TPO project has revealed considerable differences in the manner and quality of the international searches that most patent offices end up relying on in their national or regional examination proceedings. WIPO should commission an independent audit of ISRs, search methodologies and quality of search by the various international searching authorities and, in consultation with public interest groups and experts, review and make changes to improve the international search mechanisms.

- ***Broaden the scope of prior art documents cited in international searches:*** International searches appear to rely predominantly on patent literature. In the case of pharmaceutical patents, however, general textbooks are of tremendous importance in identifying prior art. As seen in the TPO filings, additional sources of prior art such as treatment guidelines can also be relied on. WIPO should encourage broadening the scope of prior art documents used by international searching authorities.

Governments

- ***Amend patent laws to include provisions against evergreening patents and ensure its rigorous implementation by patent offices:*** With a large number of patent applications claiming secondary patents on existing molecules, countries should include specific provisions in their patent laws to prevent such evergreening patents from being granted. Governments should also ensure that patent office policies and practices are rigorous and prevent evergreening of patents.

- ***Ensure strict requirement of disclosure:*** Markush claims covering millions of compounds, most of which are not revealed or specified in the patent applications, should be subject to strict disclosure standards by patent offices. Given the overwhelming numbers of such applications, specific provisions in patent laws should be considered to prevent such overbroad patents from being granted. Patent offices should also adopt policies and practices that demand adequate disclosure.

- ***Stricter examination guidelines on pharmaceutical patent applications:*** The TPO project reveals the most common forms of claims in patent applications, most of which do not actually meet the criteria of novelty and inventive step (such as claims for salts, polymorphs, etc.), or of sufficiency of disclosure (such as Markush claims). Pharmaceutical patent examination guidelines can help patent offices immediately identify such claims and provide the grounds for why these should not be granted.[**]

- ***Patent offices should request and consider TPOs:*** In order to facilitate examination, patent offices should request TPOs and consider TPOs in the national or regional examination process.

Patent Offices

- ***Patent offices should include TPOs in the list of documents that WIPO must transmit through the PCT system:*** All national and regional patent offices should immediately identify TPOs as part of the documents specifically requested by them under the PCT Rules. Unless the TPOs are transmitted proactively, patent offices and patent examiners are unlikely to try and access these documents themselves given the high burden on these offices.

- ***Patent offices should consider TPOs in national or regional patent examination:*** As can be seen through the TPO project, TPOs can bring to light prior art and analysis that is not included in the ISRs. This analysis and information should be taken into account by patent offices when doing their own searches and examination.

- ***Patent offices should conduct their own searches and encourage public participation in the review of patent applications:*** The wide differences in the quality of ISRs highlight the importance of patent offices conducting their own searches for prior art. In particular, these searches should rely on both patent and non-patent literature and other sources as well. In the field of pharmaceuticals, general textbooks are particularly important.

[**] See for e.g. UNDP (2016) "Guidelines for the Examination of Patent Applications relating to Pharmaceuticals | United Nations Development Programme" available at https://www.undp.org/publications/guidelines-examination-patent-applications-relating-pharmaceuticals

Civil Society

- ***Advocate for adoption of stricter patentability criteria and disclosure standard in national and regional patent laws and patent examination guidelines and its rigorous application by patent examiners:*** The problems created by evergreening and overbroad patent claims on pharmaceuticals in terms of restricting research and development and preventing access are now well recognised and established. Civil society groups should advocate for reform of the patent law as well as examination practices to prevent evergreening and overbroad pharmaceutical patents from being granted.

- ***Bring TPOs to the attention of national or regional patent offices:*** Civil society groups should track the filing of TPOs on patent applications on key medicines and bring them to the attention of the patent office.

- ***Access and consider prior art filed in TPOs for national or regional patent oppositions:*** Public participation in patent examination processes through patent oppositions has been one of the most successful public health interventions in the past decade. Civil society groups should actively file patent oppositions and use prior art and analysis from TPOs to support their oppositions.

1
Background

According to the World Health Organization (WHO), affordability is one of the key factors that impact access to medicines. Patents on medicines usually result in exorbitant prices, with patent holders controlling who gets access to patented medicines and at what price. Further, there has been growing concern that the quality of patents being granted in both developed and developing countries is questionable. A series of studies have shown that evergreening or secondary patents and patent applications on medicines have proliferated.[1] In addition, the burden on patent offices and patent examiners in developing countries has increased with the massive increase in patent applications, most of which come through the Patent Cooperation Treaty (PCT) mechanism administered by the World Intellectual Property Organization (WIPO).

Patent opposition mechanisms have been successfully used in several developing countries to challenge questionable pharmaceutical patent applications. In 2012, a third party observation (TPO) system was introduced as part of the PCT mechanism (see Box 1). An effective TPO system could have a significant impact on the quality of patents granted across the world. Most national patent systems rely on the PCT mechanism in terms of not only applications coming in but also the International Search Report (ISR) and the Written Opinion of the International Searching Authority (WOSA). With the sheer volume of patent applications, an effective TPO system can complement the ISR in helping to identify prior art, provide additional analysis and determine whether the subject of the application is truly novel or inventive.

Box 1

The PCT Third Party Observation System

The following is the text of Part 8 – titled "Instructions Relating to Observations by Third Parties" – of the Administrative Instructions under the Patent Cooperation Treaty:

Section 801: Third Party Observation System

(a) The International Bureau shall provide an electronic system for third parties to make observations referring to prior art which they believe to be relevant to the question of whether the invention claimed in the international application is new and/or involves an inventive step ("third party observation system").

(b) The third party observation system:
(i) shall provide a third party with the option to remain anonymous;
(ii) shall allow observations to include a brief explanation of the relevance of each prior art document referred to in the observation and to include a copy of the prior art document;
(iii) may limit the number of prior art documents which may be referred to in one observation; and
(iv) may limit the number of observations permitted to be made in relation to one international application, per third party and in total.

(c) The International Bureau shall take technical steps to prevent abuse of the third party observation system.

(d) The International Bureau may temporarily or indefinitely suspend the use of the third party observation system if it considers it necessary to do so.

[1] European Commission (2009). "Pharmaceutical Sector Inquiry Report". DG Competition Staff Working Paper, available at http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf; I-MAK (2018), "Overpatented, overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices" available at https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf and IMAK (2022), "Overpatented, overpriced: Curbing patent abuse: Tackling the root of the drug pricing crisis" available at https://www.i-mak.org/wp-content/uploads/2022/09/Overpatented-Overpriced-2022-FINAL.pdf

Section 802: Filing of a Third Party Observation

(a) An observation by a third party made in relation to an international application shall:
(i) be submitted to the International Bureau through the third party observation system as provided in Section 801;
(ii) be submitted between the date of international publication and 28 months from the priority date of the international application indicated;
(iii) be in a language of publication, with the exception that copies of submitted prior art documents may be in any language;
(iv) relate to the international application indicated;
(v) refer to prior art;
(vi) be free of viruses or other forms of malicious logic;
(vii) be free of comments or other matter not relevant to the question of novelty or inventive step of the invention claimed in the international application; and
(viii) be free of comments or other matter which are an abuse of the third party observation system.

(b) Any purported observation by a third party which, in the view of the International Bureau, appears not to be in compliance with paragraph (a) shall not be treated as a third party observation. The International Bureau shall inform the third party accordingly, unless the purported observation appears to be a clear attempt at abuse of the system. The purported observation shall not be open to public inspection and shall not be communicated to the applicant, any International Authority or any designated Office.

Section 803: Availability of an Observation and Related Information

(a) Any third party observation shall be promptly made available for public inspection, with the exception that copies of prior art documents uploaded through the system shall be made available only to the applicant, competent International Authorities and designated Offices.

(b) Where the third party requests the International Bureau to remain anonymous as provided in Section 801(b), the International Bureau shall not reveal any details of the third party to the public, the applicant, any International Authority or any designated Office.

Section 804: Notification of Receipt of an Observation to the Applicant and Comments by the Applicant in Response to an Observation

(a) The International Bureau shall notify the applicant when the first third party observation is received in relation to an international application. If further observations are received, the International Bureau shall notify the applicant of the receipt of all further observations promptly after the expiration of 28 months from the priority date.

(b) The applicant may, within 30 months from the priority date, submit comments in response to any third party observation which has been received. The comments shall be submitted in English, French or the language of publication of the international application, at the choice of the applicant, and shall be promptly made available for public inspection.

Section 805: Communication of Observations and Comments to International Authorities and Designated Offices

(a) The International Bureau shall communicate any third party observation and any comment by the applicant promptly to the International Searching Authority specified to carry out the international search, the International Searching Authority specified to carry out the supplementary international search and the International Preliminary Examining Authority specified to carry out the international preliminary examination, unless the international search report, the supplementary international search report or the international preliminary examination report, respectively, has already been received by the International Bureau.

(b) Promptly after the expiration of 30 months from the priority date, the International Bureau shall communicate any third party observation and any comment by the applicant to all designated Offices, subject to Rule 93bis. The designated Offices shall not be obliged to take either the observations or any comments into account during national processing.

2
TPO Project: Methodology

The TPO project was set up with the objective of filing TPOs concerning PCT international patent applications related to pharmaceutical compounds/drugs that may be used for the treatment of human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection and/or tuberculosis (TB).

The project initially estimated a target of eight TPOs to be filed in the first year. But in the process of figuring out the system and refining the experience of its use, in sieving through the huge number of international patent applications relating to pharmaceuticals filed per month, it was felt that to understand and analyse the impact of the TPOs, a larger number of TPOs needed to be filed. No target as such was set, but the team attempted to file as many as possible, to try to understand the range of patent applications being filed by pharmaceutical companies, universities, research institutes, etc. Due to this, the team could understand the difference between applications filed by academia and those by pharmaceutical companies.

A total of 65 TPOs were filed up to April 2020: 63 TPOs between 1 March 2019 and 31 March 2020, one test case was filed in December 2018, and one TPO for a biologic application relating to immunotherapy was filed in April 2020.

Summaries of the 65 TPOs filed up to April 2020 are in Annex 1 of this Report.

The primary reasons for this large number were:

(a) Many applications were screened as important, as they related to drugs that were already approved (i.e., structurally the claimed scaffolds and/or compounds in these applications differed only in terms of minor modifications compared with established compounds), drugs that were already in the clinical trial stage, or claimed solid forms (i.e., salt/crystalline form), prodrugs of previously known compounds, or substances listed as drugs/molecules being tracked as potentially important pipeline products by entities such as Unitaid, the Treatment Action Group (TAG), etc.
(b) There were many instances where the applicant had filed multiple patent applications on the same date for similar compounds. Prior art was easily available and re-used in the TPOs filed on those multiple applications.

Further, the objective for the first year of the project was to understand the system and the range/type of applications for patents on pharmaceutical products to treat, mitigate or prevent HIV, HCV and TB, and to test the waters to find out how the system worked.

Methodology

Project team: It was determined that a combination of legal and scientific expertise would be required to effectively file the TPOs in the short time period available for filing. The TPO project team thus comprised two experts with a legal background and two experts with a scientific background. One legal and one scientific expert were full-timers and two worked part-time. One more scientist with knowledge on biologics joined the team subsequently.

For the purposes of a time-bound, public-interest-oriented project such as this, it may be noted that recruitment can be difficult. In particular, for most persons with a master's degree or PhD in pharmaceutical-related sciences, career options usually lead to jobs in the pharmaceutical industry. In addition, it appears that in academia relating to pharmaceutical sciences, master's-level teaching on intellectual property is usually part

of an elective course and there is little or no teaching from a public interest perspective; indeed, most students studying sciences related to pharmaceuticals would be encouraged to file patents themselves. Institutes teaching the sciences often take up projects that are funded by the pharmaceutical industry. Challenging patent applications can often be counter-intuitive for most master's and PhD scholars. This challenge also stresses on the need for much greater focus in academic institutions and elsewhere on the public interest dimension of intellectual property.

Accessing scientific research databases: One of the key requirements for filing effective TPOs is access to scientific literature. Unfortunately, most scientific literature databases require expensive subscriptions. The team explored the possibility of subscribing to a certain paid database. However, on using, it was evident that it was not user-friendly at all even after a demonstration and training session. The search commands were not intuitive and based on a string of commands. In addition, the output results were cumbersome to review and use. It is of some concern that several patent offices offer this database to their examiners.

For the purposes of the TPO project, therefore, open access databases like Espacenet, the WIPO website, the United States Patent and Trademark Office (USPTO) website, Google Patents and Google Scholar have been mostly used by the project team; the results yielded were in the form of scientific research/review articles and patent documents. However, in some instances, there was a lack of information with regard to any prior art documents or to pinpoint references for certain substituents and/or substitution pattern of scaffolds/compounds claimed. The databases that allowed a search based on the chemical structure were found to be useful in some such instances. Also, in the case of HIV and HCV drugs, conference reports available in the public domain, accessed for example via the National AIDS Treatment Advocacy Project (NATAP), have also been used. Apart from this, guidelines published by public health bodies such as the US Department of Health and Human Services (HHS), the World Health Organization and regulatory bodies have also been uploaded in certain instances. For certain documents on the WIPO website that are not in English, WIPO's machine translation was available and used.

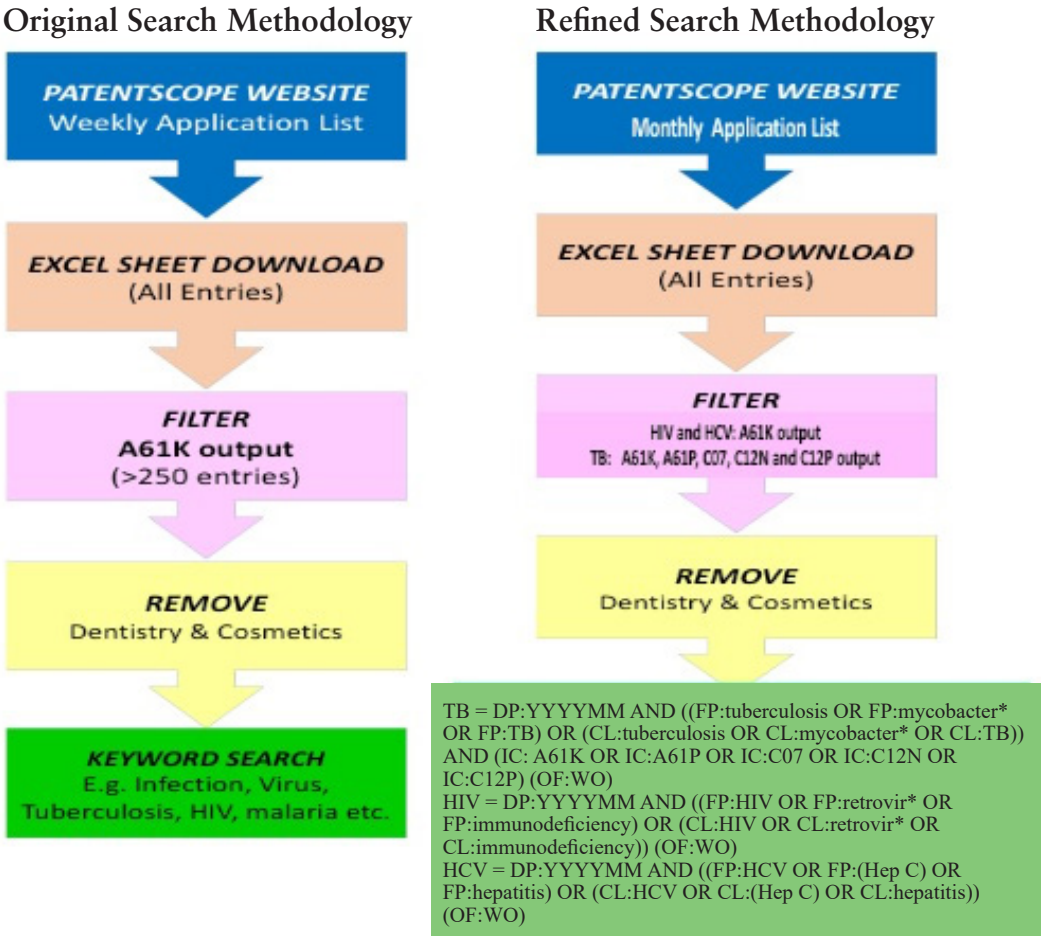
Familiarisation with the PCT system and ePCT: As TPOs can only be filed through ePCT in WIPO's IP (Intellectual Property) Portal, the team had to spend a considerable amount of time familiarising themselves with the online portal. A login account was created for filing of the TPOs. Additionally, the team studied the PCT, the PCT Regulations (which are regularly updated) and the manner and method used in the preparation of the International Search Report and the Written Opinion of the International Searching Authority. The codes used in the ISR and WOSA were also studied.

Search methodology: Every week WIPO publishes about 1,000 to 1,500 patent applications for pharmaceutical products. From among these, the applications relevant to HIV, HCV and TB needed to be screened and relevant applications needed to be identified for the purpose of filing TPOs under the project. The team tried various search strings that included using international classification codes, names of diseases, names of pharmaceutical companies, etc. in various combinations to obtain lists with the most relevant applications. The lists obtained were screened thoroughly, so as to finalise the search string that gave the most relevant lists of patent applications for the identified diseases. This led to a refinement in the originally proposed search methodology as depicted below. Due to the sheer volume of patent applications filed every week, it was determined that a monthly screening of patent applications would be more effective for selecting applications for which TPOs would be filed. The experience of the screening also showed that apart from the international classification code A61K that is considered the most relevant for pharmaceutical patent applications, additional codes were required to identify patent applications relevant to TB treatment. Finally, a search string for each disease was composed to screen the monthly list of published patent applications. The search strings used by the project team are:

- TB = DP:YYYYMM AND ((FP:tuberculosis OR FP:mycobacter* OR FP:TB) OR (CL:tuberculosis OR CL:mycobacter* OR CL:TB)) AND (IC: A61K OR IC:A61P OR IC:C07 OR IC:C12N OR IC:C12P) (OF:WO)

- HIV = DP:YYYYMM AND ((FP:HIV OR FP:retrovir* OR FP:immunodeficiency) OR (CL:HIV OR CL:retrovir* OR CL:immunodeficiency)) (OF:WO)

- HCV = DP:YYYYMM AND ((FP:HCV OR FP:(Hep C) OR FP:hepatitis) OR (CL:HCV OR CL:(Hep C) OR CL:hepatitis)) (OF:WO)



Screening methodology: Since patent applicants seldom specify the medicine, the international non-proprietary name (INN) or the disease in the title or abstract of the application or the front page, it makes it arduous to find the key applications that pertain to pharmaceutical compounds that have the potential of reaching the market. Nevertheless, the lists obtained through the search string were scanned and the claims and specifications of each application on the list were scrutinised to determine if an application was "relevant", "not relevant" or "maybe relevant" for the purposes of filing a TPO:

- "Relevant" applications are those that concern pharmaceutical compounds for the treatment of TB, HIV or HCV, their forms (e.g., salt, crystalline forms or prodrugs), combinations, etc. that directly relate to the disease or modulate a target that would directly contribute in treating the disease and that have a potential to reach the market.

- "Maybe relevant" applications are those that relate to the larger class of diseases, such as neurological, cardiovascular, bacterial diseases or viral infections, and may or may not specifically contain the name of the diseases studied under the project.

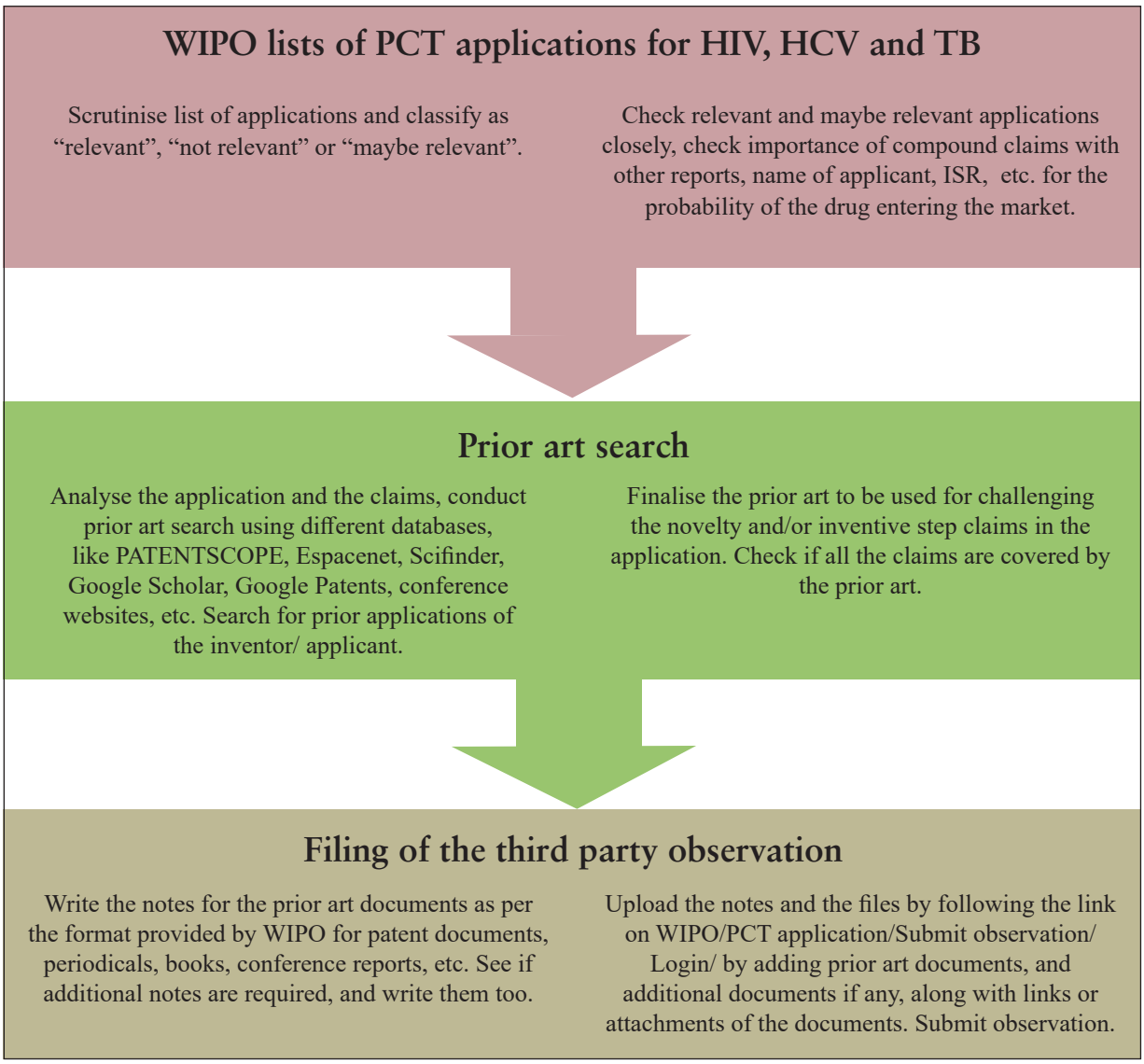
- "Not relevant" are those applications that do not directly relate to the diseases, though they have been listed due to some vague reference to the disease in the application (e.g., pain associated with HIV). These also include applications relating to medical devices and to improved pharmaceutical delivery systems (e.g., liposomes, niosomes).

Given the sheer number of applications, the project team examined the claims of only those applications on the "relevant" list, to decide which applications to file TPOs on. The final selection of the international patent application for which a TPO could be filed was guided by the claims in the application for treatment of HIV, HCV and/or TB, the class of medicines the compound fell under, the mechanism by which the compound acted, whether clinical trials had started for the compound, and the potential medical significance of the compound. The list was also cross-checked with a list of medicines (approved and under development) prepared by the project team based on approval of medicines on the United States Food and Drug Administration (FDA) website, and pipeline reports from reputable sources such as Unitaid, the Treatment Action Group (TAG) and others. Other factors considered by the project team to determine which applications to file TPOs on included identifying the companies making the applications, the drugs (if known), whether the application covered a new compound or form thereof, if a combination claimed was medically important and so on. The screening process looked not only at the applications, but also at the ISR and WOSA (if published); the quality of these documents was also assessed. Where an ISR was strong and detailed and already contained relevant prior art documents (i.e. X documents), then a TPO was not filed. TPOs were also not filed for some of the applications that were identified as relevant as the date for filing the TPO had expired or due to lack of time to conduct the research in the period remaining.

Filing of TPOs: The team filed a pilot TPO in the initial months of the project to understand the methods and requirements of filing. After understanding the TPO system, setting up the team and obtaining the lists of most relevant patent applications, TPOs were filed every month starting from March 2019.

The filing of TPOs under the project now follows an established procedure. Once the international patent application has been identified, the prior art search is undertaken, and relevant prior art is identified that would challenge the novelty and/or inventive step of the invention claimed in the application. Brief explanations of the relevance of the prior art document along with bibliographic details of the document as required for filing a TPO are drafted to be uploaded along with a copy of the document, if possible. Some patent applications that have very large file sizes and are available on the WIPO website itself are not uploaded, even if they are cited as prior art documents. The links and the digital object identifier are provided for easy access to the prior art document.

The TPO is submitted via a link that is available on the PCT bibliography data page of the application and can also be submitted via ePCT after login. The link is to the WIPO IP Portal that enables submission of the TPO through a WIPO account login. Once the TPO is submitted, it is analysed by the IB and, if accepted, uploaded on the documents page of the application, and is available to the public and the patent offices. In some instances, additional document(s) are uploaded as part of the TPO. There are mainly three kinds of additional documents: (a) a prior art document to supplement and complement the information in the main prior art document; (b) documents that contain observations on the application itself or a table comparing scaffolds/compounds claimed in the application with a prior art document; (c) "additional comments submitted with observation". The document uploaded as additional comments shows up as a separate additional document along with the TPO in the list of documents, as third party additional comments (TPAC).


WIPO lists of PCT applications for HIV, HCV and TB
Scrutinise list of applications and classify as "relevant", "not relevant" or "maybe relevant".
Check relevant and maybe relevant applications closely, check importance of compound claims with other reports, name of applicant, ISR, etc. for the probability of the drug entering the market.
Prior art search
Analyse the application and the claims, conduct prior art search using different databases, like PATENTSCOPE, Espacenet, Scifinder, Google Scholar, Google Patents, conference websites, etc. Search for prior applications of the inventor/ applicant.
Finalise the prior art to be used for challenging the novelty and/or inventive step claims in the application. Check if all the claims are covered by the prior art.
Filing of the third party observation
Write the notes for the prior art documents as per the format provided by WIPO for patent documents, periodicals, books, conference reports, etc. See if additional notes are required, and write them too.
Upload the notes and the files by following the link on WIPO/PCT application/Submit observation/ Login/ by adding prior art documents, and additional documents if any, along with links or attachments of the documents. Submit observation.

3
TPO Project: Analysis of First Year of Filing of TPOs

a. Key Features of the PCT's TPO System

As noted above, the first three months of the project were spent on familiarisation with the PCT's TPO system. The key features of how the system works are summarised below:

- TPOs can be filed from the time of international publication of the patent application until 28 months from the priority date. As patent applications are published 18 months after they are filed, this in effect provides a period of only 10 months from the date of international publication for the filing of a TPO.

- During the period when TPOs can be filed, links are provided to the system from the published international application on WIPO's PATENTSCOPE database.

- A maximum of 10 TPOs can be filed on every patent application, with only one TPO allowed per person/account.

- TPOs can be filed anonymously.

- A login account has to be created to file a TPO.

- TPOs are accepted only if submitted through the ePCT system.

- Only 10 prior art documents relating only to novelty and/or inventive step can be cited for the TPOs along with brief explanations.

- The documents cited can be uploaded but only up to three PDF files, not more than 20 MB in size per cited document, can be uploaded.

- Observations are limited in length and only a "brief explanation" of the relevance of the cited documents is allowed, i.e., up to 5,000 characters.

- In addition, a short PDF document containing additional comments is allowed for providing explanations for combining disclosures in different documents, including tables or formulae, or for presenting arguments.

- TPOs are examined by the International Bureau. If accepted, they are uploaded on the WIPO website and are available to the public, including applicants who have until 30 months from the priority date to respond. The last date for filing a TPO is 28 months from the priority date. Thus, in effect, at a minimum, a patent applicant has at least two months to respond to a TPO.

- TPO filers are given no further opportunity to comment on the patent applicant's response.

- While TPOs are made available to the public, copies of cited documents are not. These copies are made available only to the patent applicants, the designated patent offices and competent International Authorities.[2]

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2 https://www.wipo.int/pct/en/texts/ai/s803.html

- After 30 months from the priority date have passed, the TPOs and all uploaded documents are sent to the designated patent offices that have requested access to the TPOs. Under the PCT, designated offices are only proactively sent the information they have specifically requested. They may request some or all of the documents related to a patent application.[3] Accordingly, only those that have specifically requested for TPOs to be sent along with the patent application will receive the TPOs. As of 2018 (updated information is not available), 11 national patent offices have asked to have the TPOs actively transmitted to them.[4] Other offices can also download the TPOs from PATENTSCOPE but it is unclear if any are doing so.

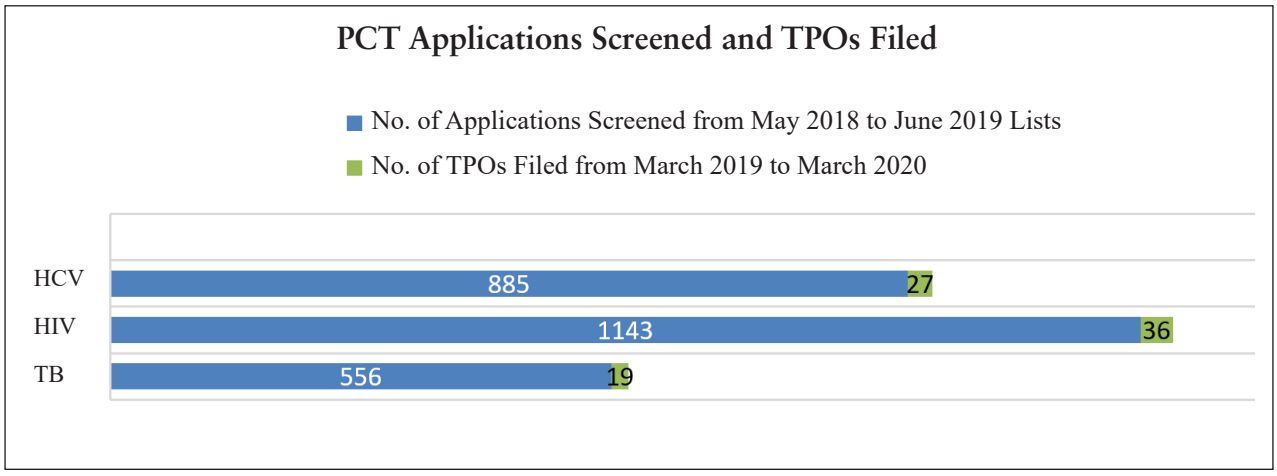
b. Key Features of Patent Applications Screening Process

Based on the refined search methodology described above, the project team screened patent applications filed and published through the PCT system on a monthly basis. Based on the search string search, the lists containing international patent applications were then further classified by relevance for the purposes of determining which applications should have TPOs filed on them.

i. ***Total applications screened for HIV, HCV and TB:*** A total of 2,584 patent applications published between May 2018 and June 2019 were identified through the search strings and then screened for TPO filing (1,143 for HIV, 885 for HCV and 556 for TB). TPOs were finally filed on a total of 65 patent applications, i.e., on 2.5% of total applications screened. The lists for the month of May 2018 were used for filing TPOs in the month of March 2019. Thus, TPOs filed in March 2020 were from lists of applications from May and June 2019.

The number of TPOs for HCV filed was 28. It may be noted that one TPO for HCV was filed in December 2018, which was in the February 2018 list, and not in the lists from May 2018 to June 2019. The number of TPOs for TB was 20. It may be noted that one TPO for a biologic TB application was filed in April 2020, which was from a list published in September 2019, and has been included in the analysis. The number of TPOs for HIV was 36. [Note: There is an overlap, where some applications contained claims for multiple diseases, for example for HIV and HCV, or HIV and TB, or HIV, HCV and TB, etc. Thus, Box 2 below may show a figure of more than 65 TPOs.]

Box 2

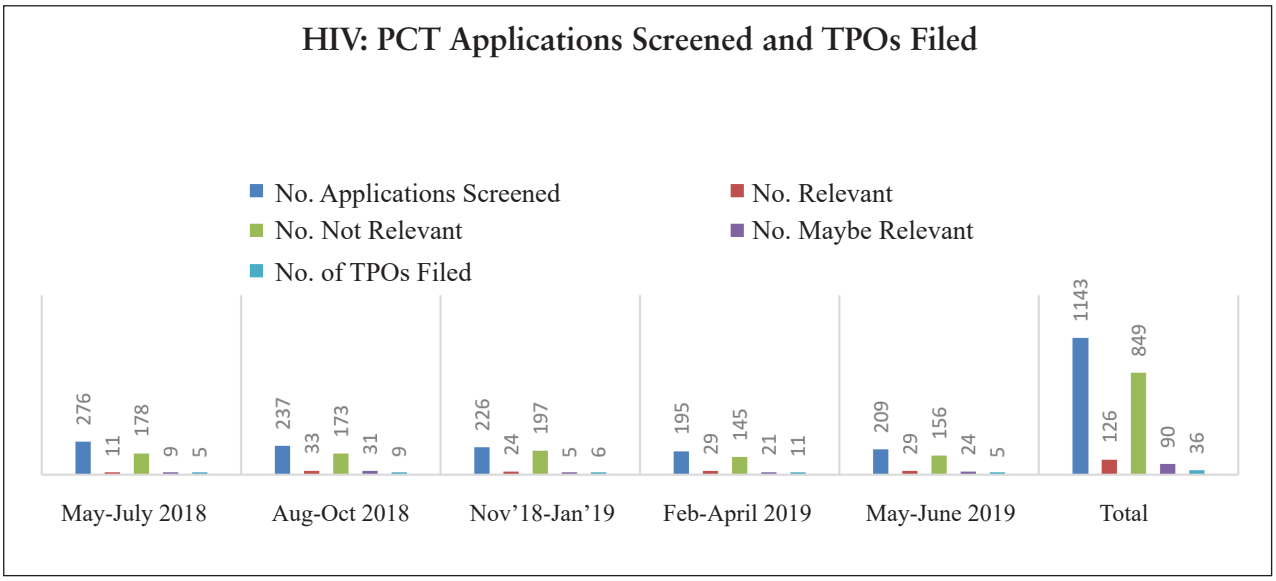


[3] https://www.wipo.int/pct/en/texts/rules/r93bis.html

[4] https://www.wipo.int/edocs/mdocs/pct/en/pct_wg_11/pct_wg_11_11.pdf

ii. ***Month-wise screening of patent applications relevant for HIV*** (see Box 3)***:*** A total of 1,143 PCT applications were found to be published from May 2018 to June 2019 through the search string for HIV. The HIV lists contained an average of 82 international patent applications per month, of which an average of nine applications per month were marked "relevant", an average of 60 were marked "maybe relevant" and the rest were all marked "not relevant".[5] A total of 126 applications were marked as relevant and a total of 36 TPOs were eventually filed. The team tried to further refine the search string; however, this string was found to provide the shortest and most relevant list.

Box 3

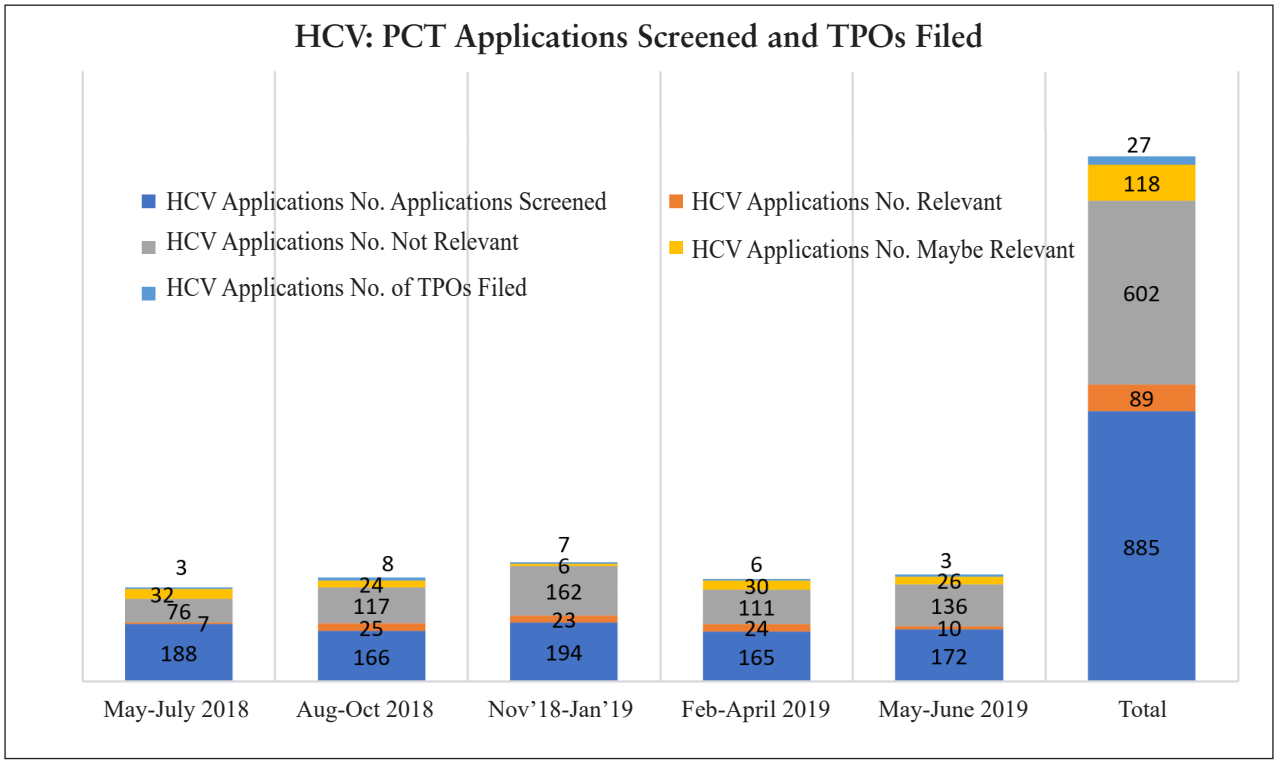


iii. ***Month-wise screening of patent applications relevant for HCV*** (see Box 4)***:*** The month-wise lists of HCV-related international patent applications were shorter than the HIV lists, but a few applications were found to overlap with the HIV applications, as the claims involved both HIV and HCV. The screening of the HIV and HCV lists began from the month of June 2018. A total of 885 PCT applications were found to be published from May 2018 to June 2019 through the search string for HCV. The HCV lists contained an average of 63 international patent applications per month identified through the search string. Screening of the applications (which began in June 2018) resulted in an average of seven applications per month that were marked "relevant", 46 that were marked "maybe relevant" and nine that were marked "not relevant".[6] A total of 89 applications were found to be relevant for HCV and a total of 28 TPOs were eventually filed for drugs used for the treatment of HCV. It may be noted that 27 TPOs were filed for HCV from applications found in lists between May 2018 and June 2019, and one TPO was filed in December 2018 which was from the February 2018 list, making it a total of 28 TPOs filed for applications relating to HCV.

[5] It may be noted that the May 2018 list of HIV was not screened, but was only checked for the number of hits using the search string. The average of HIV relevant, not relevant, and maybe relevant hits has been taken for 13 months and not 14 months.

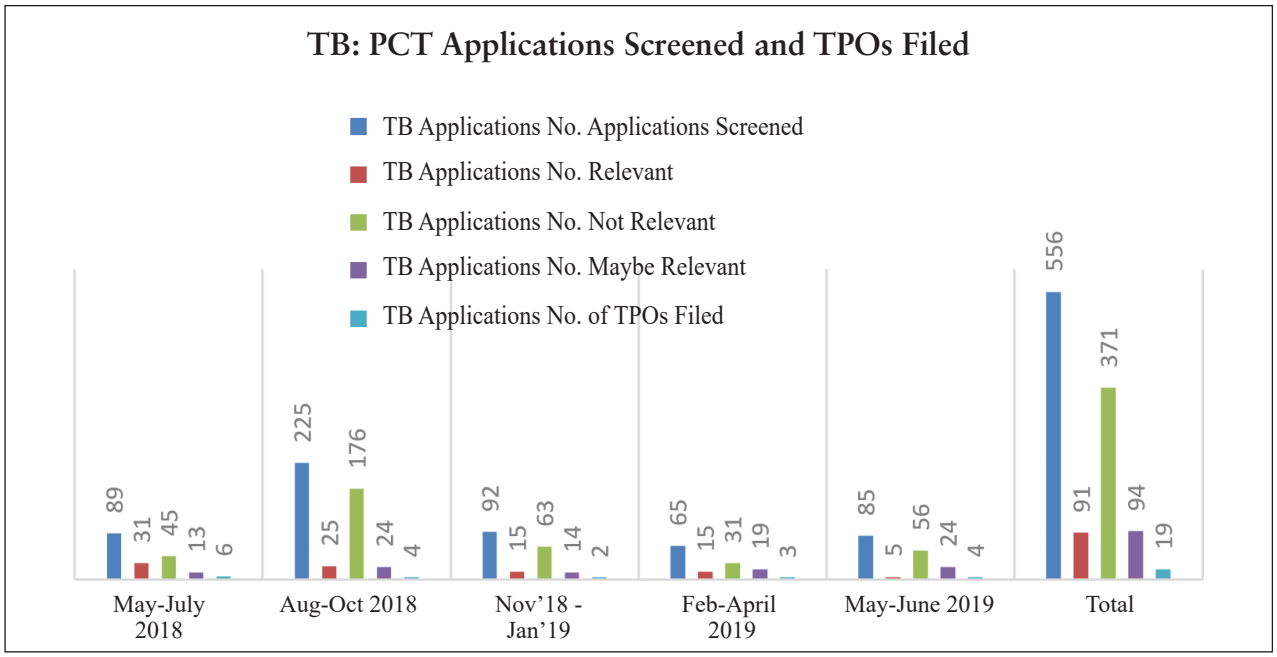
[6] It may be noted that the May 2018 list of HCV was not screened, but was only checked for the number of hits using the search string. The average of HCV relevant, not relevant and maybe relevant hits has been taken for 13 months and not 14 months.

Box 4



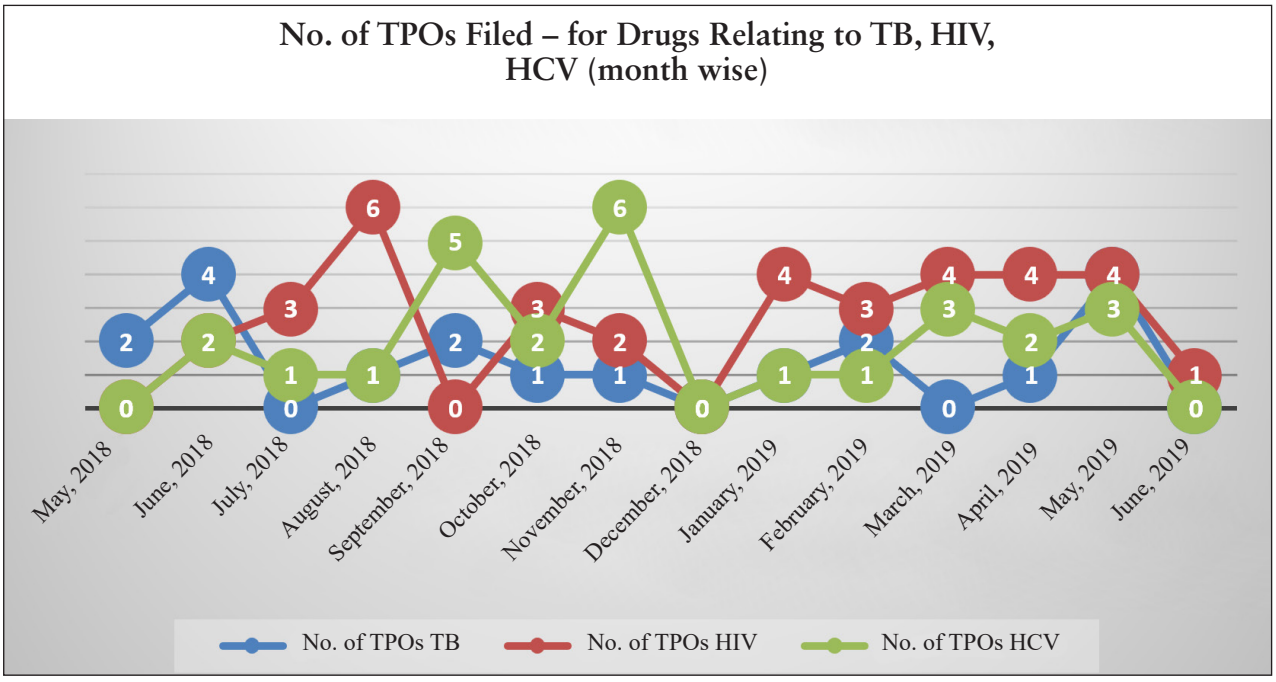
iv. ***Month-wise screening of patent applications relevant for TB*** (see Box 5)***:*** Similarly, a total of 556 PCT applications were found to be published from May 2018 to June 2019 through the search string for TB. The number of TB-related international patent applications screened averaged about 40 applications per month, of which an average of seven applications per month were marked "relevant", seven were marked "maybe relevant" and the rest (26) were marked "not relevant". A total of 91 applications were found to be relevant for TB and a total of 19 TPOs were eventually filed for drugs used for TB from March 2019 to March 2020. It may be noted that one TPO for TB that was filed in March 2020 was from the publication of September 2019 which was included in the analysis. Thus, a total of 20 TPOs were filed for TB drugs.

Box 5



v. ***Month-wise patent applications selected for filing TPOs:*** The patent applications finally selected for the filing of TPOs and the diseases covered are depicted in Box 6 below. One patent application was previously screened and selected for a TPO in December 2018 as a test case. In addition, there were three applications for which TPOs were drafted or prior art research was conducted but TPOs were ultimately not filed as the applications were withdrawn or the link for filing the TPO was not available subsequently. It may be noted that while applications related to viral diseases generally showed an overlap, in some applications both viral and bacterial diseases were targeted by the compound(s) claimed. These were primarily applications where a pharmaceutical compound was claimed to act on a specific target, wherein modulation of this target would play a role in treating many diseases.

Box 6

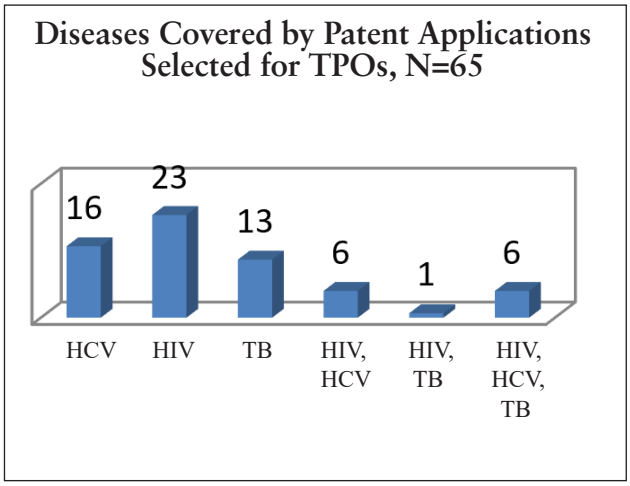


c. Key Features of Selected Patent Applications

The monthly screening process resulted in identifying applications for which 65 TPOs were filed. Some key features of the selected patent applications are presented below:

i. ***Diseases covered:*** Of the 65 patent applications for which TPOs were filed, 23 primarily related to HIV, 16 primarily related to HCV and 13 primarily related to TB (see Box 7). Of the remaining applications, six disclosed compounds that could be used in the treatment of HIV and HCV, one disclosed compounds for HIV and TB, and six disclosed compounds potentially related to all three diseases relevant for the project, i.e., HIV, HCV and TB. Several of the applications that covered Markush[7] structures also referred to several other diseases that could be covered. Of the 65 applications, 25 applications claimed only one disease and 40 applications claimed more

Box 7

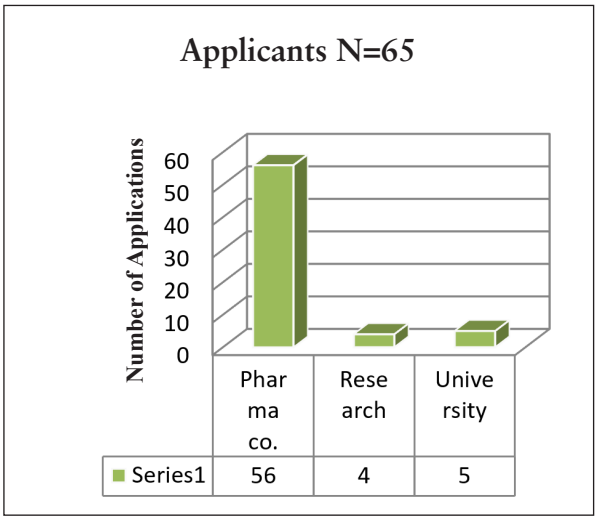


[7] "Markush" refers to claims that consist of a generic chemical structure with multiple options that allow for the protection, under a single patent, of up to several millions of molecules.

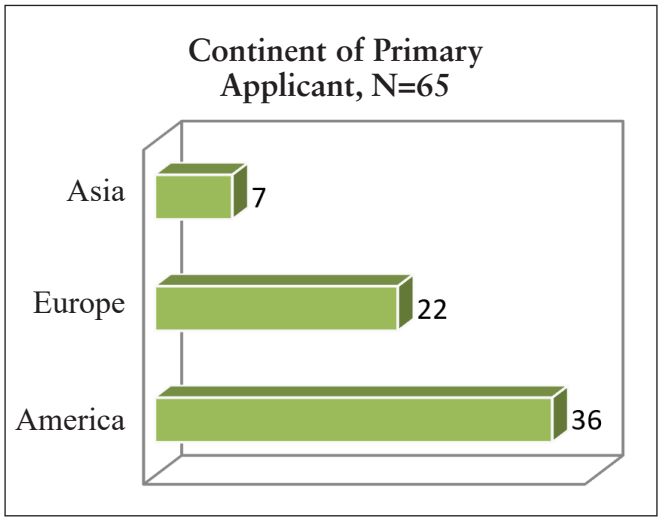
than one disease, (which could be related to HIV, HCV, TB, or other diseases), of which 10 applications covered more than 10 diseases. The other diseases claimed were leprosy, buruli ulcer, ulcerative colitis, psoriasis, rheumatoid arthritis, RIP-kinase mediated diseases, various types of cancers, bacterial infections, fungal infections, prosthetic joint infections, neurological disorders, depressive disorders, Huntington's disease, Parkinson's disease, autoimmune diseases, liver diseases, herpes, HPV, Crohn's disease, NASH, musculoskeletal disease or disorder, ophthalmological disease or disorder, viral infections, etc.

ii. ***Patent applicants:*** Of the 65 patent applications selected for the filing of TPOs, the majority, i.e., 56 applications, were filed by pharmaceutical companies; five were filed by universities and four by research institutes (see Box 8). There was one application made jointly by a pharmaceutical company and a university, two applications made jointly by a pharmaceutical company and an individual, one application made jointly by a university and a public health institute, and one application made jointly by a university and an individual. The applicants were from different countries (see Box 9), though most applications were from the USA (36), followed by Great Britain (12) and China (4). Applicants in the remaining applications were from Singapore, Switzerland, Sweden, Germany, Belgium, Ukraine, Norway, Ireland and India.

Box 8

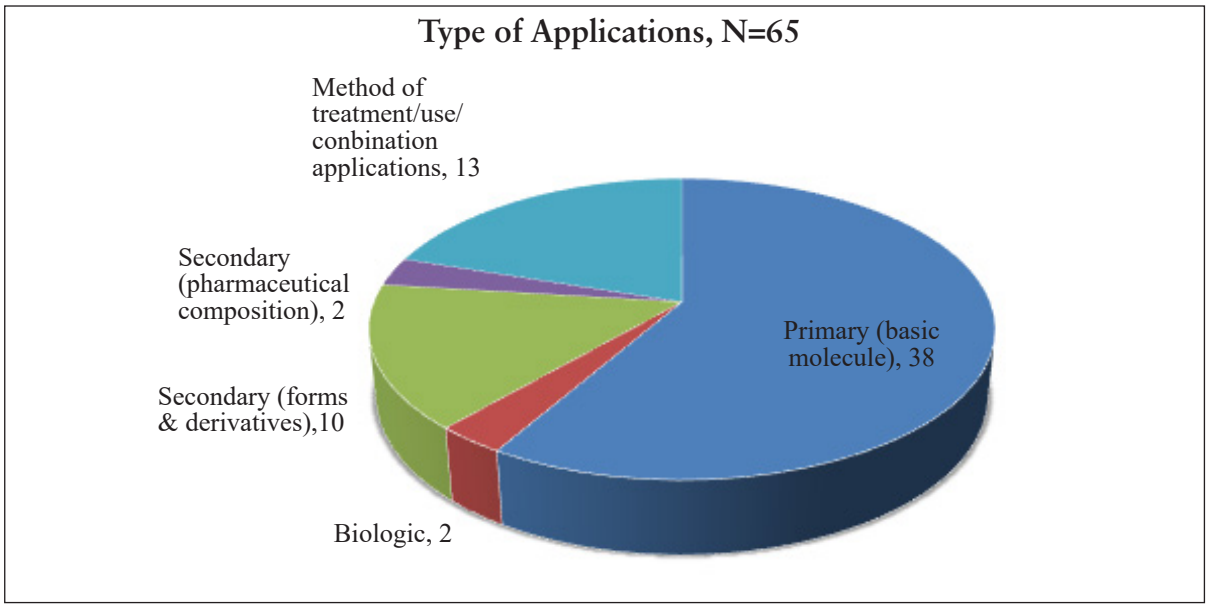


Box 9



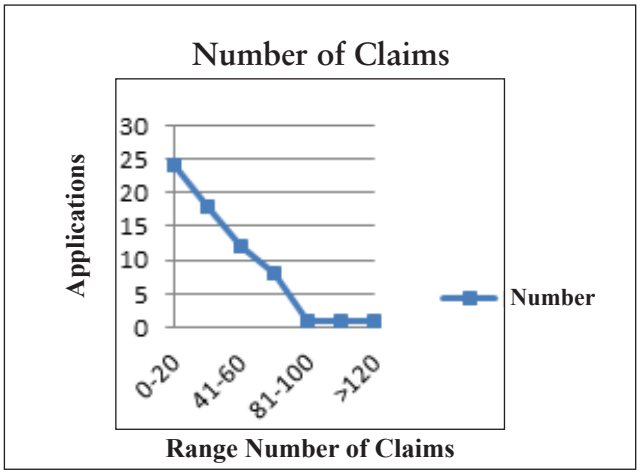
iii. ***Primary and secondary applications:*** The patent applications for which TPOs were filed were mainly primary applications (58%) with claims for basic molecules or compounds, and secondary claims for salt forms, crystalline forms, amorphous forms, prodrugs, hydrate forms and pharmaceutical compositions with specific activity or for derivatives of known compounds (see Box 10). Other applications were secondary applications where the claims were primarily for methods of treatment, or use of the compounds. Two applications covered biologic products. For the purpose of the analysis under the TPO project, secondary applications were those that made claims for compositions, combinations, methods of treatment, use of the compound in treatment and forms of the drug or known compound. There were 25 such applications for which a TPO was filed. The number of claims in these applications ranged from 11 to 87.

Box 10

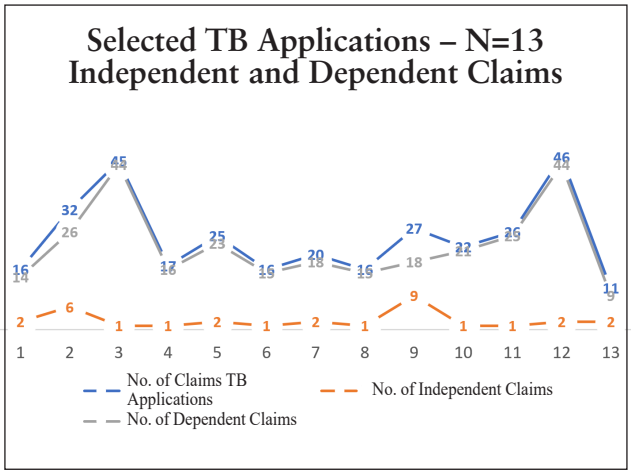


iv. ***Number and types of claims (independent and dependent):*** Of the 65 patent applications selected for the filing of TPOs, the number of claims ranged from 11 to 143, with the highest in an application for a biologic product claiming the treatment of HIV, HCV and TB as well as other diseases. The total number of claims in all 65 applications was 2,306. While most applications had 40 or fewer claims, a few had more than 81 claims and one application had 143 claims. (See Box 11)

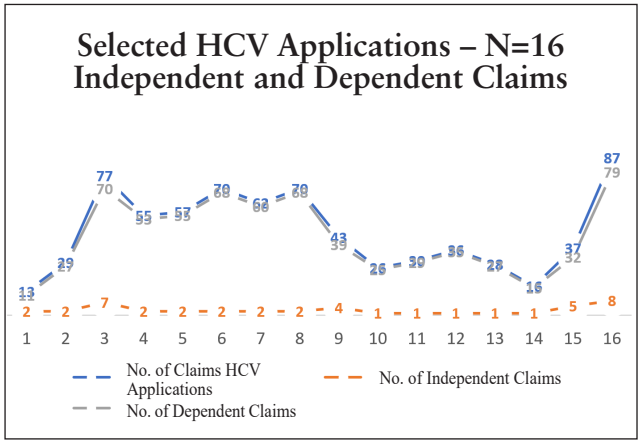
Box 11



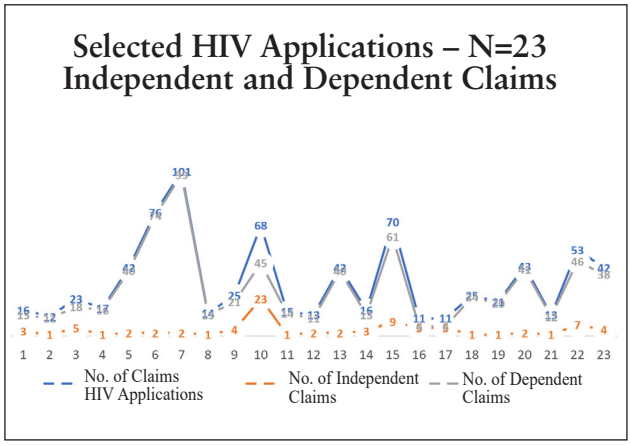
Box 12



Box 13



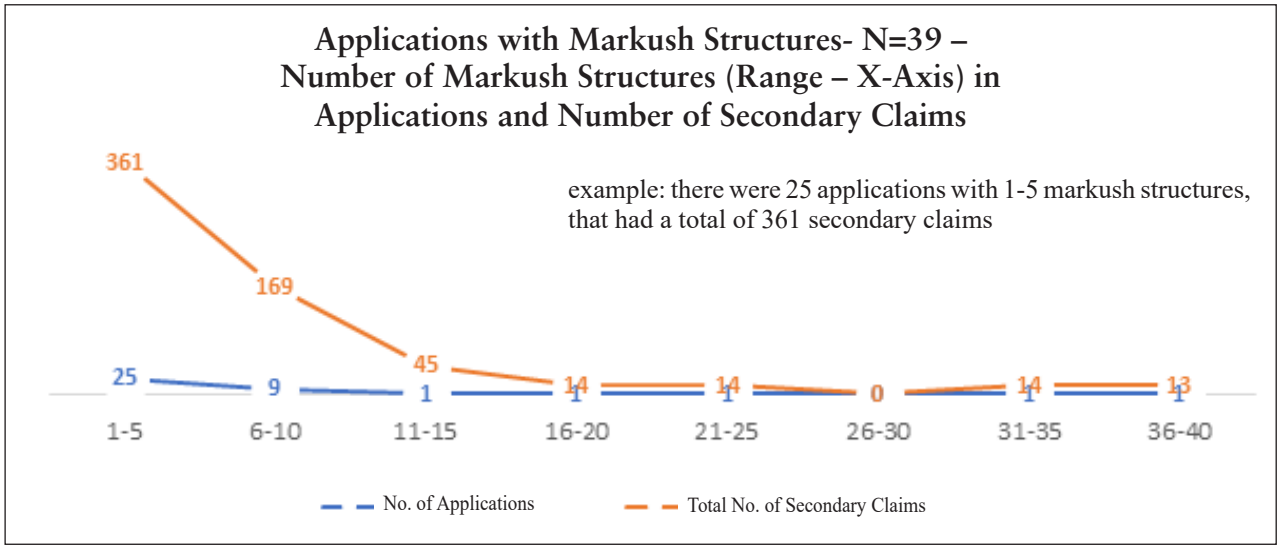
Box 14



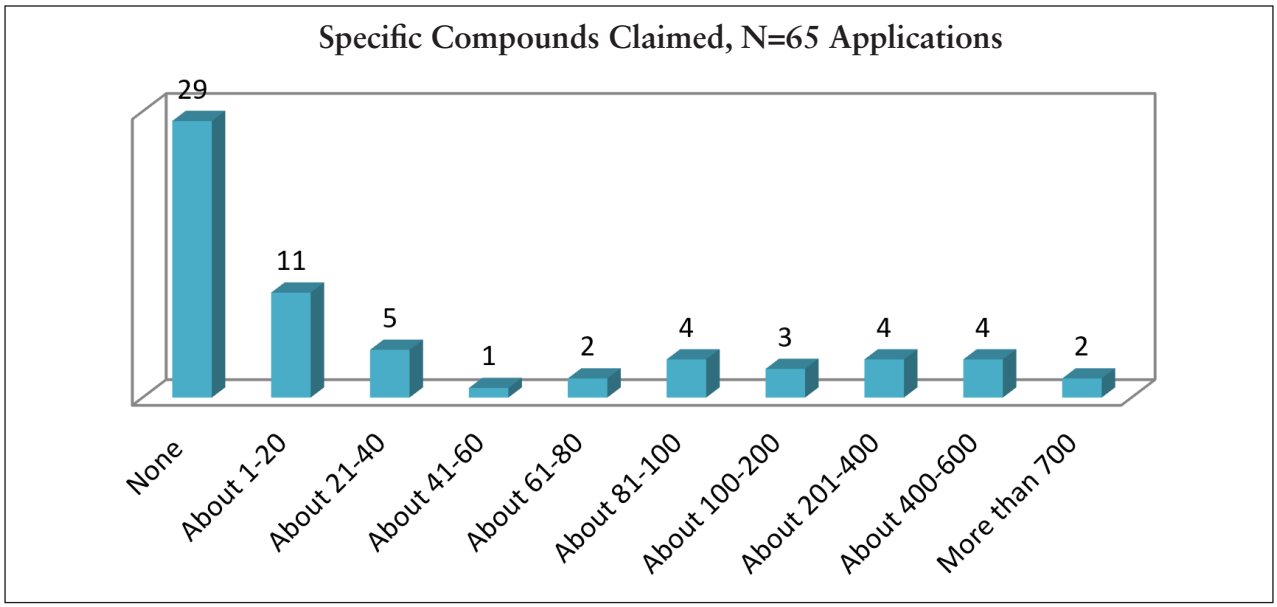
Most of the selected patent applications featured between one and three independent claims. One secondary application primarily claiming methods of treatment had 23 independent claims. The number of independent claims was between one and 23, while dependent claims ranged from six to 136. (See Box 12-14)

v. ***Number of basic molecule applications:*** Of the 65 patent applications selected for the filing of TPOs, 39 applications were primarily for basic molecules and all 39 had claims with Markush structures. Of these, 25 applications had claims with about 1-5 Markush structures, and nine applications had 6-10 Markush structures. There was one application each that claimed 11, 19, 25, 35 and 37 Markush structures. The number of Markush structures claimed ranged from one to 37 and the number of specific compounds claimed as a result of the Markush structures ranged from one to 1,440. It is interesting to note that of the 39 applications, 28 were by pharmaceutical companies, between two and five applications with Markush structures were filed by universities (either alone or with an individual or pharmaceutical company), and one by a research institute (see Box 15). Nearly 45% of the applications did not claim any specific compounds. However, 35% of the applications claimed specific compounds in the range of one to 100 compounds. There were two applications that claimed 738 and 1,440 specific compounds, respectively (see Box 16).

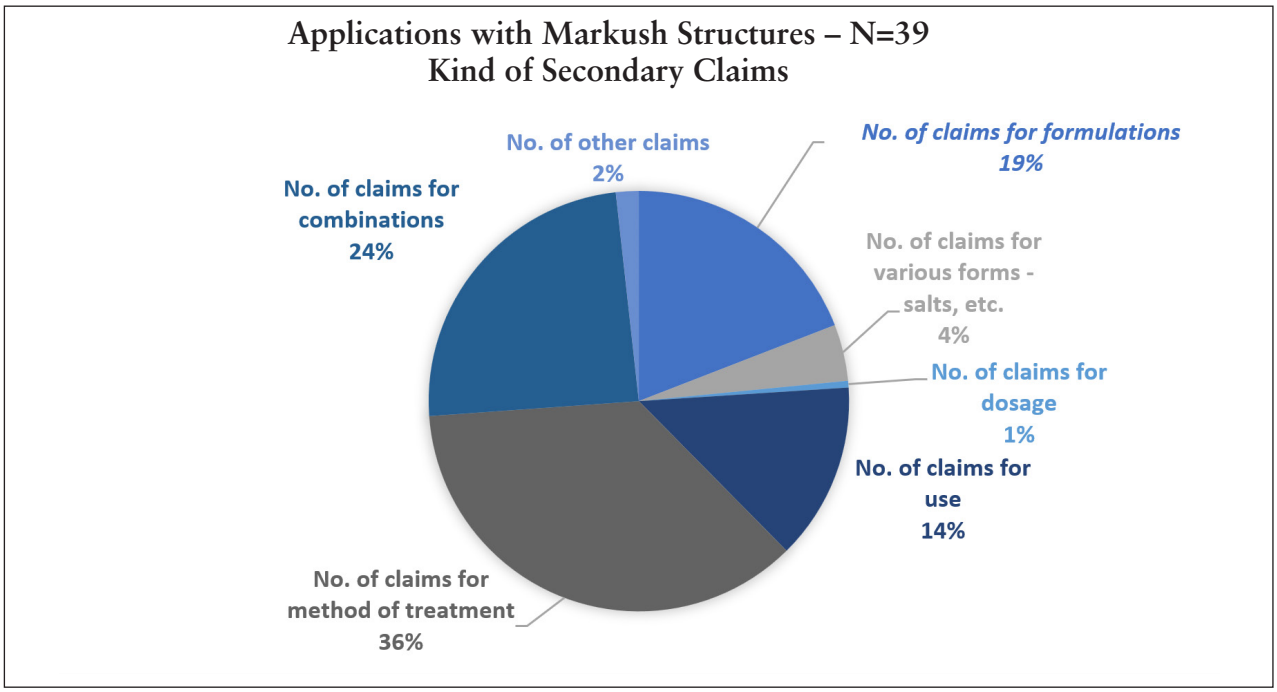
Box 15



Box 16



Box 17



Box 17 shows the range of secondary claims included in patent applications claiming Markush structures and specific compounds, which include secondary claims of combinations, method and use, dosage, forms of the compound, including salt forms, formulations, etc.

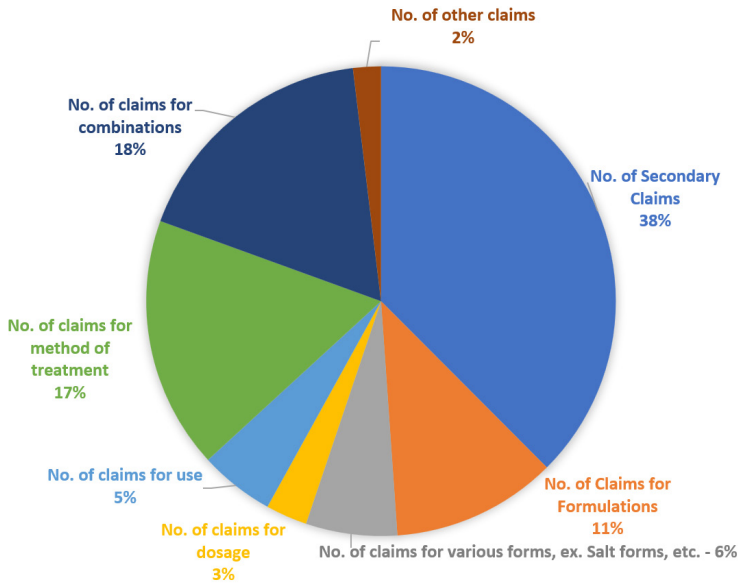
vi. ***Number of secondary claims:*** All of the 65 patent applications selected for the filing of TPOs included secondary claims. The number of secondary claims in the selected patent applications ranged from three to 143. Secondary claims included claims for formulations, various forms of the compound, like salt forms, crystalline forms, prodrugs of compounds, etc. The applications also had secondary claims relating to dosage, method of treatment and use of the compound. Some secondary claims were for combinations too. There were 18 applications that also contained claims for processes; some applications also contained claims related to steady states, kits and product by process.

vii. ***Types of secondary claims:*** Of the secondary claims contained in the 65 patent applications where TPOs were filed, several featured multiple secondary claims (see Box 18). These included:

- 64 applications claimed formulations; the number of formulation claims ranged from 0 to 55.
- 14 applications claimed different forms (salts, etc); the number of form claims ranged from 0 to 76.
- 14 applications included claims for dosages; the number of dose claims ranged from 0 to 31.
- 45 applications included claims for use; the number of use claims ranged from 0 to 22.
- 57 applications included method of treatment claims; the number of method of treatment claims ranged from 0 to 94.

Box 18

Types of Secondary Claims in All Applications – N=65



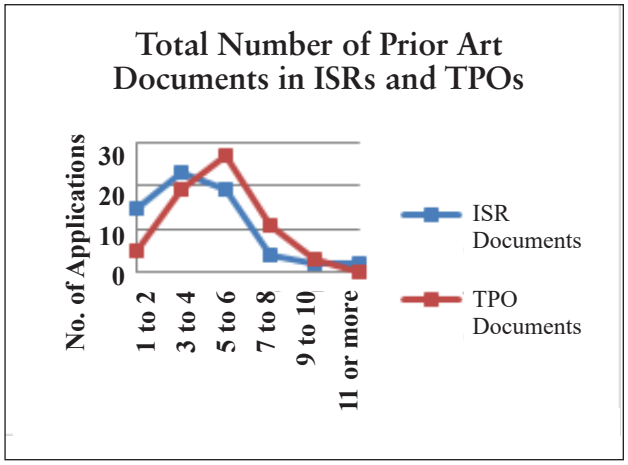
4
Key Features of TPOs Filed

During the pilot phase, i.e. the time for the setting up of the project team, the refinement of the search methodology and familiarisation with the ePCT system, the team filed one initial TPO to test the system. Systematic filing of the TPOs commenced in March 2019. With an actual time period of only 10 months from the date of publication of the patent application to file the TPO, the first few TPOs were extremely brief.

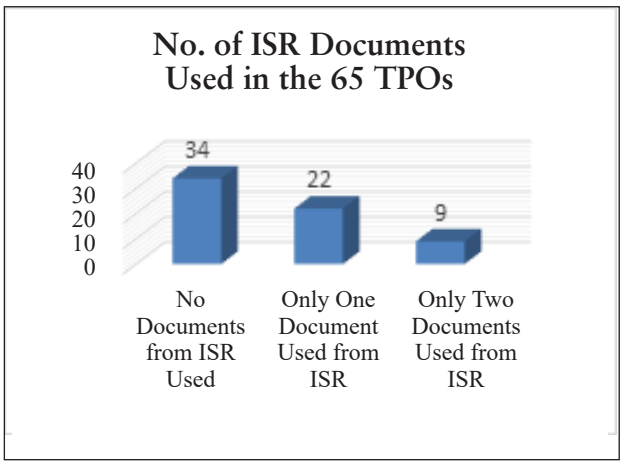
At the time of the filing of all TPOs, the ISRs and the WOSAs for all the patent applications were available. For the 65 patent applications for which TPOs were filed, the patent offices responsible for the ISRs were as follows: (i) European Patent Office (EPO) (Netherlands): 31 (ii) USPTO: 22 (iii) Korean Intellectual Property Office: 5 (iv) State Intellectual Property Office of the People's Republic of China: 4 (v) Intellectual Property Office of Singapore: 2 (vi) Ukraine Intellectual Property Institute. As of 30 August 2020, for 64 of the patent applications, the International Preliminary Reports of Patentability (IPRPs) were also available. It may be noted that for four of the applications, the IPRP was not available online even a couple of months after the filing of the TPOs. Three of the IPRPs became available online at a later stage, but one IPRP was still not available as at 30 August 2020. The International Preliminary Examination Report (IPER) was not available for any of the selected patent applications; it may be noted that the IPER is generated only when a patent applicant requests this, otherwise the Written Opinion of the International Searching Authority (WOSA) is published as the IPRP.[8]

i. ***Number of prior art documents used in the ISRs and the TPOs:*** For the patent applications selected for the TPOs, the number of prior art documents identified in the ISRs ranged from one to 11. The number of notes referring to prior art documents used in the TPOs ranged from one to the maximum allowed of 10 (see Box 19). In 31 of the 65 TPOs filed, some of the prior art documents used in the ISRs were also included (see Box 20); however the TPO used different arguments on the basis of these prior art documents to challenge novelty and/or inventive step than the arguments used in the ISR. In 34 TPOs, none of the prior art documents used in the ISR were used (see Box 20).

Box 19



Box 20



[8] For more information on ISR, WOSA, IPRP and IPER see https://www.wipo.int/edocs/mdocs/aspac/en/wipo_reg_pct_tyo_13/wipo_reg_pct_tyo_13_t5.pdf

The TPOs complement the prior art documents used in the ISRs and make available to the patent offices a wide range of prior art documents for the PCT applications filed. The prior art documents available to the national and regional patent offices would be a combination of the documents referred to in the ISRs and the TPOs. For the 65 applications where TPOs were filed, the number of prior art documents available to patent offices from both the ISRs and the TPOs would be in a range of three to 19 documents that challenge the patent applicant's claims on grounds of lack of novelty, inventive step or both (see Box 19).

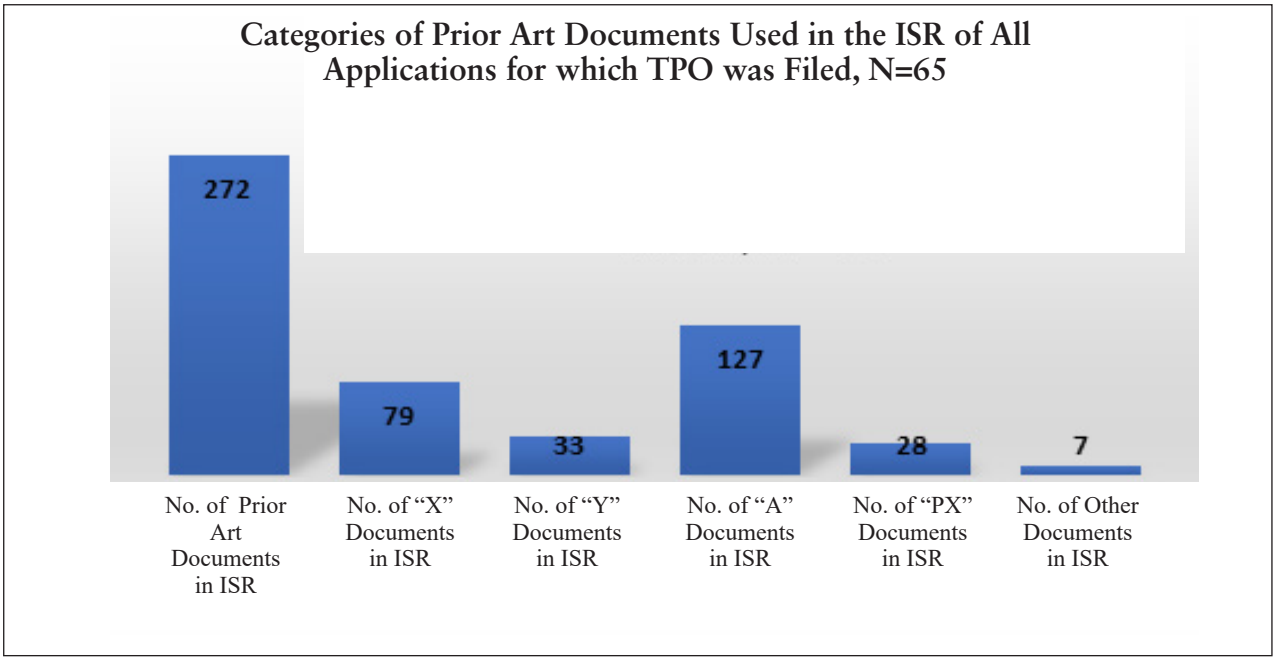
ii. ***Types of prior art documents filed in the ISRs:*** The ISRs categorise prior art documents in a particular manner (see Box 21).[9] In the ISRs for the 65 patent applications where TPOs were filed, the number of "X" documents used ranged from 0 to 10, the number of "Y" documents ranged from 0 to 5, the number of "A" documents used ranged from 0 to 7, and the number of "P" documents ranged from 0 to 4. Only one ISR used an additional category of prior art documents; in that ISR, an "L" document was cited to show that the patent application could not claim the protection of the priority date as it was not the first filed application and the "L" document, being the first filed application, anticipated the claims of the present application (see Box 22).

Box 21

Categories of Citations

- X: Particularly relevant if taken alone. Objection: Lack of novelty or lack of inventive step with one document
- Y: Particularly relevant if combined with another Y-document. Objection: Lack of inventive step by combination of two (or more) documents, always in pairs
- A: Technological background, no objection of lack of novelty or inventive step
- O: Non-written (e.g. oral) disclosure
- P: Intermediate document, published after priority date but before filing date of the application, used in combination with X, Y, A (eg. PX)
- T: Theory or principle underlying the invention, could be later document, published after filing date or priority date
- E: Earlier patent document, but published on, or after the filing date
- D: Cited in the application
- L: Cited for other reasons, such as throwing a doubt on priority claims
- &: Document member of the same patent family

Box 22

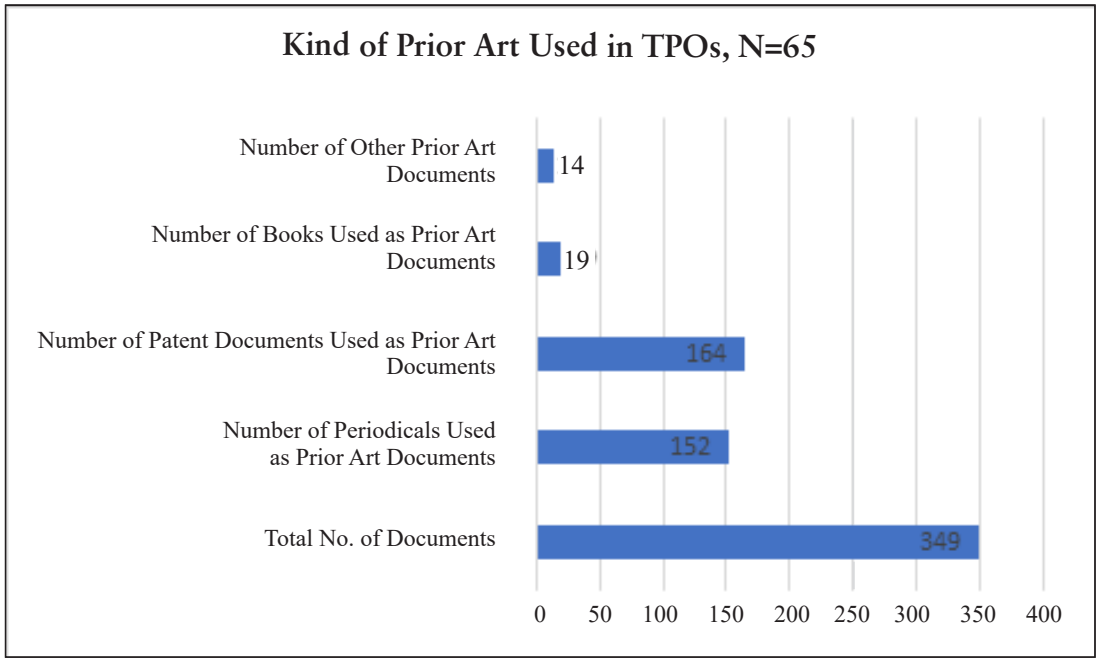


[9] https://www.wipo.int/edocs/mdocs/aspac/en/wipo_ip_kul_11/wipo_ip_kul_11_ref_t20.pdf

iii. ***Types of prior art documents filed in the TPOs:*** The prior art documents cited in the TPOs challenged either novelty or inventive step or both. Apart from one TPO where only one prior art document was cited, in the rest of the TPOs, the number of prior art documents cited ranged from two to 10. Most TPOs focused on citing documents challenging inventive step or both novelty and inventive step. In the TPOs, the number of documents cited to challenge only novelty ranged from 0 to 1, to challenge only inventive step ranged from 0 to 9 and the number of prior art documents to challenge both novelty and inventive step ranged from 0 to 7.

iv. ***Sources of prior art filed in the TPOs:*** The TPOs relied on both patent and non-patent literature (see Box 23). The number of periodicals used as prior art ranged from 0 to 8, the number of patent documents ranged from 0 to 6 and the number of books used as prior art ranged from 0 to 3. In one TPO, treatment guidelines were also used as prior art. In another, publications relating to results of clinical trials were used. Drug labels detailing ingredients from the US FDA were also used in one TPO. Other types of prior art used in the TPOs included conference papers, abstracts, posters and presentations. Machine translations of prior art documents that were not in English were also uploaded in some TPOs.

Box 23



5
Reflections from the TPO Project

All the TPOs filed by the project team have been accepted by the International Bureau of WIPO. The applicants in at least two applications for which a TPO was filed have responded to the TPO submitted. Their responses are also available to the national and regional patent offices on PATENTSCOPE. Of the 65 applications for which TPOs were filed, data regarding entry into the national phase was available for some applications as of 7 October 2022 (See Annex 1). However, this data is dynamic and may not reflect the actual status in various designated/selected countries. For some applications that have reached the national phase in Europe, the TPOs have been taken note of by the EPO, which asked the patent applicant to respond to the prior art and arguments in the TPO. The observations of the EPO in some of the key cases are highlighted in the case studies in Annex 2.

The TPO project highlights the importance of the TPO system and the role it can play in facilitating patent examination, improving the quality of patents granted globally. At the end of one year of filing 65 TPOs, over almost one and a half years of the TPO project, the following comments and observations emerge:

a. On the TPO filing system

i. ***Need for improvement of information on front page (title and abstract) of patent application:*** Search and screening of patent applications is made difficult by the lack of transparency due to how the applications are drafted. As the titles and abstracts which are on the front page rarely mention the medicine or the disease, determining which patent applications may be of public health importance requires a scan of the specification and claims. Abstracts will often have the structure claimed but not mention the disease it is aimed at. The experience of the patent searches highlights the importance of disclosing the international non-proprietary name in patent applications.

ii. ***Brief explanations insufficient for TPO arguments:*** In the case of pharmaceuticals in particular, many applications tend to claim structures. To challenge the novelty or inventive step of such structures, visual representations are important. The box for explanations in the TPO template however permits only text and imposes a character limit, which constrains the ability to provide detailed explanations. The box also does not allow Greek characters, superscripts and subscripts that would make reading formulae simpler. Further restrictions on documents that can be uploaded, such as on the size of the PDF file (A4 only, up to 20 MB only), do not sufficiently allow use of multiple images to provide a comparison between the citation and the patent application. For some applications the number of claims is more than 100. However, in the bibliography portion for the prior art, there is a character limit that restricts the TPO filer from writing in detail about the claims covered by the prior art document.

iii. ***Difficulties in using the filing system:*** There are several barriers in the use of the TPO system. The first relates to the various restrictions on the size of documents mentioned above; for instance, the requirement that all documents be of A4 size and only up to 20 MB makes it challenging to file a TPO. Not all prior art documents can be converted to A4 size. For such documents to be cited in the TPO, only an online link or the digital object identifier (DOI) can be provided, with the result that the patent office may not necessarily be able to get access to the document. Additionally, although the website for filing TPOs has been revamped, it still creates problems for filers. For instance, it is difficult to upload a large prior art document (more than 100 pages). If the document cannot be attached to the TPO, the entire process has to be restarted. The status and the amount of time left to upload a document should be shown, and the option of cancelling attachments which are spooling to get uploaded should be provided in the system.

iv. ***Document limit insufficient for effective TPO filings:*** For Markush structure applications, it is a challenge to find a prior art document that would cover all the claims. Further, limiting the number of prior art documents to only 10 is restrictive when the claims are wide-ranging. In fact, the ISR in two of the applications for TB, WO2018109504 (by University of Oslo & anr.) and WO2018151681 (by Nanyang Technology University & National University of Singapore), had cited 11 documents, 10 of which were "X" documents. The TPOs filed referred to only one of the ISR documents in both the applications and cited eight and six additional prior art documents respectively. Both these applications were filed by universities.

v. ***Lack of information for TPO filers:*** According to the TPO filing system, the link for filing TPOs remains active till the end of the time period provided for filing. However, in the case of four applications (WO2018170664, WO2018188047, WO2019013789, WO2019013790), the link to submit TPOs disappeared before the time period expired and no explanation was provided as to why the link disappeared. The efforts of the team in preparing arguments and prior art were wasted. It is possible that the applicant may have withdrawn the application, but if that was the case, an explanation indicating this ought to have been provided.

vi. ***Limitations on grounds of challenge:*** As noted above, a significant number of patent applications on pharmaceuticals disclose multiple Markush structures and can claim hundreds of compounds. These applications typically reveal very broad mechanisms of action and although the application of the Markush structures is claimed for multiple diseases and conditions, the applications do not in fact provide any support for these claims. This has been the case with the four patent applications filed by Enanta Pharmaceuticals highlighted in Case Study 6 in Annex 2. With applications such as these that claim (at times multiple) Markush structures, one of the primary grounds for opposition would normally be insufficiency of disclosure. However, the TPO system envisages challenges only to novelty and inventive step. This reveals a huge drawback of the TPO system's one-size-fits-all approach to challenging patents regardless of the nature and peculiarities of the field of technology involved, in this case the pharmaceutical field.

b. On the International Search Reports

i. ***Need for review of search approaches of international searching authorities:*** In the process of filing TPOs and examining ISRs on selected patent applications, a pattern has emerged in the search approach for prior art undertaken by international searching authorities. In several ISRs, especially those relating to secondary applications, the focus is on prior art related to the specific compound or those that are structurally similar, and not on prior art documents demonstrating knowledge of general science, common knowledge or state of the art; the TPOs have thus focused on the general common knowledge and added in textbooks and periodical articles on known forms, salts etc. When looking at a new compound, the TPOs have focused on finding general articles on that or similar structures.

Other issues of concern that have arisen relate to Markush structures; in particular, two patent applications (WO2018116108 and WO2018116107) filed by the same entity, on the same date, claim very similar structures; yet the prior art documents cited in the ISRs are different. In several cases, the ISRs appear to have not cited crucial prior art documents. Often the ISRs do not cite textbooks and other periodical documents that disclose the information that would be obvious to a person skilled in the art to make the product claimed in the application. In Annex 2, Case Study 1, the case of the patent application for a potential TB drug – ethionamide(eto)/prothionamide – is discussed. This drug will shortly enter Phase II clinical trials. It has been largely funded through public funds, and has been developed in collaboration with private parties and a university. The applicants have used compounds that are known and obvious to a person skilled in the art. An application for a patent appears to be unwarranted and should be opposed. However, the ISR finds that the claims on this patent application are both novel and inventive. The predominant citation of general state of the art documents can also be seen in Case Study 3 in Annex 2 that analyses a patent application filed on a known TB drug, sanfetrinem.

ii. ***Variations in quality of ISRs:*** It is important to note that the ISRs are not all of the same quality, nor do they employ the same approach to searches and use of prior art documents. For instance, only some ISRs use general knowledge documents and articles, which should really be an approach followed in all the ISRs. For instance, some patent applications (WO2018149608, WO2018144390, WO2019027920, WO2019060692) covered only solid state and/or salts but the ISRs did not include any general documents. Similarly, several applications claim combinations; available treatment guidelines or documents showing standard of care can act as prior art in such cases, as was done in several of the TPOs (see TPOs on WO2018175185, WO2019016679, WO2019030625, WO2019084020, WO2018206466 and WO2019030626). For instance, the TPO on WO2018158280, which covers a TB drug filed by Janssen, cites the relevant WHO treatment guidelines, as evidence of prior art.

The wide variation in the quality of the ISRs arises from the fact that they are prepared by different patent offices that follow different search approaches. It is evident that a disproportionately high number of ISRs were published by the EPO and USPTO. In most ISRs published by the EPO, no brief explanation regarding the background of the documents cited was given; such explanations were at least present in some of the ISRs published by the USPTO. Only in a few instances was the ISR issued by the office of a country other than the country of origin of the applicant. For some applicants which had a base in the US, the USPTO issued the ISR, though the applications were European applications; in five applications which listed the US as the country of the applicant, the Korean Patent Office issued the ISR. As for the ISRs published by the patent offices in China, Singapore and Ukraine, these were for applications filed by applicants from the same country (e.g., both the applications filed by Singapore's Nanyang Technological University were handled by the Intellectual Property Office of Singapore).

c. On the patent applications

i. ***Secondary claims and applications, method of treatment claims and Markush structures appear to define the pharmaceutical patent field:*** The patent applications on which TPOs have been filed confirm what several studies have shown and health groups have argued for some time now: that evergreening patent applications are a common feature of patent filing strategies, that there is a routine use of Markush structures when claiming basic molecules (usually leading to multiple selection patents resulting in a long line of patents and patent applications emanating from the original Markush patent), and the significant presence of method of treatment claims in patent applications. This can be observed through the case summaries in Annex 1. Although there has been an acknowledgement and recognition that these patterns of pharmaceutical patent filing result in an abuse of the system, patent offices in developed and developing countries still tend to grant these patents. It will be interesting to see the fate of these applications as they enter the national phase and whether national patent offices that receive or would have access to the TPOs filed in these cases take note of the challenges to the novelty and inventive step of these applications and reject the claims or require them to be amended.

ii. ***Multiple companies attempt to evergreen the same molecule:*** An interesting observation from the project relates to the different ways in which evergreening of patents, particularly of commercial or promising molecules, takes place. While it is evident that originator companies continue filing multiple patent applications on the same molecule for years if not decades, it appears that multiple companies other than the originator company also file such evergreening patents on these molecules. For instance, TPOs have been filed on patent applications related to cabotegravir, an important HIV medicine. While ViiV, the originator, continues to file evergreening patent applications on this drug, an application for crystalline forms of cabotegravir has also been filed by Sandoz. This has also emerged in the case of Q203, a promising molecule for the treatment of multidrug-resistant (MDR) TB. As discussed in Case Study 2 in Annex 2, there are three patent applications related to Q203 where TPOs have been filed. All three are by different, unrelated applicants; while two of the applications attempt to patent Q203 in combination with other existing TB medicines, one application claims multiple methods of treatment with Q203. Also discussed in Case Study 4, Annex 2 is the case of bictegravir, which has been approved as a treatment for HIV. Although it was patented and introduced by Gilead Sciences, two patent applications have been filed by ViiV Healthcare attempting to patent bictegravir as part of a combination with other existing HIV medicines.

iii. ***Cordoning off vast areas of research; overwhelming the patent system:*** As noted above, a large number of applications where TPOs were filed claimed Markush structures, i.e., "claims that include general formulae with multiple options that allow for the protection, under a single patent, of up to several millions of molecules patents. In addition, it is virtually impossible to make prior art searches for thousands or millions of compounds. They also pose a transparency problem, since it is very difficult for third parties to identify patent applications that would merit a pre or post-grant opposition."[10] In the patent applications opposed under this project, thousands of compounds have been identified. The case study on patent applications filed on ASK-1 inhibitors in Annex 2 (Case Study 6) highlights the serious concerns for research and development as well as for the patent system raised by such applications. This case study highlights patent applications filed by biotechnology company Enanta Pharmaceuticals relating to ASK-1 inhibitors. An analysis of the applications shows that they are trying to create exclusive rights on nearly all possible developments within this particular research area. Thus, they have claimed every possible variation of the core known to have ASK-1 inhibitory activity and compounds that may be derived from such parent Markush structures. Even the modifications made to the scaffolds across the applications could have been anticipated by a person skilled in the art and covered in a single application. This is a classic example of a single applicant claiming closely associated Markush scaffolds across a number of patent documents and keeping the scope of the Markush scaffold so broad that its interpretation leads to an enormous number of compounds being claimed and an entire area of research being cordoned off. If granted, patent applications like these will prevent research in the area by other researchers, scientists and entities for fear of encroaching on the patent rights. They also create significant pressure on the patent office reviewing such applications that can cover such a multitude of compounds.

iv. ***Failure to disclose public funding:*** Surprisingly, only five of the patent applicants revealed any public funding for the inventions claimed. As noted above, the majority of the applications selected for TPOs were from the US. A recent study of 210 new drugs approved by the US FDA between 2010 and 2016 revealed that each and every one of the drugs had received US National Institutes of Health (NIH) funding, totalling more than USD100 billion; over 90% of the funding represented basic research.[11] Under the US Bayh-Dole Act, patent applicants are required to reveal federal government funding in their applications.[12] The importance of this requirement has recently come to the forefront in the context of COVID-19 vaccines produced by the US company Moderna, which has launched phase III clinical trials on the back of a huge investment from the US government and a supply agreement for selling the vaccines to the government. However, its vaccine technology has been developed with US federal funding, which it has not revealed in any of the 124 patents it has obtained in its 10-year history as a company; nor have any such disclosures been made in the company's 154 pending patent applications. Specifically, the company's vaccine technology was developed initially for vaccines for zika and chikungunya with USD25 million in funding from the US government. Public interest groups are demanding that the failure to disclose public funding should lead to the government taking title to the patents.[13]

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10 Correa CM. Pharmaceutical innovation, incremental patenting and compulsory licensing. Geneva: South Centre; 2011 (p. 12).
11 https://www.pnas.org/content/115/10/2329
12 https://www.keionline.org/wp-content/uploads/2018/03/KEI-Briefing-Note-2018-1.pdf
13 https://www.keionline.org/33763

d. Reach of TPOs

One of the concerns that arise in this context is that very few patent offices have opted to receive the TPOs. As noted above, under PCT rules, information on patent applications is transmitted to patent offices only if they have specifically requested it.[14] Those that have not specifically requested transmission of TPOs will have to proactively seek out the TPOs. Civil society groups should consider methods of bringing the TPOs to the attention of their national or regional patent offices and monitor how their patent offices take note of and use ISR and TPO documents. For instance, among the patent applications on which TPOs have been filed were applications for new forms of cabotegravir and tenofovir alafenamide, important HIV medicines. Another patent application on which a TPO was filed is for the analogues of atazanavir, which included GS-PI1 which is reported as a preclinical candidate in the 2017 TAG pipeline report.[15] These applications have now entered the national phase in some countries. It would be important for civil society organisations to take note of these developments and bring the TPOs to the notice of their national or regional patent offices.

[14] See https://www.wipo.int/pct/en/texts/ai/s805.html, https://www.wipo.int/pct/en/texts/rules/r93bis.html and https://www.wipo.int/pct/en/texts/rules/r47.html

[15] Treatment Action Group, "TAG Pipeline Report 2017 HIV TB HCV", available at https://www.treatmentactiongroup.org/wp-content/uploads/2017/07/Pipeline-Report_2017_FINAL.pdf

6
Recommendations

Setting up of the TPO system in the context of WIPO's PCT system was an important step forward towards improving the quality of patents granted across the world. It is thus imperative to continue improving its effectiveness and encouraging its use.

Observations from filing TPOs appear to confirm the public health critiques of the patent system regarding the evergreening of patents. In addition, they reveal that the operation of the PCT system does not support improving the quality of patents granted. The TPO system itself is difficult to use and, for smaller competitors or civil society groups, is too cumbersome and time-consuming even though the need for better prior art searches is evident from the quality of ISRs. Unfortunately, the administration of the patent system, internationally and nationally, has a direct impact on the lives and health of patients globally. A system biased in favour of low-quality patents and patent applicants has resulted in well-documented profiteering in the pharmaceutical sector. As such, the PCT system, including the TPO mechanism, requires an urgent public-interest- and public-health-based audit, review and overhaul.

World Intellectual Property Organization

- ***Disclose INN on front page of patent applications:*** There is a need to improve information on the front page of the patent application, to increase transparency and facilitate screening and identification of relevant patent applications that are important from a public health perspective.

- ***Audit of pharmaceutical patent applications:*** The TPO project reflects the findings of several studies[16] highlighting the extent to which pharmaceutical patent applications cover secondary claims or broad Markush claims that impact research and development and access. This is increasingly a problem with this particular area of technology. An audit of the pharmaceutical applications filed through the PCT would highlight the extent of the problem, and measures to address this should be discussed at the relevant WIPO Committees as well as the WIPO General Assembly with the participation of health and public interest groups.

- ***Review and remove restrictions on TPO filings:*** As noted above, several procedural requirements and restrictions, such as on the size of documents, limits on documents and word limits, make filing of TPOs very difficult. As a process designed to improve the quality of patents, the TPO filing mechanism needs to be simplified to encourage proper and effective use.TPO filers should also have the opportunity to comment on patent applicants' response to the filed TPO.

- ***Expand the grounds on which TPOs can be filed:*** The grounds for challenging patent applications through TPOs should be expanded beyond novelty and inventive step. In particular, the large number of patent applications claiming Markush structures should be challenged for lack of disclosure, as should overbroad or non-specific claims. With the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) allowing, and most countries including in their legislation an exemption of methods of treatment from patenting, this should also be permitted as a ground for challenge.

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16 "Pharmaceutical Sector Inquiry Report". DG Competition Staff Working Paper, available at http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf; WIPO (2011), Patent Landscape Report on Ritonavir (WIPO Publication 946) available at https://www.wipo.int/edocs/pubdocs/en/patents/946/wipo_pub_946.pdf

- ***Conduct audits of international searches:*** The TPO project has revealed considerable differences in the manner and quality of the international searches that most patent offices end up relying on in their national or regional examination proceedings. WIPO should commission an independent audit of ISRs, search methodologies and quality of search by the various international searching authorities and, in consultation with public interest groups and experts, review and make changes to improve the international search mechanisms.

- ***Broaden the scope of prior art documents cited in international searches:*** International searches appear to rely predominantly on patent literature. In the case of pharmaceutical patents, however, general textbooks are of tremendous importance in identifying prior art. As seen in the TPO filings, additional sources of prior art such as treatment guidelines can also be relied on. WIPO should encourage broadening the scope of prior art documents used by international searching authorities.

Governments

- ***Amend patent laws to include provisions against evergreening patents and ensure its rigorous implementation by patent offices:*** With a large number of patent applications claiming secondary patents on existing molecules, countries should include specific provisions in their patent laws to prevent such evergreening patents from being granted. Governments should also ensure that patent office policies and practices are rigorous and prevent evergreening of patents.

- ***Ensure strict requirement of disclosure:*** Markush claims covering millions of compounds most of which are not revealed or specified in the patent applications should be subject to strict disclosure standards by patent offices. Given the overwhelming numbers of such applications, specific provisions in patent laws should be considered to prevent such overbroad patents from being granted. Patent offices should also adopt policies and practices that demand adequate disclosure.

- ***Stricter examination guidelines on pharmaceutical patent applications:*** The TPO project as well as several studies have revealed the most common forms of claims in patent applications most of which do not actually meet the criteria of novelty and inventive step (such as claims for salts, polymorphs, etc.), or of sufficiency of disclosure (such as Markush claims). Pharmaceutical patent examination guidelines can help patent offices immediately identify such claims and provide the grounds for why these should not be granted.[17]

- ***Patent offices should request and consider TPOs:*** In order to facilitate examination, patent offices should request TPOs and consider TPOs in the national or regional examination process.

Patent Offices

- ***Patent offices should include TPOs in the list of documents that WIPO must transmit through the PCT system:*** All national and regional patent offices should immediately identify TPOs as part of the documents specifically requested by them under the PCT Rules. Unless the TPOs are transmitted proactively, patent offices and patent examiners are unlikely to try and access these documents themselves given the high burden on these offices.

- ***Patent offices should consider TPOs in national or regional patent examination:*** As can be seen through the TPO project, TPOs can bring to light prior art and analysis that is not included in the ISRs. This analysis and information should be taken into account by patent offices when doing their own searches and examination.

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[17] See for e.g. UNDP (2016) "Guidelines for the Examination of Patent Applications relating to Pharmaceuticals | United Nations Development Programme" available at https://www.undp.org/publications/guidelines-examination-patent-applications-relating-pharmaceuticals

- ***Patent offices should conduct their own searches and encourage public participation in the review of patent applications:*** The wide differences in the quality of ISRs highlight the importance of patent offices conducting their own searches for prior art. In particular, these searches should rely on both patent and non-patent literature and other sources as well. In the field of pharmaceuticals, general textbooks are particularly important.

Civil Society

- ***Advocate for adoption of stricter patentability criteria and disclosure standard in national and regional patent laws and patent examination guidelines and its rigorous application by patent examiners:*** The problems created by evergreening and overbroad patent claims on pharmaceuticals in terms of restricting research and development and preventing access are now well recognised and established. Civil society groups should advocate for reform of the patent law as well as examination practices to prevent evergreening and overbroad pharmaceutical patents from being granted.

- ***Bring TPOs to the attention of national or regional patent offices:*** Civil society groups should track the filing of TPOs on patent applications on key medicines and bring them to the attention of the patent office.

- ***Access and consider prior art filed in TPOs for national or regional patent oppositions:*** Public participation in patent examination processes through patent oppositions has been one of the most successful public health interventions in the past decade. Civil society groups should actively file patent oppositions and use prior art and analysis from TPOs to support their oppositions.

ANNEX 1
Case Summaries

Table of Contents

Part A: Case Summaries – HIV Applications

<table>
<tr><td>TPO No.[1]</td><td>8</td></tr>
<tr><td>Appl. No.[2]</td><td>PCT/IB2018/050021 : WO2018127800</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018127800</td></tr>
<tr><td>Applicants</td><td>ViiV Healthcare UK (No. 5) Limited</td></tr>
<tr><td>Priority Date</td><td>03.01.2017</td></tr>
<tr><td>Details</td><td>This application claims pyridin-3-yl acetic acid derivatives for the treatment of HIV.</td></tr>
<tr><td>Claims</td><td>The application has 16 claims, of which 3 are independent claims and 13 are dependent. One Markush structure is claimed. Overall, there are 2 specific compounds included in the claims. Of the 16 claims, 7 are secondary claims, 4 are formulation claims and 3 use claims and 2 are for methods of treatment. Two of the claims include combinations.

Of the 4 formulation claims, 1 claim is for a composition claim per se, 1 claim is for a composition of a combination per se and 2 claims are method of treatment claims. Of the 2 combination claims, 1 claim overlaps with formulation claims (as it is for composition of combination) and 1 claim overlaps with method of treatment claims. The 2 method of treatment claims both overlap with formulation claims.</td></tr>
<tr><td>ISR</td><td>The ISR cited 5 documents as prior art. Of these, 1 was X and 4 were PX documents.</td></tr>
<tr><td>TPO</td><td>The TPO cited 4 prior art documents; all 4 challenged both novelty and inventive step. Three of the prior art documents were patent documents and 1 was a periodical.</td></tr>
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[1] TPO No. refers to publisher's internal reference number
[2] Appl. No. provides information on the International Application No. and the Publication Number
[3] National phase as of 07.10.2022 reflects information provided on WIPO's patentscope database as at that date. However, this data is dynamic and may not provide accurate information on the actual status of the patent application.

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<tr><td>Applicants</td><td>ViiV Healthcare UK (No. 5) Limited</td></tr>
<tr><td>Priority Date</td><td>03.01.2017</td></tr>
<tr><td>Details</td><td>The application also claims pyridin-3-yl acetic acid derivatives for the treatment of HIV. The only difference in the Markush scaffolds of WO’800 and WO’801 is that both monocyclic and bicyclic rings can be substituted at position 4 of the pyridine ring in WO’800 and is specifically claimed to be isoquinoline (bicyclic) ring in WO’801.</td></tr>
<tr><td>Claims</td><td>The application has 12 claims, of which 1 is an independent claim and 11 are dependent. One Markush structure is claimed but no specific compounds are claimed. Of the 12 claims, 7 are secondary claims, 4 are formulation claims and 3 use claims and 2 are for methods of treatment. Two of the claims include combinations.

Of the 4 formulation claims, 1 claim is for a composition claim per se, 1 claim is for a composition of a combination per se and 2 claims are method of treatment claims. Of the 2 combination claims, 1 claim overlaps with formulation claims (as it is for composition of combination) and 1 claim overlaps with method of treatment claims. The 2 method of treatment claims both overlap with formulation claims.</td></tr>
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TPO No.	10
Appl. No.	PCT/US2018/012098 : WO2018128993
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018128993
Applicants	OyaGen, Inc.
Priority Date	04.01.2017
Details	The application covers pharmaceutical composition of compounds that inhibit the self-association of Viral Infectivity Factor (Vif) in HIV-infected cells. The application claims pharmaceutical composition of compounds that inhibit Vif self-association, enhance APOBEC3G activity or cause RNA mutations that produce defective virions. The 3 compounds specifically listed and claimed as having this activity are all known compounds and have been sourced from other entities. The 3 compounds for which compositions are claimed belong to the class of camptothecins (one of which is a modified analogue of irinotecan) which are known to have anti-cancer activity. The application claims compositions of these compounds for anti-HIV activity.
Claims	The application has 23 claims, of which 5 are independent claims and 18 are dependent. All 23 claims are secondary claims, of which 22 are formulation claims. There are no Markush structures claimed. There are 3 method of treatment claims, 7 claims are for combinations. The applicant claims pharmaceutical compositions of specific isomeric forms of 3 compounds, their salts and prodrug of 1 of them. The applicant does not claim the compounds or the prodrug per se. Of the 22 formulation claims, 20 are for the composition per se and 2 overlap with method of treatment claims. Of the 3 method of treatment claims, 1 is a method of treatment claimed per se and 2 overlap with formulation and combination claims. Of the 7 combination claims, 5 overlap with formulation claims and 2 overlap with method of treatment claims. All of the 5 independent claims in this application are characterised by the mechanism of action. Several dependent claims too are characterised by mechanism of action. However, for this application, none of these are counted as “Other claims”.
ISR	The ISR cited 8 documents as prior art. Of these, 1 was AX, 2 were Y, 5 were A. In the ISR, the document listed for novelty (X) was also listed for inventive step (Y).
TPO	The TPO cited 5 prior art documents; 1 prior art document challenged only inventive step while 4 prior art documents challenged both novelty and inventive step. One of the prior art documents was a patent document and 4 were periodicals.
Date of Filing of TPO	The TPO was filed on 06.05.2019.
National Phase as of 07.10.2022	

Office	Entry Date	National Number	National Status
Canada	12.06.2019	3047000	
United States of America	04.07.2019	16476094	Published 21.11.2019 Granted 14.09.2021
EPO	05.08.2019	2018736145	

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<tr><td>Appl. No.</td><td>PCT/US2018/014761 : WO2018140368</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018140368</td></tr>
<tr><td>Applicants</td><td>Merck Sharpe & Dohme Corp</td></tr>
<tr><td>Priority Date</td><td>26.01.2017</td></tr>
<tr><td>Details</td><td>The application covers a substituted quinolizine derivative for the treatment of HIV. The application claims prodrugs of an already known molecule. This known molecule is very similar to established carbamoyl pyridones such as dolutegravir. Dolutegravir has 2 nitrogen atoms in the saturated ring attached to the pyridine ring whereas the molecule in the application has only 1 nitrogen atom in the saturated ring attached to the pyridine ring.</td></tr>
<tr><td>Claims</td><td>The application has 17 claims, of which 1 is an independent claim and 16 are dependent. All 17 claims are secondary claims, of which 2 are formulation claims. There are 17 claims covering different forms like salts etc. There are no Markush structures claimed. There are 2 claims for use, 3 method of treatment claims and 2 claims are for combinations.

The application claims prodrugs of a known compound. The prodrug is represented by a Markush structure (Formula I). Because the claims all relate to prodrugs (and not a basic molecule), the claim for the Markush structure of prodrugs is not counted as Markush structure. As all 17 claims relate to prodrugs, these are all counted as secondary claims and also as “other forms” claims. Of the 2 formulation claims, 1 claim is for a composition per se and 1 claim overlaps with a combination claim. Of the 3 method of treatment claims, 1 claim overlaps with a combination claim. Of the 2 combination claims, 1 claim overlaps with a formulation claim and 1 claim overlaps with a method of treatment claim.</td></tr>
<tr><td>ISR</td><td>The ISR cited 4 documents as prior art, all of which are A documents.</td></tr>
<tr><td>TPO</td><td>The TPO cited 7 prior art documents, of which 5 challenged only novelty and 2 challenged both novelty and inventive step. Two of the prior art documents were patent documents and 5 were periodicals.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 25.05.2019.</td></tr>
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05.12.2020
Granted
29.09.2020</td></tr>
<tr><td>EPO</td><td>26.08.2019</td><td>2018744124</td><td></td></tr>
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<tr><td>Appl. No.</td><td>PCT/US2018/015502 : WO2018140762</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018140762</td></tr>
<tr><td>Applicants</td><td>Institute for Cancer Research d.b.a The Research Institute of Fox Chase Cancer Center</td></tr>
<tr><td>Priority Date</td><td>26.01.2017</td></tr>
<tr><td>Details</td><td>The application covers a method for inhibiting HIV-1 integrase multimerisation. The applicant followed a procedure of screening a commercial library which has been described in a prior art patent document by the applicant itself to discover compounds with a specific activity for treatment of HIV. On doing so, the applicant discovered compounds from the commercial library that exhibited such activity, categorised them into two scaffolds and claimed them for the treatment of HIV.</td></tr>
<tr><td>Claims</td><td>The application has 42 claims, of which 2 are independent claims and 40 are dependent. All 42 claims are secondary claims, of which 2 are formulation claims. All 42 claims are method of treatment claims.

All claims are drafted as method of treatment claims. The applicant claims method of treatment of HIV with 2 Markush structures and 18 specific compounds. These are not included in columns P and Q as the application itself is a secondary application claiming method of inhibiting HIV-1 multimerisation with claimed compounds. The 2 formulation claims overlap with method of treatment claims.</td></tr>
<tr><td>ISR</td><td>The ISR cited 3 documents as prior art. Of these, 2 were Y, 1 was A.</td></tr>
<tr><td>TPO</td><td>The TPO cited 4 prior art documents, of which 1 was a document also cited by the ISR. Two of the prior art documents challenged only inventive step and two challenged both novelty and inventive step. Two of the prior art documents were patent documents and 2 were periodicals.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 27.05.2019.</td></tr>
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<tr><th>Office</th><th>Entry Date</th><th>National Number</th><th>National Status</th></tr>
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Granted 12.01.2021</td></tr>
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TPO No.	14
Appl. No.	PCT/US2018/015770 : WO2018144390
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018144390
Applicants	Gilead Sciences Inc.
Priority Date	31.01.2017
Details	The application covers crystalline forms of a known drug tenofovir alafenamide for treatment of HIV. The basic molecule is a nucleoside reverse transcriptase inhibitor (NRTI). The application claims crystalline forms of salts of tenofovir alafenamide such as hemipamoate-I, II, sebacate-I, napsylate-I, orotate-I, II, III, vanillate, bisxenofoate salt forms.
Claims	The application has 76 claims, of which 2 are independent claims and 74 are dependent. All 76 claims are secondary claims, of which 12 are formulation claims. All 76 claims cover various forms of tenofovir alafenamide such as salts and crystalline forms thereof. There are 4 claims for use, 6 claims for method of treatment and 4 claims for combinations. Of the 12 formulation claims, 8 claims are for composition per se and 4 claims are for combinations. As all 76 claims relate to salts and their crystalline forms, these are all counted as secondary claims and also as "other forms" claims. Of the 6 method of treatment claims, 4 are for method of treatment per se and 2 overlap with use claims. All 4 combination claims are drafted as formulation claims.
ISR	The ISR cited 4 documents as prior art. Of these, 2 were X, 1 was Y, 1 was A. In the ISR, 2 of the documents listed for novelty (X) were also listed for inventive step (Y), and of the documents listed for inventive step (Y) 1 document was also an A document.
TPO	The TPO cited 7 prior art documents. Four of the prior art documents challenged only inventive step and three challenged both novelty and inventive step. Four of the prior art documents were patent documents, 2 were periodicals and 1 was a book. In the TPO, for citation 4, a (machine) translated version in English of the Korean patent (i.e., 1 additional document) was uploaded.
Date of Filing of TPO	The TPO was filed on 31.05.2019.
National Phase as of 07.10.2022	

Office	Entry Date	National Number	National Status
Australia	26.06.2019	2018216738	Published 11.07.2019
Canada	28.06.2019	3049028	Divisional 15.08.2022
Japan	29.07.2019	2019541123	
China	30.07.2019	201880009292.1	Published 13.09.2019
India	08.08.2019	201917032116	
Republic of Korea	28.08.2018	1020217034440	Divisional 23.04.2021 Published 05.11.2021 Refused 05.08.2022
EPO	02.09.2019	2018705239	

TPO No.	16
Appl. No.	PCT/US2018/016893 : WO2018145021
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018145021
Applicants	Gilead Sciences Inc.
Priority Date	06.02.2017
Details	The application covers atazanavir analogues (i.e., protease inhibitors) for treating HIV infection.
Claims	The application has 101 claims, of which 2 are independent claims and 99 are dependent. The claims cover 6 Markush structures and 246 specific compounds. There are 43 secondary claims, of which 12 are formulation claims. There is 1 claim for dosage, 20 for use, 12 method of treatment claims and 40 claims for combinations. Of the 6 Markush structures, 1 is the main Markush structure and the other 5 are derivative Markush structures. The dosage claim is a unitary dosage claim that is drafted as a use claim. Of the 40 combination claims, 11 claims overlap with the pharmaceutical composition claims, 11 overlap with the method of treatment claims and 18 overlap with the use claims.
ISR	The ISR cited 2 documents as prior art. Of these, 1 was X, 1 was A.
TPO	The TPO cited 6 prior art documents, including 2 that were also cited in the ISR. Three of the prior art documents challenged only inventive step and 3 challenged both novelty and inventive step. Four of the prior art documents were patent documents and 2 were periodicals. (Two additional periodical documents were filed along with the first periodical citation uploaded in the TPO.)
Date of Filing of TPO	The TPO was filed on 06.06.2019.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Canada	25.07.2019	3051588	Granted 23.08.2022
Israel	25.07.2019	268282	
Australia	31.07.2019	2018215546	Published 22.08.2019
New Zealand	31.07.2019	755929	Divisional 30.08.2018 Published 13.05.2021 Granted 30.11.2021
Singapore	31.07.2019	11201907058T	
Mexico	02.08.2019	MX/a/2019/009212	Published 07.10.2019
Costa Rica	05.08.2019	CR2019-000354	Published 19.09.2019
Dominican Republic	05.08.2019	DOP2019000201	Published 30.08.2019
Japan	05.08.2019	2019542392	
Peru	05.08.2019	001536-2019	Published 18.09.2019
Philippines	05.08.2019	12019501786	

Eurasian Patent Organization	09.08.2019	201991684	Published 29.01.2020 Granted 30.04.2022
India	09.08.2019	201917032272	
South Africa	22.08.2019	2019/05573	
Republic of Korea	03.09.2019	1020227027022	Divisional 04.08.2022 Published 22.08.2022
Ukraine	03.09.2019	A201909440	Published 10.02.2020 Granted 10.03.2021
EPO	06.09.2019	2018706072	Granted 21.04.2021
China	29.09.2019	201880023198.1	Published 03.12.2019
Saudi Arabia	01.03.2022	519402405	

TPO No.	17
Appl. No.	PCT/EP2018/051819 : WO2018149608
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018149608
Applicants	Sandoz AG
Priority Date	16.02.2017
Details	The application covers crystalline forms of cabotegravir sodium. The basic molecule cabotegravir is an integrase inhibitor.
Claims	The application has 14 claims, of which 1 is an independent claim and 13 are dependent. All 14 claims are secondary claims. There are 3 claims for new forms like salts etc. There are 2 claims for use. The claims relate to over 10 diseases including HIV, viral infections caused by DNA virus, RA virus, herpes virus, hepadnavirus, papilloma virus, adenoviruses. Of the 3 claims for forms, 2 claims relate to one crystalline form and 1 claim relates to a pharmaceutical composition which includes the amorphous form. There are also 4 process claims. Of the 6 formulation claims, 1 overlaps with a use claim and 1 overlaps with a dosage claim.
ISR	The ISR cited 5 documents as prior art, all of which are A.
TPO	The TPO cited 5 prior art documents. Three of the prior art documents challenged only inventive step and 2 challenged both novelty and inventive step. One of the prior art documents was a patent document and 4 were periodicals. (One translated copy from Chinese to English of a patent application was uploaded along with original document.)
Date of Filing of TPO	The TPO was filed on 16.06.2019.
National Phase as of 07.10.2022	

Office	**Entry Date**	**National Number**	**National Status**
Australia	09.08.2019	2018221379	Published 29.08.2019
Canada	09.08.2019	3053201	
United States of America	13.08.2019	16485541	Published 10.12.2020 Granted 22.06.2021
Mexico	15.08.2019	MX/a/2019/009810	Published 14.01.2020 Granted 13.12.2021
EPO	16.09.2019	2018703516	Granted 18.11.2020
Russian Federation	16.09.2019	2019125378	Published 16.03.2021
China	16.10.2019	201880025341.0	Published 17.12.2019

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<tr><td>TPO No.</td><td>19</td></tr>
<tr><td>Appl. No.</td><td>PCT/US2018/018973 : WO2018156595</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018156595</td></tr>
<tr><td>Applicants</td><td>Emory University</td></tr>
<tr><td>Priority Date</td><td>21.02.2017</td></tr>
<tr><td>Details</td><td>The application covers compounds which act as chemokine CXCR4 receptor modulators and is a basic molecule application.</td></tr>
<tr><td>Claims</td><td>The application has 25 claims, of which 4 are independent claims and 21 are dependent. There are 4 Markush structures claimed that cover 322 specific compounds. Ten claims are secondary claims and 3 are formulation claims. There are 2 claims for use, 4 claims for method of treatment and 4 claims for combinations. The claims relate to over 10 diseases including HIV, viral infection, abnormal cellular proliferation, retinal degeneration, inflammatory diseases, immunostimulant, immunosuppressant, cancer.

Apart from salts, prodrugs of the compounds are also claimed. Of the 3 formulation claims, 1 claim overlaps with a combination claim. Of the 4 combination claims, 1 claim is drafted as a formulation claim and 2 claims are drafted as method of treatment claims.</td></tr>
<tr><td>ISR</td><td>The ISR cited 4 documents as prior art. Of these, 2 were Y and 2 were A.</td></tr>
<tr><td>TPO</td><td>The TPO cited 5 prior art documents. Four of the prior art documents challenged only inventive step and 1 challenged both novelty and inventive step. Two of the prior art documents were patent documents and 3 were periodicals.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 21.06.2019.</td></tr>
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<tr><td>United States of America</td><td>21.08.2019</td><td>16487825</td><td>Published 20.02.2020</td></tr>
<tr><td>Australia</td><td>10.09.2019</td><td>2018225556</td><td>Published 03.10.2019</td></tr>
<tr><td>Canada</td><td>18.09.2019</td><td>3057071</td><td></td></tr>
<tr><td>EPO</td><td>23.09.2019</td><td>2018757622</td><td></td></tr>
<tr><td>China</td><td>21.10.2019</td><td>201880026481.X</td><td>Published 06.12.2019</td></tr>
<tr><td>Israel</td><td></td><td>292923</td><td>Divisional 10.05.2022</td></tr>
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TPO No.	29
Appl. No.	PCT/US2018/027418: WO2018191579
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018191579
Applicants	Contravir Pharmaceuticals, Inc.
Priority Date	14.04.2017
Details	The application covers a method of treating and/or preventing HIV or HBV by administering a combination of a modified cyclophilin inhibitor (known compounds) and reverse transcriptase inhibitors for the treatment of HIV, HBV.
Claims	The application has 68 claims, of which 23 are independent claims and 45 are dependent. All 68 claims are secondary claims and 6 are formulation claims. There are 23 claims for dosage, 16 claims for use, 49 claims for method of treatment and 68 claims for combinations. Sixty-five of the 68 claims are drafted as method of treatment or use claims. The applicant claims method of treatment with/use of a combination of cyclosporine analogue (1 Markush structure) with reverse transcriptase inhibitors (1 primary + 1 derivative Markush structure). Amongst the reverse transcriptase inhibitors, they specifically claim tenofovir, a specific prodrug of tenofovir and certain specific salts of the prodrug. Of the 6 formulation claims, 1 claims the composition per se, 1 claims the composition for method of treatment and 4 claim the composition for use. One of these use claims also specifically claims a synergistic composition. All the dose/dosage-related claims are drafted as method of treatment claims. There is also a process claim and a claim for a kit.
ISR	The ISR cited 6 documents as prior art. Of these, 4 were X, 2 were PX. Of the 4 X documents in the ISR, 3 were also listed as Y documents.
TPO	The TPO cited 6 prior art documents. One of the prior art documents challenged only inventive step and 5 challenged both novelty and inventive step. Two of the prior art documents were patent documents, 3 were periodicals and 1 of them was an “other” prior art document (specifically, poster of a conference proceeding). Four additional documents were filed along with the main prior art documents; of these, 2 periodical documents were uploaded in support of a periodical article and the other 2 were additional press release documents uploaded in support of the “other” prior art document.
Date of Filing of TPO	The TPO was filed on 12.08.2019.
National Phase as of 07.10.2022	No national phase entries

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<tr><td>Appl. No.</td><td>PCT/IB2018/053014 : WO2018203235</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018203235</td></tr>
<tr><td>Applicants</td><td>ViiV Healthcare UK (No.5) Limited</td></tr>
<tr><td>Priority Date</td><td>02.05.2017</td></tr>
<tr><td>Details</td><td>The application claims compounds for the treatment of HIV. The mechanism of action is not disclosed.</td></tr>
<tr><td>Claims</td><td>The application has 15 claims, of which 1 is an independent claim and 14 are dependent. There are 2 Markush structures claimed and 270 specific compounds. Ten claims are secondary claims and 2 are formulation claims. There are 3 claims for use, 5 claims for method of treatment and 2 claims for combinations.

Of the 2 Markush structures claimed, 1 is a derivative of the general Markush structure. Another formula is also specifically claimed, but it is a stereoisomer of the second derivative Markush structure and therefore has not been counted as a separate third Markush structure. All 3 use claims are drafted in the form of compounds for use claims. Of the 5 method of treatment claims, 2 are for combinations. Both the combination claims are drafted as method of treatment claims.</td></tr>
<tr><td>ISR</td><td>The ISR cited 2 documents as prior art, both of which are A.</td></tr>
<tr><td>TPO</td><td>The TPO cited 2 prior art documents, both of which challenged both novelty and inventive step. Both prior art documents were patent documents.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 02.09.2019.</td></tr>
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23.03.2022</td></tr>
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11.03.2020
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<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019016679</td></tr>
<tr><td>Applicants</td><td>ViiV Healthcare Company</td></tr>
<tr><td>Priority Date</td><td>18.07.2017</td></tr>
<tr><td>Details</td><td>The application claims a pharmaceutical combination comprising the integrase strand transfer inhibitor, cabotegravir, with the nucleoside reverse transcriptase translocation inhibitor (NRTTI), 4'-ethynyl-2-fluoro-2'-deoxyadenosine, known as EFdA (MK-8591, islatravir). It is listed as being in Phase II clinical trials in the TAG Pipeline Report 2018.

The pharmaceutical combination claimed in the application is a combination of cabotegravir (formula I) and EFdA (MK-8591, islatravir), both of which are known drugs for the treatment and prevention of HIV.</td></tr>
<tr><td>Claims</td><td>The application has 13 claims, of which 2 are independent claims and 11 are dependent. All 13 are secondary claims, 1 is a formulation claim and 1 is a new form claim. There are 3 claims for use, 7 claims for method of treatment and 13 claims for combinations.

All the claims pertain to a combination of cabotegravir and islatravir for the prevention or treatment of HIV. The applicant claims sodium salt of cabotegravir (formula I) in two of the claims (1 claim is for combination and 1 claim is for method of treatment).</td></tr>
<tr><td>ISR</td><td>The ISR cited 3 documents as prior art, all of which are Y.</td></tr>
<tr><td>TPO</td><td>The TPO cited 6 prior art documents. Two of these challenged only inventive step and 4 challenged both novelty and inventive step. One prior art document was used after the priority date but before the filing date. In the TPO, the P document was used for both novelty and inventive step. Three of the prior art documents were patent documents and 3 were periodicals. Three additional documents were filed; 1 additional periodical article was filed each with Citations 2 and 3 (both periodical articles) and 1 additional document (US Department of Health and Human Services guideline) was filed with Citation 4 (a periodical article).</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 18.11.2019.</td></tr>
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<tr><td>Appl. No.</td><td>PCT/US2018/042937 : WO2019018676</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019018676</td></tr>
<tr><td>Applicants</td><td>Janssen Sciences and Gilead Sciences</td></tr>
<tr><td>Priority Date</td><td>20.07.2017</td></tr>
<tr><td>Details</td><td>The application claims method of treatment with single unit dosage form of darunavir (or its hydrate or solvate), cobicistat, emtricitabine and tenofovir alfenamide, or a salt thereof, for treatment of HIV, and single unit dosage forms.

The applicant claims a once daily single unit dosage form of a combination of 4 known drugs and method of treatment using the same. For the method of treatment claims, it also sets out the patient’s conditions prior to the administration of the combination (e.g., the viral load of HIV prior to administration, presence or absence of certain mutations, previous discontinued first regimen etc.), treatment outcome and the previous treatment that the subject was on. Further, the applicant claims the known doses of the known anti-HIV drugs that are combined into a single unit and the process of making the single unit dosage form, more specifically in tablet form.</td></tr>
<tr><td>Claims</td><td>The application has 42 claims, of which 2 are independent claims and 40 are dependent. All 42 are secondary claims. There are 16 formulation claims and 3 are claims for new forms. There are 9 claims for dosage and 34 claims for method of treatment and 42 claims for combinations.

All the claims are directed to a single unit dosage form, either as method of treatment or single unit dosage forms per se. However, because of the manner in which they are drafted, not all of them are counted as formulation claims. Of the 16 formulation claims, 6 are formulation claims per se (single unit dosage form), 9 are drafted as method of treatment claims and 1 is product by process claim (product by process). Of these 16 formulation claims, 9 also include dose/dosage limitations (4 formulation claims per se and 5 method of treatment claims).</td></tr>
<tr><td>ISR</td><td>The ISR cited 5 documents as prior art, all of which are X.</td></tr>
<tr><td>TPO</td><td>The TPO cited 5 prior art documents, including 2 that were also cited in the ISR. One of these challenged only inventive step and 4 challenged both novelty and inventive step. Two of the prior art documents were patent documents, 2 were periodicals and 1 “other” prior art document was a poster of a conference proceeding. Three additional documents were uploaded.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 20.11.2019.</td></tr>
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<tr><td>Mexico</td><td>17.01.2020</td><td>MX/a/2020/000694</td><td>Published 13.08.2020</td></tr>
<tr><td>Canada</td><td>20.01.2020</td><td>3070713</td><td></td></tr>
<tr><td>Brazil</td><td>28.01.2020</td><td>112020000842</td><td></td></tr>
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TPO No.	42
Appl. No.	PCT/IB2018/055349 : WO2019016732
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019016732
Applicants	ViiV Healthcare Company and Janssen Sciences
Priority Date	21.07.2017
Details	The application claims method of treating HIV comprising administering long-acting intramuscular administration (4 weeks or less, or 8 weeks) of a combination of cabotegravir and rilpivirine (or their pharmaceutical salts). [Integrase inhibitor (cabotegravir); non-nucleoside reverse transcriptase inhibitor (rilpivirine)]
Claims	The application has 16 claims, of which 3 are independent claims and 13 are dependent. All 16 are secondary claims. All 16 claim methods of treatment. And all 16 claim combinations. There are 9 dosage claims. All claims relate to HIV. All the claims are for method of treating HIV comprising administering long-acting intramuscular administration of a combination of cabotegravir and rilpivirine (or their pharmaceutically acceptable salts). Therefore, they are all method of treatment claims as well as combination claims. The 9 dosage claims are claims which mention either the doses of the components or the frequency of administration. Some of the method of treatment claims are with respect to discontinuing a previous treatment regimen (n = 4), patient's condition prior to administration of the claimed long-acting combination (n = 1) and treatment outcomes after 96 weeks (n = 3).
ISR	The ISR cited 3 documents as prior art, of which 2 are X documents and 1 is an A document.
TPO	The TPO cited 2 prior art documents, both of which challenged both novelty and inventive step. One was a patent document and 1 was another document. One additional document was also filed. The 1 “other” prior art document used was a poster from a conference proceeding. For this document, the additional document (being the relevant extracts of the abstract book) was uploaded.
Date of Filing of TPO	The TPO was filed on 21.11.2019.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Israel	12.01.2020	271987	
Canada	17.01.2020	3070319	
United States of America	17.01.2020	16631868	Published 14.05.2020
Japan	20.10.2020	2020502979	
Mexico	20.01.2020	MX/a/2020/000790	Published 08.12.2020
Republic of Korea	17.02.2020	1020207004521	Published 24.03.2020
Australia	20.02.2020	2018304591	Published 05.03.2020
EPO	21.02.2020	2018749568	
Russian Federation	21.02.2020	2020102304	Published 23.08.2021
China	20.03.2020	201880061354.3	Published 05.05.2020

<table>
<tr><td>TPO No.</td><td>43</td></tr>
<tr><td>Appl. No.</td><td>PCT/US2018/044415 : WO2019027920</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019027920</td></tr>
<tr><td>Applicants</td><td>Gilead Sciences Inc.</td></tr>
<tr><td>Priority Date</td><td>01.08.2017</td></tr>
<tr><td>Details</td><td>The application claims crystalline and amorphous forms of GS-9131 (a prodrug of GS-9148), and its vanillate, phosphate and xinafoate salts and phosphate acetonitrile solvate for treating viral infections like HIV. The application relates to various forms of GS-9131, i.e., rovafovir etalafenamide, an oral nucleoside reverse transcriptase inhibitor. It is presently in Phase II clinical trials for the treatment of HIV. GS-9131 is listed in the TAG Pipeline Report 2018.</td></tr>
<tr><td>Claims</td><td>The application has 70 claims, of which 9 are independent claims and 61 are dependent. All 70 are secondary claims. There are 14 claims for formulations, 53 claims for various forms such as salts and 1 claim for dosage. There are 2 claims for use, 2 claims for methods of treatment and 10 claims for combinations. All claims relate to HIV.

Of the 14 claims for formulations, 6 are for pharmaceutical compositions and 8 are for solid dosage forms. Some of the claims are directed to single layer, multilayer and bilayer tablets. There are 53 claims directed to various forms of GS-9131 itself or its salts, i.e., two crystalline forms of GS-9131; two crystalline forms of vanillate salt of GS-9131; one crystalline form each of phosphate, xinafoate salt and phosphate acetonitrile solvate Form I of GS-9131; and amorphous form of GS-9131 or a pharmaceutically acceptable salt, co-crystal or solvate thereof. The various forms are characterised by one or more known techniques such as XRPD, DSC, TGA thermogram and dynamic vapour sorption isotherm. There is 1 claim where the solid dosage form is formulated for once-a-day dosing. This has been counted as a dosage claim. Of the 2 use claims, 1 is a use claim per se and 1 is drafted as a claim for a solid dosage form for use. Of the 10 combination claims, 2 are for compositions further comprising 1 to 3 additional therapeutic agents active against HIV. Eight claims are further dependent claims relating to pharmaceutical composition and solid dosage form, which may include such combinations.</td></tr>
<tr><td>ISR</td><td>The ISR cited 1 document as prior art, which was an X document.</td></tr>
<tr><td>TPO</td><td>The TPO cited 10 prior art documents, including the 1 document cited in the ISR. Eight of the documents challenged only inventive step and 2 challenged both novelty and inventive step. Of these prior art documents, 3 were periodicals, 6 were patent documents and 1 was another document, being a poster presented in a conference proceeding.

Three additional documents were filed along with the 10 prior art documents. Of these, 2 documents (being a description of the poster and a periodical article showing the disclosure of the combination) were uploaded for the 1 “other” document (i.e., conference proceeding). One additional periodical document was uploaded in support of a patent document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 02.12.2019.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><th>Office</th><th>Entry Date</th><th>National Number</th><th>National Status</th></tr>
<tr><td>EPO</td><td>02.03.2020</td><td>2018755368</td><td>Granted 28.07.2021</td></tr>
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<tr><td>TPO No.</td><td>45</td></tr>
<tr><td>Appl. No.</td><td>PCT/IB2018/055828 : WO2019030625</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019030625</td></tr>
<tr><td>Applicants</td><td>ViiV Healthcare Company</td></tr>
<tr><td>Priority Date</td><td>09.08.2017</td></tr>
<tr><td>Details</td><td>The application claims methods of treating or preventing HIV in a patient using a combination of bictegravir and lamivudine and optionally other agents as well as compositions containing such compounds. [Integrase inhibitor (bictegravir); nucleoside transcriptase inhibitor (lamivudine)]</td></tr>
<tr><td>Claims</td><td>The application has 11 claims, of which 5 are independent claims and 6 are dependent. All 11 are secondary claims. There are 10 claims for formulations and 3 claims for dosage. There are 2 claims for use, 3 claims for methods of treatment and 11 claims for combinations. There are also 4 other claims. All claims relate to HIV.

The claims are directed to a combination of bictegravir and lamivudine or their pharmaceutically acceptable salts. Of the 10 claims for formulations, 3 are for compositions per se (including dose), 3 are method of treatment claims (including with the pharmaceutical compositions of the individual drugs), 2 are for kits comprising composition and 2 are for use of the composition (kit or combination). Of the 3 dosage claims, 1 specifically mentions the dose. Two further dependent “use” claims impliedly include the dose limitation. The 2 use claims are for use of the composition, kit or combination. The 3 method of treatment claims include preventing or treating HIV with a combination of bictegravir and lamivudine (or their salts) or formulations thereof. All the 11 claims relate to the combination of bictegravir and lamivudine. Of the 11 claims, 4 specifically claim the combination of the 2 active ingredients or their salts, their formulations and dose. Three are method of treatment claims, 2 are for kits and 2 are claims for the use of the claimed composition, kit or combination. Of the 4 “other” claims, 2 are claims for kits per se and 2 relate to use of the claimed kits (apart from the claimed combination or composition).</td></tr>
<tr><td>ISR</td><td>The ISR cited 3 documents as prior art, of which 2 were Y documents and 1 was a PX document.</td></tr>
<tr><td>TPO</td><td>The TPO cited 4 prior art documents, including one of the documents cited in the ISR. Three of the documents challenged only inventive step and 1 challenged both novelty and inventive step. Three were periodicals and 1 was a patent document. One additional document was also uploaded in support of a periodical article, being the supplementary information of the said periodical article.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 09.12.2019.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><th>Office</th><th>Entry Date</th><th>National Number</th><th>National Status</th></tr>
<tr><td>United States of America</td><td>04.02.2020</td><td>16636477</td><td>Published 06.08.2020</td></tr>
<tr><td>Japan</td><td>07.02.2020</td><td>2020507085</td><td></td></tr>
<tr><td>EPO</td><td>09.03.2020</td><td>2018844317</td><td>Published 17.06.2020</td></tr>
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<tr><td>TPO No.</td><td>46</td></tr>
<tr><td>Appl. No.</td><td>PCT/IB2018/055829 : WO2019030626</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019030626</td></tr>
<tr><td>Applicants</td><td>ViiV Healthcare Company</td></tr>
<tr><td>Priority Date</td><td>09.08.2017</td></tr>
<tr><td>Details</td><td>The application claims compositions of a combination of bictegravir (an HIV integrase inhibitor) and emtricitabine (nucleoside reverse transcriptase inhibitor) and method of treating and preventing HIV using this combination.</td></tr>
<tr><td>Claims</td><td>The application has 11 claims, of which 5 are independent claims and 6 are dependent. All 11 are secondary claims. There are 5 claims for formulations and 3 claims for dosage. There are 2 claims for use, 3 claims for methods of treatment and 11 claims for combinations. There are also 4 other claims. All claims relate to HIV.

All the claims pertain to a combination of bictegravir and emtricitabine for the prevention or treatment of HIV. One claim that specifically claims only the combination (not composition, kit, method of treatment, etc.) also generally claims the salt forms of the compounds. Of the 5 formulation claims, 1 claims the composition (and kits and combination) for use in medical therapy and 1 claims the composition (and kits and combination) for use in method of treatment. Thus 2 of the 5 formulation claims also include claims to a kit and a combination for use in therapy and use in method of treatment. Of the 5 formulation claims, 1 also claims the doses of each of the 2 drugs and 2 claims pertain to a separate dosage form or single dosage form. The 2 claims for use claim a composition, kit and combination for (i) use in medical therapy and (ii) method of treatment respectively. The claim for use for method of treatment is not counted as a method of treatment claim. Of the 4 “other” claims, 2 are specifically only for kits. As noted above, 2 claims for use in medical therapy and use in method of treatment also refer to kits (and pharmaceutical compositions and combination). These, too, have been counted as “other” claims.</td></tr>
<tr><td>ISR</td><td>The ISR cited 4 documents as prior art, of which 1 is an X document, 2 are Y documents and 1 is a PX document. The X document referred to in the ISR is also marked as a Y document.</td></tr>
<tr><td>TPO</td><td>The TPO cited 5 prior art documents, including 1 document cited in the ISR. All 5 documents challenged both novelty and inventive step. Three were periodicals and 2 were patent documents. The supplementary material of one of the periodical articles was uploaded as an additional document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 09.12.2019.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><td>United States of America</td><td>04.02.2020</td><td>16636452</td><td>Published 04.06.2020</td></tr>
<tr><td>Japan</td><td>07.02.2020</td><td>2020506979</td><td></td></tr>
<tr><td>EPO</td><td>09.03.2020</td><td>2018843567</td><td>Published 17.06.2020</td></tr>
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TPO No.	49
Appl. No.	PCT/IB2018/056982 : WO2019053617
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019053617
Applicants	GlaxoSmithKline Intellectual Property Development Limited
Priority Date	12.09.2017
Details	This application claims macrocyclic salicyclamide derivatives which act as ecto-5′-nucleotidase (ecto-5'-NT, CD73) inhibitors which could be used for treating cancer and HIV, among others. The application covers a basic molecule, i.e., ecto-5′-nucleotidase (ecto-5'-NT), that are CD73 inhibitors.
Claims	The application has 25 claims, of which 1 is an independent claim and 24 are dependent. There are 4 Markush structures claimed which cover 63 specific compounds. Nineteen of the claims are secondary claims. There are 2 claims for formulations and 1 claim for dosage. There are 3 claims for use, 13 claims for methods of treatment and 2 claims for combinations. There is also 1 other claim. The claims cover over 10 diseases, including cancer (various forms), AIDS, HIV, infections, atherosclerosis and ischemia-reperfusion injury. Of the 4 Markush structures, 1 is a primary Markush structure and the other 3 are derived from it. Of the 2 formulation claims, 1 also mentions a dose range of the active ingredient and excipient. Of the 3 claims for use, 1 is drafted as a claim for compound for use. Of the 13 method of treatment claims, 2 are for combinations. Both the combination claims are drafted as method of treatment claims.
ISR	The ISR cited 2 documents as prior art, of which 1 is an A document and there is 1 other document. The “other” document referred to in the ISR is a PA document.
TPO	The TPO cited 5 prior art documents, including 1 document cited in the ISR. Two of these challenged only inventive step while 3 challenged both novelty and inventive step. One document was published after the priority date but before the filing date and challenged both novelty and inventive step. Of the prior art documents cited in the TPO, 2 were periodicals and 3 were patent documents. The ISR document used in the TPO was the P (i.e., PA) document (published after the priority date but before the filing date of the application).
Date of Filing of TPO	The TPO was filed on 13.01.2020.
National Phase as of 07.10.2022	No national phase entries

<table>
<tr><td>TPO No.</td><td>53</td></tr>
<tr><td>Appl. No.</td><td>PCT/US2018/052503 : WO2019060860</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019060860</td></tr>
<tr><td>Applicants</td><td>Suzhou Yunxuan Yiyao Keji Youxian Gongsi and Zhang Xiaohu</td></tr>
<tr><td>Priority Date</td><td>25.09.2017</td></tr>
<tr><td>Details</td><td>The application claims heteroaryl compounds that are useful in the therapies targeting C-X-C chemokine receptor type 4 (CXCR4) inhibitors, and use of these CXCR4 inhibitors for therapeutic intervention in infectious diseases, inflammatory diseases, tumours and cancers. The application covers a basic molecule which is a chemokine receptor type 4 inhibitor.</td></tr>
<tr><td>Claims</td><td>The application has 21 claims, of which 1 is an independent claim and 20 are dependent. There are 10 Markush structures claimed which cover 198 specific compounds. Three of the claims are secondary claims. There is 1 claim for formulations. There is 1 claim for use and 1 claim for combinations. The claims cover over 10 diseases, i.e., HIV infection, myocardial infarction, rheumatoid arthritis, myasthenia gravis, juvenile diabetes, glomerulonephritis, autoimmune thyroiditis, graft rejection, etc.

The claims cover hydrate, solvate, stereoisomer and tautomer forms. Of the 10 Markush structures, 1 is the primary Markush structure and the remaining 9 Markush structures are derived from it. The 1 use claim is drafted as a claim for a compound for treating various diseases.</td></tr>
<tr><td>ISR</td><td>The ISR cited 5 documents as prior art, all of which are A documents.</td></tr>
<tr><td>TPO</td><td>The TPO cited 5 prior art documents, including 1 document cited in the ISR. Two of the documents challenged only inventive step while 3 challenged both novelty and inventive step. Two were periodicals and 3 were patent documents. One of the A documents of the ISR was used as prior art in the TPO; however, instead of the US version cited in the ISR, the WO equivalent of the document was used.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 27.01.2020</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><th>Office</th><th>Entry Date</th><th>National Number</th><th>National Status</th></tr>
<tr><td>United States of America</td><td>24.03.2020</td><td>16649983</td><td>Published 30.07.2020
Granted 26.07.2022</td></tr>
<tr><td>Japan</td><td>25.03.2020</td><td>2020538760</td><td></td></tr>
<tr><td>Republic of Korea</td><td>08.04.2020</td><td>1020207010206</td><td>Published 27.05.2020</td></tr>
<tr><td>EPO</td><td>28.04.2020</td><td>2018859565</td><td>Published 05.08.2020</td></tr>
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TPO No.	56
Appl. No.	PCT/IB2018/057724 : WO2019069269
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019069269
Applicants	GlaxoSmithKline Intellectual Property Development Limited
Priority Date	05.10.2017
Details	The application claims combination of diamidobenzimidazoles (or their tautomers or salts) with one or more additional pharmaceutical agents active against HIV to treat, prevent and cure HIV. It also claims method of curing HIV with diamidobenzimidazoles (which work as STING modulators) and the use of diamidobenzimidazoles for curing HIV.
Claims	The application has 43 claims, of which 2 are independent claims and 41 are dependent. All 43 are secondary claims. There are 9 claims for use and 26 claims for combinations. There are 18 claims for method of treatment. The claims relate to HIV. The first 26 claims relate to combination of diamidobenzimidazoles (or their tautomers or salts) with one or more additional pharmaceutical agents active against HIV to treat, prevent and cure HIV. The remaining claims relate to method of curing HIV with diamidobenzimidazoles (which work as STING modulators) and the use of diamidobenzimidazoles for curing HIV. Though the applicant does not claim the diamidobenzimidazole compounds per se, it claims their combination with other agents or their subsequent use (curing HIV infection). For these secondary claims, the applicant claims diamidobenzimidazole compounds with 4 Markush structures and 15 specific compounds. Of the 4 Markush structures, 1 is the primary Markush structure (I-N) and 3 are derivative Markush structures (I, I-N-B' and I-N-b'). Among the 3 derivative Markush structures, 1 (I-N-b') is a further derivative of another (I-N-B'). Amongst the diamidobenzimidazoles, it claims 10 specific compounds and geometric isomers of 4 of them. Of the 9 claims for use, 7 are directed to the combination and 2 to the compounds per se. Of the 7 use claims for combination, 4 are drafted as claims for the “combination for use”. Of the 2 use claims for the compounds per se, 1 claim is for the use of diamidobenzimidazole compounds for curing HIV and 1 claim is drafted as a claim to use of the claimed diamidobenzimidazole compounds for manufacture of medicament to cure HIV. Of the 18 method of treatment claims, 3 are for method of preventing, treating or curing HIV using a combination; 15 are for method of curing HIV with the diamidobenzimidazole compounds. Of the 26 combination claims, 17 are for the combination per se, 3 claims are for method of treating, preventing or curing HIV with the claimed combination and 6 claims are for use of the claimed combination (of which 3 are drafted as claims for combinations for use).
ISR	The ISR cited 3 documents as prior art, of which 2 are A documents and 1 is another document. The “other” document in the ISR is an L document, "which may throw doubts on priority claim(s) ... or other special reason (as specified)". This document has been used in the TPO to assail novelty as it discloses the same diamidobenzimidazole compounds and their combination which form the subject matter of the present application. In the alternative, this document is cited as a PX document.
TPO	The TPO cited 3 prior art documents, including 1 document cited in the ISR. One of the documents challenged only novelty, 1 challenged only inventive step while 1 challenged both novelty and inventive step. Two of the documents were published after the priority date but before the filing date. Of the 2 documents used after the priority date, 1 is the document marked as "L" in the ISR. As per the WOSA, the application cannot claim the protection of the priority date as it is not the first filed application and the L document, being the first filed application, anticipates the claims of the present application. This document has been used in the TPO to assail novelty as it discloses the same diamidobenzimidazole compounds and their combination which form the subject matter of the present application. In the alternative, this has also been used as a PX document in the TPO.

<table>
<tr><td></td><td>The WOSA states that as the priority document of the present application is not the first application filed for the invention, the priority claimed for the subject matter is invalid. Therefore, the filing date of the present application, i.e., 4.10.2018, is the relevant priority date.

All 3 of the prior art documents cited in the TPO were patent documents, and an additional document filed with the TPO was also a patent document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 05.02.2020.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><th>Office</th><th>Entry Date</th><th>National Number</th><th>National Status</th></tr>
<tr><td>United States of America</td><td>01.04.2020</td><td>16652780</td><td>Published 05.08.2021</td></tr>
<tr><td>Japan</td><td>03.04.2020</td><td>2020519389</td><td></td></tr>
<tr><td>Australia</td><td>06.04.2020</td><td>2018344902</td><td>Published 23.04.2020</td></tr>
<tr><td>EPO</td><td>06.05.2020</td><td>2018795802</td><td></td></tr>
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<tr><td>TPO No.</td><td>58</td></tr>
<tr><td>Appl. No.</td><td>PCT/US2018/054825 : WO2019074826</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019074826</td></tr>
<tr><td>Applicants</td><td>ViiV Healthcare Company</td></tr>
<tr><td>Priority Date</td><td>13.10.2017</td></tr>
<tr><td>Details</td><td>The application claims a "bi-layer tablet formulation comprising HIV integrase strand transfer inhibitor dolutegravir with the nucleoside reverse transcriptase inhibitor lamivudine".</td></tr>
<tr><td>Claims</td><td>The application has 13 claims, of which 1 is an independent claim and 12 are dependent. All 13 are secondary claims. There are 8 claims for dosage use and 13 claims for combinations.

All the 13 claims are for formulations, i.e., a bilayer tablet formulation comprising dolutegravir and lamivudine. With respect to specific forms, the 1 independent claim specifically mentions dolutegravir sodium, while all the other dependent claims only mention dolutegravir. Of the 8 dosage claims, 6 specifically mention the dose of the ingredients while 2 are dependent claims which impliedly include the dose limitations. Four claims for the tablets are characterised by the AUC parameters (n = 4), of which 2 are for AUC in fasted patients and 2 claims are characterised by dissolution parameters. All these are counted as formulation claims.</td></tr>
<tr><td>ISR</td><td>The ISR cited 4 documents as prior art, of which 1 is an X document and 3 are A documents. The international application was published without the ISR. The ISR (mailed 27 December 2018), search strategy and WOSA (mailed 27 December 2018) were all published after the TPO was filed.</td></tr>
<tr><td>TPO</td><td>The TPO cited 7 prior art documents. Two of the documents challenged only inventive step while 5 challenged both novelty and inventive step. Three of the prior art documents were periodicals, 2 were patent documents, 1 was a book and there was 1 other document. Three additional documents were also filed.

In the TPO, the 1 "other" prior art document used was a conference proceeding (for which both the eposter and oral abstract were uploaded). Of the 3 additional documents filed, 2 were US FDA labels for the active ingredients. The other was, as mentioned above, the oral abstract of the conference proceeding.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 13.02.2020</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><td>Israel</td><td>30.03.2020</td><td>273704</td><td></td></tr>
<tr><td>Australia</td><td>31.03.2020</td><td>2018347990</td><td>Published 23.04.2020</td></tr>
<tr><td>United States of America</td><td>01.04.2020</td><td>16652768</td><td>Published 23.07.2020</td></tr>
<tr><td>Canada</td><td>06.04.2020</td><td>3078624</td><td></td></tr>
<tr><td>China</td><td>10.04.2020</td><td>201880066314.8</td><td>Published 05.06.2020</td></tr>
<tr><td>Japan</td><td>10.04.2020</td><td>2020520646</td><td></td></tr>
<tr><td>EPO</td><td>13.05.2020</td><td>2018866268</td><td></td></tr>
<tr><td>Russian Federation</td><td>13.05.2020</td><td>2020118376</td><td>Published 16.10.2020</td></tr>
<tr><td>Mexico</td><td>13.07.2020</td><td>MX/a/2020/003377</td><td>Published 16.10.2020</td></tr>
<tr><td>Brazil</td><td>15.09.2020</td><td>112020006783</td><td></td></tr>
<tr><td>Republic of Korea</td><td></td><td>1020207010456</td><td>Published 17.06.2020</td></tr>
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<tr><td>TPO No.</td><td>59</td></tr>
<tr><td>Appl. No.</td><td>PCT/US2018/055554 : WO2019075291</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019075291</td></tr>
<tr><td>Applicants</td><td>Gilead Sciences, Inc.</td></tr>
<tr><td>Priority Date</td><td>13.10.2017</td></tr>
<tr><td>Details</td><td>The application claims oxoimidazolidine derivatives and their salts as HIV protease inhibitors. It also claims pharmaceutical compositions thereof and methods for treating HIV and also combinations with other anti-HIV agents. The application covers a basic molecule.</td></tr>
<tr><td>Claims</td><td>The application has 53 claims, of which 7 are independent claims and 46 are dependent claims. There are 5 Markush structures covering 372 specific compounds. There are 8 secondary claims. There are 6 formulation claims, 2 method of treatment claims and 6 claims for combinations. All claims relate to HIV.

Of the 5 Markush structures, 1 is the primary Markush structure (Formula I) and 4 are derivative Markush structures (Formula Ia to Id). The primary Markush structure is claimed in both Claims 1 and 2 but has been counted only once. Of the 6 formulation claims, 1 is for a pharmaceutical composition per se and 5 claims are for pharmaceutical compositions comprising 1 to 4 additional therapeutic agents. One specifically claims only tenofovir and its various forms as the additional agent. Of the 2 method of treatment claims, 1 is for a method of treatment with the claimed compound and 1 claim is for method of treatment in combination with 1 to 4 additional therapeutic agents.</td></tr>
<tr><td>ISR</td><td>The ISR cited 2 documents as prior art, of which 1 is an A document and 1 is another document. The 1 “other” document cited in the ISR is an AP document.</td></tr>
<tr><td>TPO</td><td>The TPO cited 3 prior art documents. Two of the documents challenged only inventive step while 1 challenged both novelty and inventive step. Of the prior art documents cited in the TPO, 1 was a periodical and 2 were patent documents. One additional document was filed.

The additional document is a PX document in further support of a prior art patent document. Thus, a PX document was not added as a standalone prior art document, but was referred to in another note.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 13.02.2020.</td></tr>
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<tr><td>Eurasian Patent Organization</td><td>17.03.2020</td><td>202090530</td><td>Published 30.10.2020
Withdrawn 12.10.2021</td></tr>
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<tr><td>Costa Rica</td><td>01.04.2020</td><td>CR2020-000149</td><td>Published 22.05.2020</td></tr>
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	Japan	10.04.2020	2020520483	
	Philippines	13.04.2020	12020550256	
	Dominican Republic	06.05.2020	DOP2020000078	Published 15.10.2020
	Republic of Korea	12.05.2020	1020207013543	Published 18.06.2020
	EPO	13.05.2020	2018796285	
	Ukraine	13.05.2020	A202001859	Published 25.06.2020 Withdrawn 24.09.2021
	Peru	15.05.2020	000525-2020	Published 29.12.2020
	Mexico	13.07.2020	MX/a/2020/003430	Published 13.08.2020

TPO No.	65
Appl. No.	PCT/US2018/066744 : WO2019126464
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019126464
Applicants	Lentigen Technology, Inc.
Priority Date	20.12.2017
Details	The application claims nucleic acid and amino acid sequences for chimeric antigen receptors (CARs) containing HIV envelope antigen binding domains (mD1.22, m36.4 and/or C46). It also claims recombinant expression vectors, host cells, antigen binding fragments and pharmaceutical compositions relating to the CARs and methods of treating or preventing HIV infection in a subject, and methods of making CAR-T cells. This application covers a biologic.
Claims	The application has 42 claims, of which 4 are independent claims and 38 are dependent. Twelve are secondary claims, 6 are formulation claims and 5 are claims for method of treatment. All 42 claims are for combinations. There are also 4 other claims. The claims cover more than 10 diseases including HIV, cancer and HIV-associated diseases. Of the 6 formulation claims, 3 are for pharmaceutical compositions per se (i.e., 1 independent claim for composition comprising an anti-HIV effective amount of a population of human T cells, wherein the T cells comprise a nucleic acid sequence that encodes a CAR, and 2 dependent claims including 1 for the transmembrane domain of the claimed CAR) and 3 claims are method of treatment claims for treating HIV, cancer disorder or condition associated with an elevated expression of an HIV-1 envelope antigen by administration of the claimed pharmaceutical composition (i.e., 2 independent claims and 1 dependent claim for the transmembrane domain of the claimed CAR). Of the 5 method of treatment claims, 1 claim is a method for providing an anti-HIV immunity in a mammal by administration of the claimed T cell, 1 claim is a method of treating or preventing HIV-1 by administration of the claimed CAR to the mammal, and the other 3 claims are for method of treatment claims for treating HIV/AIDS, cancer disorder or condition associated with an elevated expression of an HIV-1 envelope antigen by administration of the claimed pharmaceutical composition. Of the 4 “other” claims, 2 claims are for a process to produce CAR-expressing cell, 1 claim is for making a cell by transduction of a T cell with a vector comprising a promoter, and 1 claim is a method for generating a population of RNA engineered cells. The application claims CAR molecules (bispecific and trispecific mono and duo CAR) comprising at least one extracellular antigen binding domain comprising an anti-HIV envelope antigen binding domain (mD1.22, m36.4 and/or C46) encoded by nucleotide sequences and amino acid sequences, at least one transmembrane domain and at least one intracellular signalling domain. The applicant claims that the claimed pharmaceutical composition is for treating cancer or diseases, disorders or conditions with an elevated expression of HIV-1 envelope antigen. Also, in the description these AIDS defining diseases have been listed. Therefore, the number of diseases is considered as >10.
ISR	The ISR cited 7 documents as prior art, of which 6 are A documents and 1 is a PX document. The application was initially published without the ISR (A2). The later published A3 version on 08.08.2019 was published along with the ISR.
TPO	The TPO cited 8 prior art documents. Six of these challenged only inventive step and 2 challenged both novelty and inventive step. One of the documents challenging inventive step was after the priority date but before the filing date. Of the prior art documents cited in the TPO, 4 were periodicals and 4 were patent documents. Four additional documents were filed with the TPO. Of the 4 additional documents, a periodical and a patent document were uploaded in support of a periodical article (i.e., n = 2) and 1 periodical article was uploaded to support a periodical article (n = 1). The other additional document, a comparative table, was uploaded to show the similarity in disclosures between the prior art patent document and the claims of the application.

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<tr><td>EPO</td><td>20.07.2020</td><td>2018890907</td><td></td></tr>
<tr><td>China</td><td>18.08.2020</td><td>201880089736.7</td><td>Published 17.11.2020</td></tr>
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Part B: Case Summaries – HCV Applications

TPO No.[1]	1
Appl. No.[2]	PCT/CN2017/096814 : WO2018028634
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018028634
Applicants	Sunshine Lake Pharma Co. Ltd
Priority Date	11.08.2016
Details	The application is for salt forms of known compound previously described in a patent document. The said compound exhibits inhibitory activity against HCV NS3/4A protein. Thus, this is an application for HCV.
Claims	The application has 13 claims, all of which are secondary claims. There are 2 independent claims, 1 for the base addition salt and 1 for the acid addition salt of the compound. There are 4 claims that specifically claim the salt forms. As the patent application is for salt forms, apart from the 4 specific claims for the salts, all other claims (including formulations, use, method of treatment, etc.) too claim the compound in the salt form. There are 9 formulation claims, 8 combination claims, 4 claims for use and 2 claims for method of treatment. Of the 9 formulation claims, 3 claims are for pharmaceutical compositions per se, 4 claim use of the composition (apart from use of the salts) and 2 claim method of treatment with the composition (apart from method of treating with the salts). Of the 8 combination claims, 2 claims are specifically for compositions (i.e., formulations) of such combinations, 4 claim use of combinations (apart from use of the salts of the claimed compound) and 2 claim method of treatment using the combination (apart from method of treating with the salts of the claimed compound).
ISR	The ISR, WOSA and International Preliminary Report on Patentability (IPRP) have been published; the State Intellectual Property Office of the P.R. China is the ISA. The ISR has 3 documents, of which 2 attacked the novelty of all the claims and an additional document (published after the priority date, but before the filing date) also attacked the novelty of all the claims. Though the search strategy has not been separately published, the ISR lists the electronic databases searched as well as the search terms used.
TPO	The TPO cited 7 documents, none of which were cited in the ISR. The TPO has 2 documents that assail the lack of inventive step and 5 documents that assail the lack of novelty and/or inventive step of the claims made in the application. The TPO used 5 articles published in periodicals and 2 patent documents. The TPO introduced general journal articles relating to salt selection that show the state of the art in the field.

[1] TPO No. refers to publisher's internal reference number
[2] Appl. No. provides information on the International Application No. and the Publication Number

Date of Filing of TPO	The TPO was filed on 11.12.2018.
National Phase as of 07.10.2022[3]	No national phase entries

[3] National phase as of 07.10.2022 reflects information provided on WIPO's patentscope database as at that date. However, this data is dynamic and may not provide accurate information on the actual status of the patent application.

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<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018134254</td></tr>
<tr><td>Applicants</td><td>Heparegenix GMBH</td></tr>
<tr><td>Priority Date</td><td>17.01.2017</td></tr>
<tr><td>Details</td><td>The application is for basic molecules that are MKK4 (mitogen activated protein kinase 4) inhibitors for promoting liver regeneration or reducing or preventing hepatocyte death. The claimed MKK4 inhibitors are alleged to selectively inhibit protein kinase MKK4 over protein kinases JNK and MKK7.

This is an application for HCV and more than 10 other diseases, such as Hep B, E, autoimmune hepatitis, alcoholic hepatitis, primary biliary cirrhosis and other liver diseases.</td></tr>
<tr><td>Claims</td><td>Of the 29 claims, 2 are independent claims and 27 are dependent claims. The independent claims also claim the pharmaceutically acceptable salts, solvates and optical isomers thereof. Subsequent dependent claims and secondary claims too claim the compounds, pharmaceutically acceptable salts, solvates and optical isomers thereof.

The application claims 2 Markush structures and 84 specific compounds. Of the 2 Markush structures claimed, 1 is a derivative of the other.

There are 11 secondary claims, of which 7 are for use and 1 each for method of treatment, formulation and dosage. The 1 “other” claim characterises the claimed compounds by the mechanism of action. It has not been counted as a method of treatment claim.</td></tr>
<tr><td>ISR</td><td>The ISR, WOSA and IPRP have been published; the European Patent Office, Rijswijk, Netherlands, is the ISA.

The ISR has 2 X documents.

The search strategy has been published. It indicates a search using the IPC codes.</td></tr>
<tr><td>TPO</td><td>The TPO does not refer to any of the documents cited in the ISR.

The TPO refers to 5 documents, of which 2 are used only for novelty and 3 are used for both novelty and inventive step. Of the 5 documents, 2 are periodicals and 3 are patent documents.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 15.05.2019.</td></tr>
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Granted 07.07.2022</td></tr>
<tr><td>United States of America</td><td>15.07.2019</td><td>16478006</td><td>Published 05.12.2019
Granted 22.06.2021</td></tr>
<tr><td>Japan</td><td>16.07.2019</td><td>2019559391</td><td></td></tr>
<tr><td>China</td><td>17.07.2019</td><td>201880007339.0</td><td>Published 27.09.2019
Granted 27.05.2022</td></tr>
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	Brazil	23.07.2019	112019014593	
	Australia	29.07.2019	2018209164	Published 15.08.2019
	India	29.07.2019	201947030479	Published 09.08.2019
	New Zealand	29.07.2019	755835	Published 30.08.2019
	EPO	19.08.2019	2018702425	Granted 22.06.2022

TPO No.	15
Appl. No.	PCT/US2018/016301: WO2018144640
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018144640
Applicants	Atea Pharmaceuticals, Inc
Priority Date	01.02.2017
Details	The application is an application for a salt form. It claims the hemisulphate salt of a known modified guanosine nucleotide prodrug for the treatment of hepatitis C virus and for HCV-related diseases such as HCV-related chronic liver inflammation, liver cancer, cirrhosis and fatigue. The basic molecule is an NS5B polymerase inhibitor. The NS5B polymerase inhibitor is AT511 (prodrug) and the hemisulphate form is now identified as AT527. It is now also being explored for COVID-19.
Claims	All the 77 claims are secondary claims, of which 7 are independent and 70 are dependent claims. Of the 77 claims, 36 are for formulations, 4 are for various forms (i.e., hemisulphate salt and crystalline form thereof), 27 are for dosage, 9 are use claims, 28 are method of treatment claims, 5 are combination claims and 18 are other claims. Of the 3 claims that characterise the crystalline form, 2 claims characterise the crystalline form claimed in terms of storage conditions. Of the 27 dosage claims, 9 overlap as formulation claims. Fourteen of the dosage claims overlap as method of treatment claims. Four of the dosage claims overlap as use claims. Twelve claims characterise the salt form or metabolite with steady state trough plasma values and 6 claims characterise the AUC of the metabolite.
ISR	The ISR, WOSA and IPRP have been published; the USPTO is the ISA. The ISR has 7 documents, of which 4 are Y documents and 3 are A documents. The search strategy has been published. The search strategy indicates a focus on sulphuric acid of nucleoside or nucleotide and phosphoramide and guanosine.
TPO	The TPO cites 5 documents, including 1 patent document cited in the ISR. The ISR document used in the TPO is an earlier patent document of the applicant. The TPO refers to the WO equivalent of the US patent document referred to in the ISR. In the TPO, 4 of the documents are cited only for inventive step and 1 is cited for both novelty and inventive step. Of the 5 documents, 3 are periodicals and 2 are patent documents. The 3 periodical articles are articles that set out the general state of the art regarding salts and solid states. The applicant has filed a response to the TPO. The response is primarily with regard to the compound not ever having been used in the hemisulphate form which is being claimed. The applicant denies that using the hemisulphate form is obvious to a person skilled in the art.
Date of Filing of TPO	The TPO was filed on 03.06.2019.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Canada	20.06.2019	3048033	
Australia	28.06.2019	2018215203	Published 18.07.2019
New Zealand	28.06.2019	754996	Published 26.07.2019 Divisional 15.09.2021 Granted 28.06.2022
Georgia	01.07.2019	15124/1	Published 11.07.2022
Singapore	02.07.2019	11201906163T	
Israel	15.07.2019	295609	Divisional 14.08.2022
Ukraine	19.07.2019	A201907086	Published 10.01.2020
India	23.07.2019	201917029812	
Brazil	30.07.2019	112019014738	
Japan	30.07.2019	2019541346	
Mexico	31.07.2019	MX/a/2019/009114	Published 11.11.2019 Granted 01.08.2022
China	01.08.2019	201880009871.6	Published 17.09.2019
Eurasian Patent Organization	29.08.2019	201991810	Published 31.01.2020
EPO	02.09.2019	2018747587	
Russian Federation	02.09.2019	2019127284	Published 02.03.2021
Republic of Korea		1020217039328	Published 13.12.2021

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<tr><td>Appl. No.</td><td>PCT/US2018/022488: WO2018170165</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018170165</td></tr>
<tr><td>Applicants</td><td>Metacrine, Inc.</td></tr>
<tr><td>Priority Date</td><td>15.03.2017</td></tr>
<tr><td>Details</td><td>The application is for a basic molecule, i.e., farnesoid X receptor agonists for the treatment of HCV and more than 10 other diseases such as HIV-associated steatohepatitis and cirrhosis, gastrointestinal diseases, ulcerative colitis, non-alcoholic steatohepatitis (NASH), biliary cirrhosis, Crohn’s disease, etc.

The applicant filed 5 applications pertaining to farsenoid X receptors on the same date. The scaffolds claimed in the present application are very similar to the scaffolds described in Metacrine’s other applications WO’166, WO’167, WO’173 and WO’182, with only minor changes in the substituents substituted.</td></tr>
<tr><td>Claims</td><td>Of the 55 claims, 2 are independent claims and 53 are dependent claims.

The application claims 10 Markush structures and 94 specific compounds. Of the 10 Markush structures, 1 is the primary Markush structure and the remaining 9 Markush structures are derived from it. The application discloses 1 more Markush structure (Formula X). However, this is not claimed.

The application also claims pharmaceutically acceptable salts and solvates of the claimed compounds.

There are 25 secondary claims, of which 3 are formulation claims, 22 are method of treatment claims and 1 is a combination claim (drafted as a method of treatment claim; there is no claim for a combination per se).</td></tr>
<tr><td>ISR</td><td>The ISR, WOSA and IPRP have been published; the Korean Intellectual Property Office is the ISA.

The ISR cites 5 documents, of which 2 are X documents, 2 are A documents and 1 is a PX document.

Though the search strategy has not been separately published, the ISR lists the electronic databases searched as well as the search terms used.</td></tr>
<tr><td>TPO</td><td>The TPO cites 5 documents, of which 2 were also cited in the ISR. Of these 5 documents, 1 document is used to assail novelty (a PX document) and the other 4 are used to assail inventive step. Of the documents cited, 1 is a periodical and the other 4 are patent documents.

In the TPO, the novelty ground is based on a PX document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 15.07.2019.</td></tr>
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<tr><td>Applicants</td><td>Metacrine, Inc.</td></tr>
<tr><td>Priority Date</td><td>15.03.2017</td></tr>
<tr><td>Details</td><td>The application is for a basic molecule, i.e., farnesoid X receptor agonists for the treatment of HCV and more than 10 other diseases such as HIV-associated steatohepatitis and cirrhosis, gastrointestinal diseases, ulcerative colitis, non-alcoholic steatohepatitis (NASH), biliary cirrhosis, Crohn’s disease, etc.

The applicant filed 5 applications pertaining to farsenoid X receptors on the same date. The scaffolds claimed in the present application are very similar to the scaffolds described in Metacrine’s other applications WO’165, WO’167, WO’173 and WO’182, with only minor changes in the substituents substituted.</td></tr>
<tr><td>Claims</td><td>Of the 57 claims, 2 are independent claims and 55 are dependent claims.

The application claims 10 Markush structures and 65 specific compounds. Of the 10 Markush structures, 1 is the primary Markush structure and the remaining 9 Markush structures are derived from it. The application discloses 1 more Markush structure (Formula X). However, this is not claimed.

The application also claims pharmaceutically acceptable salts and solvates of the claimed compounds.

There are 25 secondary claims, of which 3 are formulation claims, 22 are method of treatment claims and 1 is a combination claim (drafted as a method of treatment claim; there is no claim for a combination per se).</td></tr>
<tr><td>ISR</td><td>The ISR, WOSA and IPRP have been published; the Korean Intellectual Property Office is the ISA.

The ISR cites 5 documents, of which 2 are X documents, 2 are A documents and 1 is a PX document.

Though the search strategy has not been separately published, the ISR lists the electronic databases searched as well as the search terms used.</td></tr>
<tr><td>TPO</td><td>The TPO cites 5 documents, of which 2 were also cited in the ISR. Of these 5 documents, 1 document is used to assail novelty (a PX document) and the other 4 are used to assail inventive step. Of the documents cited, 1 is a periodical and the other 4 are patent documents.

In the TPO, the novelty ground is based on a PX document.</td></tr>
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30.04.2020
Granted
30.03.2021</td></tr>
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<tr><td>China</td><td>15.11.2019</td><td>201880032220.9</td><td>Published
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<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018170167</td></tr>
<tr><td>Applicants</td><td>Metacrine, Inc.</td></tr>
<tr><td>Priority Date</td><td>15.03.2017</td></tr>
<tr><td>Details</td><td>The application is for a basic molecule, i.e., farnesoid X receptor agonists for the treatment of HCV and more than 10 other diseases such as HIV-associated steatohepatitis and cirrhosis, gastrointestinal diseases, ulcerative colitis, non-alcoholic steatohepatitis (NASH), biliary cirrhosis, Crohn’s disease, etc.

The applicant filed 5 applications pertaining to farsenoid X receptors on the same date. The scaffolds claimed in the present application are very similar to the scaffolds described in Metacrine’s other applications WO’165, WO’166, WO’173 and WO’182, with only minor changes in the substituents substituted.</td></tr>
<tr><td>Claims</td><td>Of the 70 claims, 2 are independent claims and 68 are dependent claims.

The application claims 5 Markush structures and 104 specific compounds. Of the 5 Markush structures, 1 is the primary Markush structure and the remaining 4 Markush structures are derived from it.

The application also claims pharmaceutically acceptable salts and solvates of the claimed compounds.

There are 24 secondary claims, of which 3 are formulation claims, 21 are method of treatment claims and 1 is a combination claim (drafted as a method of treatment claim; there is no claim for a combination per se).</td></tr>
<tr><td>ISR</td><td>The ISR, WOSA and IPRP have been published; the Korean Intellectual Property Office is the ISA.

The ISR cites 5 documents, of which 2 are X documents, 2 are A documents and 1 is a PX document.

Though the search strategy has not been separately published, the ISR lists the electronic databases searched as well as the search terms used.</td></tr>
<tr><td>TPO</td><td>The TPO cites 5 documents, of which 2 were also cited in the ISR. Of these 5 documents, 1 document is used to assail novelty (a PX document) and the other 4 are used to assail inventive step. Of the documents cited, 1 is a periodical and the other 4 are patent documents.</td></tr>
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<tr><td>Applicants</td><td>Metacrine, Inc.</td></tr>
<tr><td>Priority Date</td><td>15.03.2017</td></tr>
<tr><td>Details</td><td>The application is for a basic molecule, i.e., farnesoid X receptor agonists for the treatment of HCV and more than 10 other diseases such as HIV-associated steatohepatitis and cirrhosis, gastrointestinal diseases, ulcerative colitis, non-alcoholic steatohepatitis (NASH), biliary cirrhosis, Crohn’s disease, etc.

The applicant filed 5 applications pertaining to farsenoid X receptors on the same date. The scaffolds claimed in the present application are very similar to the scaffolds described in Metacrine’s other applications WO’165, WO’166, WO’167 and WO’182, with only minor changes in the substituents substituted.</td></tr>
<tr><td>Claims</td><td>Of the 62 claims, 2 are independent claims and 60 are dependent claims.

The application claims 9 Markush structures and 85 specific compounds. Of the 9 Markush structures, 1 is the primary Markush structure and the remaining 8 Markush structures are derived from it. The application discloses 2 more Markush structures (Formula XI and XII). However, these are not claimed.

The application also claims pharmaceutically acceptable salts and solvates of the claimed compounds.

There are 25 secondary claims, of which 3 are formulation claims, 22 are method of treatment claims and 1 is a combination claim (drafted as a method of treatment claim; there is no claim for a combination per se).</td></tr>
<tr><td>ISR</td><td>The ISR, WOSA and IPRP have been published; the Korean Intellectual Property Office is the ISA.

The ISR cites 5 documents, of which 2 are X documents, 2 are A documents and 1 is a PX document.

Though the search strategy has not been separately published, the ISR lists the electronic databases searched as well as the search terms used.</td></tr>
<tr><td>TPO</td><td>The TPO cites 5 documents, of which 2 were also cited in the ISR. Of these 5 documents, 1 document is used to assail novelty (a PX document) and the other 4 are used to assail inventive step. Of the documents cited, 1 is a periodical and the other 4 are patent documents.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 15.07.2019.</td></tr>
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<tr><td>United States of America</td><td></td><td>16494266</td><td>Published 30.04.2020</td></tr>
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<tr><td>TPO No.</td><td>25</td></tr>
<tr><td>Appl. No.</td><td>PCT/US2018/022513: WO2018170182</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018170182</td></tr>
<tr><td>Applicants</td><td>Metacrine, Inc.</td></tr>
<tr><td>Priority Date</td><td>15.03.2017</td></tr>
<tr><td>Details</td><td>The application is for a basic molecule, i.e., farnesoid X receptor agonists for the treatment of HCV and more than 10 other diseases such as HIV-associated steatohepatitis and cirrhosis, gastrointestinal diseases, ulcerative colitis, non-alcoholic steatohepatitis (NASH), biliary cirrhosis, Crohn’s disease, etc.

The applicant filed 5 applications pertaining to farsenoid X receptors on the same date. The scaffolds claimed in the present application are very similar to the scaffolds described in Metacrine’s other applications WO’165, WO’166, WO’167 and WO’173, with only minor changes in the substituents substituted.</td></tr>
<tr><td>Claims</td><td>Of the 70 claims, 2 are independent claims and 68 are dependent claims.

The application claims 9 Markush structures and 540 specific compounds. Of the 9 Markush structures, 1 is the primary Markush structure and the remaining 8 Markush structures are derived from it.

The application also claims pharmaceutically acceptable salts and solvates of the claimed compounds.

There are 25 secondary claims, of which 3 are formulation claims, 22 are method of treatment claims and 1 is a combination claim (drafted as a method of treatment claim; there is no claim for a combination per se).</td></tr>
<tr><td>ISR</td><td>The ISR, WOSA and IPRP have been published; the Korean Intellectual Property Office is the ISA.

The ISR cites 5 documents, of which 2 are X documents, 2 are A documents and 1 is a PX document.

Though the search strategy has not been separately published, the ISR lists the electronic databases searched as well as the search terms used.</td></tr>
<tr><td>TPO</td><td>The TPO cites 5 documents, of which 2 were also cited in the ISR. Of these 5 documents, 1 document is used to assail novelty (a PX document) and the other 4 are used to assail inventive step. Of the documents cited, 1 is a periodical and the other 4 are patent documents.

In the TPO, the novelty ground is based on a PX document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 15.07.2019.</td></tr>
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<tr><td>Japan</td><td>02.09.2019</td><td>2019547663</td><td></td></tr>
<tr><td>Australia</td><td>03.09.2019</td><td>2018236275</td><td>Published 26.09.2019</td></tr>
<tr><td>Canada</td><td>09.09.2019</td><td>3056019</td><td></td></tr>
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<tr><td>Mexico</td><td>13.09.2019</td><td>MX/a/2019/010907</td><td>Published 10.12.2019</td></tr>
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United States of America	13.09.2019	16494272	Granted 01.02.2022
Brazil	24.09.2019	112019019154	
Eurasian Patent Organization	30.09.2019	201992051	Published 31.03.2020
EPO	15.10.2019	2018768017	
Republic of Korea	15.10.2019	1020197030348	Published 25.10.2019
China	15.11.2019	20188003254.0	Published 31.12.2019
India		20191741302	Published 22.11.2019

TPO No.	31
Appl. No.	PCT/CN2018/084674: WO2018196823
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018196823
Applicants	Birdie Biopharmaceuticals, Inc. and Zeng Zhaohui
Priority Date	27.04.2017
Details	The application claims 2-amino-quinoline derivatives that are agonists of toll-like receptors 7 and 8 (TLR7/8), its pharmaceutical compositions, and methods of use of the compounds and compositions to treat various diseases, such as viral diseases, cancer and allergic diseases, including HCV infection.
Claims	The application has 43 claims, of which 4 are independent claims and 39 dependent claims. There are 4 Markush structures – 1 is the main Markush structure and 3 are derived from the main structure. About 47 specific compounds have been claimed, and additionally optionally substituted compounds have also been claimed. There are 4 secondary claims, of which 1 is for a formulation (that includes the dosage too), 1 is for the use of the compounds and 2 are for method of treatment. The compounds claimed are for treatment of three broad categories of diseases – viral diseases, cancer and allergies, and specifically HCV too.
ISR	The ISR/WOSA/IPRP were published, with the State Intellectual Property Office of the P.R. of China being the office of ISA. The ISR contains 3 general documents.
TPO	The TPO contained 3 documents, 1 of which would affect inventive step and 2 would affect both novelty and inventive step of the claims in the application. Two of the prior art documents referred to in the TPO were periodical articles and 1 was a patent document. An additional document was attached in support of the prior art annexed.
Date of Filing of TPO	The TPO was filed on 27.8.2019.
National Phase as of 07.10.2022	

Office	Entry Date	National Number	National Status
China	28.08.2019	201880014574.0	Published 31.12.2019
Australia	04.10.2019	2018259831	Published 31.10.2019
New Zealand	04.10.2019	757892	Published 25.10.2019
Singapore	13.10.2019	11201909325R	
Canada	23.10.2019	3061187	
Mexico	23.10.2019	MX/a/2019/012676	Published 05.03.2020
Japan	25.10.2019	2019558496	
United States of America	25.10.2019	16608581	Published 20.02.2020 Granted 06.07.2021
Israel	27.10.2019	270219	
Brazil	05.11.2019	112019022246	
Republic of Korea	27.11.2019	1020197033158	Published 23.12.2019
India	20.11.2019	201917047246	Published 03.01.2019
EPO	27.11.2019	2018792253	
Russian Federation	27.11.2019	201913877	Published 27.05.2021 Withdrawn 19.01.2022

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<tr><td>Appl. No.</td><td>PCT/US2018/032579: WO2018209354</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018209354</td></tr>
<tr><td>Applicants</td><td>Enanta Pharmaceuticals, Inc.</td></tr>
<tr><td>Priority Date</td><td>12.05.2017</td></tr>
<tr><td>Details</td><td>The application claims compounds with a parent Markush structure which inhibit the apoptosis signal-regulating kinase 1 (ASK-1), which is associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease and cardiovascular disease. More specifically, ASK-1 has been associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The parent Markush structure comprises a pyridine or phenyl ring which at position 2 is substituted with an amide group which is further attached to a 5 or 6 membered heteroaryl ring (A) which itself is further attached to a 5 membered ring comprising 2, 3 or 4 nitrogen atoms (R). The central pyridine or phenyl ring is also substituted at position 4 with an imidazole ring, which itself is further substituted (R3); and is also substituted at position 5 (R2) (claim 1 of WO’354). Also, to note that all claimed Markush scaffolds and compounds are derived from a known Gilead molecule selonsertib (primary indication: non-alcoholic steatohepatitis); wherein the only difference between this known compound and compounds of the present application are minor modifications to the substituents attached on the peripheral ring.</td></tr>
<tr><td>Claims</td><td>The application has 26 claims (1 independent and 25 dependent claims), of which 13 are secondary claims wherein 1 claim is for formulation, 1 is for use and 11 for method of treatment. Of the 37 Markush structures, 1 is an independent structure and the remaining 36 are dependent. The 36 derivative Markush structures are classified into 9 groups/ families, each containing 4 variations (i.e., Formulae Ia to Id, IIa-1 to IIa-4, IIb-1 to IIb-4, IVa-1 to IVa-4, IVb-1 to IVb-4, Va-1 to Va-4, Vb-1 to Vb-4, VIa-1 to VIa-4, VIb-1 to VIb-4).The applicant claims 600 specific compounds in one claim. The applicant also claims pharmaceutically acceptable salt and esters of these claimed compounds. There is one other claim which claims 71 specific compounds. But, as per the trend of subsequent applications, these 71 should be a subset of the 600 specific compounds previously claimed. This has not been verified by cross-checking each of the compounds.</td></tr>
<tr><td>ISR</td><td>The ISR comprises 5 documents, of which 2 have been listed for inventive step (Y) and 3 documents are as listed to describe only the general state of the art and not considered to be of particular relevance (A). For all 4 of the Enanta applications (see below), the ISR has been authored by the same ISA.</td></tr>
<tr><td>TPO</td><td>The TPO was filed on 12.09.2019 and comprised 3 prior art documents. Of the 3 documents, 1 document was not uploaded to the WIPO website. Two of the 3 documents were patent applications and 1 was a periodical article. Also, 2 documents (i.e., patent documents) were used for both novelty and inventive step and 1 periodical article was used only for inventive step.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 12.09.2019.</td></tr>
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<tr><td>Singapore</td><td>06.11.2019</td><td>11201910327V</td><td></td></tr>
<tr><td>Israel</td><td>07.11.2019</td><td>270525</td><td></td></tr>
<tr><td>Japan</td><td>07.11.2019</td><td>2019561233</td><td></td></tr>
<tr><td>Mexico</td><td>07.11.2019</td><td>MX/a/2019/013275</td><td>Published 13.08.2020</td></tr>
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Sri Lanka	08.11.2019	20855	
Australia	14.11.2019	2018266911	Published 05.12.2019
New Zealand	14.11.2019	759204	Published 29.11.2019
Brazil	19.11.2019	11201923449	
Republic of Korea	09.12.2019	1020197036358	Published 21.01.2020
India	10.12.2019	201947051124	Published 13.12.2019
EPO	12.12.2019	2018798479	
Russian Federation	12.12.2019	2019140447	Published 15.06.2021
China	07.01.2020	201880045573.2	Published 06.03.2020

TPO No.	36
Appl. No.	PCT/US2018/034429: WO2018218044
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018218044
Applicants	Enanta Pharmaceuticals, Inc.
Priority Date	25.05.2017
Details	The application claims compounds with a parent Markush structure which inhibit the apoptosis signal-regulating kinase 1 (ASK-1), which is associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease and cardiovascular disease. More specifically, ASK-1 has been associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The parent Markush structure comprises a 5+6 bicyclic fused ring wherein the 5 membered ring may contain up to 2 heteroatoms and the 6 membered ring may be either a phenyl or pyridine ring. The 6 membered ring of the bicyclic ring is attached to an amide group which is further attached to a heteroaryl ring containing up to 3 nitrogen atoms, which itself is further substituted (R1, R2). The 5 membered ring of the bicyclic ring is also further substituted (R3) (claim 1 of WO'044). Compounds derived from the above parent Markush structure act on an identical target ASK-1 and are claimed for the purpose of treating disorders/diseases relating to liver dysfunction as in the previous application WO'354. Also, the parent Markush structure and compounds claimed in the present application WO'044 are similar to the Markush structures claimed in Enanta's 3 other applications. However, the closest structural similarity can be found with the Markush structure of WO'354 wherein the parent Markush structure is comprised of a central phenyl/pyridine ring (6 membered ring) substituted with an imidazole ring, which has been replaced in the present application with a bicyclic ring structure containing phenyl/pyridine ring fused to an imidazole ring (or oxazole, thiazole rings) at an analogous position.
Claims	The application has 30 claims (1 independent and 29 dependent claims), of which 14 are secondary claims wherein 2 claims are for formulation, 1 is for use and 11 for method of treatment. Of the 25 Markush structures, 1 is the primary Markush structure (Formula I) and 24 are derivative Markush structures. Of the 24 derivative Markush structures, 8 are Markush structures (IIa-h) belonging to Formula II and another 4 are Markush structures (IIIa-d) belonging to Formula III. The applicant claims 738 specific compounds and pharmaceutically acceptable salts thereof. There is one further claim which claims 75 specific compounds. These 75 should be a subset of the 738 specific compounds previously claimed. This has been verified by cross-checking each of the compounds.
ISR	The ISR comprises 3 documents; all of them listed to describe only the general state of the art and not considered to be of particular relevance (A). The application was initially published as an A2 document without the ISR; it was based on this that the TPO was filed. After the TPO was filed, the ISR was made available in the documents section of the application on 06.03.2020. Also, even though there is 1 common document referred to by both the TPO and the ISR, this has not been included in "No. of ISR documents used in TPO". For all 4 of the Enanta applications, the ISR has been authored by the same ISA. Of the four, 3 of these applications (i.e., WO'042, WO'044 and WO'051) comprise a central fused ring in the scaffold; for these 3 applications, the prior art documents listed in the ISRs are identical.
TPO	The TPO was filed on 24.09.2019 and comprises 4 prior art documents. Of the 4 documents, 1 document was not uploaded to the WIPO website. Three of the 4 documents were patent applications and 1 was a periodical article. Also, 2 documents (i.e., patent documents) were used for both novelty and inventive step and 2 documents (patent and periodical article each) were used only for inventive step. A single patent document, i.e., WO2016049069, was used as a prior art document in both the present application and the previous application WO'354. Also, all 4 prior art documents used in the TPO of the present application were also used in 2 other Enanta applications, WO'042 and WO'051.

Date of Filing of TPO	The TPO was filed on 24.09.2019.
National Phase as of 07.10.2022	No national phase entries

TPO No.	37
Appl. No.	PCT/US2018/034423: WO2018218042
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018218042
Applicants	Enanta Pharmaceuticals, Inc.
Priority Date	25.05.2017
Details	The application claims compounds with a parent Markush structure which inhibit the apoptosis signal-regulating kinase 1 (ASK-1), which is associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease and cardiovascular disease. More specifically, ASK-1 has been associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The parent Markush structure comprises a 6 + 6 bicyclic fused ring wherein a 6 membered aromatic ring containing up to 2 nitrogen atoms is fused to another 6 membered ring (either a phenyl or pyridine ring). The phenyl/pyridine ring of the bicyclic ring is attached to an amide group which is further attached to a heteroaryl ring containing up to 3 nitrogen atoms which itself is further substituted (R1, R2). The other 6 membered ring of the bicyclic ring is also further substituted (R3 and R4) (claim 1 of WO'042). Compounds derived from the above parent Markush structure act on an identical target ASK-1 and are claimed for the purpose of treating disorders/diseases relating to liver dysfunction as in the previous applications WO'354 and WO'044. Also, the parent Markush structure and compounds claimed in the present application WO'042 are similar to the Markush structures claimed in the other three Enanta applications. However, the closest structural similarity can be found with the Markush structure of WO'044 wherein the scaffold also comprises a central phenyl/pyridine ring (6 membered ring). However, in WO'044 this central ring is fused to an imidazole ring (or oxazole, thiazole rings), a 5 membered ring containing 2 nitrogen atoms which has been replaced in the present application, with a 6 membered pyrimidine ring also containing 2 nitrogen atoms.
Claims	The application has 36 claims (1 independent and 35 dependent claims), of which 14 are secondary claims wherein 2 claims are for formulation, 1 is for use and 11 for method of treatment. Of the 35 Markush structures, 1 is the primary Markush structure (Formula I) and 34 are derivative Markush structures. Of the 34 derivative Markush structures, 8 are Markush structures (IIa-h) belonging to Formula II and another 8 are Markush structures (IIIa-h) belonging to Formula III. The applicant claims 1440 specific compounds and pharmaceutically acceptable salts and esters thereof. There is one further claim which claims 41 specific compounds. These 41 should be a subset of the 1440 specific compounds previously claimed. This has been verified by cross-checking each of the compounds.
ISR	The ISR comprises 3 documents, all of them listed to describe only the general state of the art and not considered to be of particular relevance (A). For all 4 of the Enanta applications, the ISR has been authored by the same ISA; and for 3 of these applications (i.e., WO'042, WO'044 and WO'051) which comprise a central fused ring in the scaffold, the prior art documents listed in the ISR are identical. However, at the time of filing the TPO for WO'042, the ISR was available, unlike with the previous described application WO'044. One of the documents (US 8378108 by Gilead Sciences Inc.) listed in the ISR has been used as a prior art document for the TPO (WO version of the patent, i.e., WO2011008709) and has been included in "No. of ISR documents used in TPO".

TPO	The TPO was filed on 25.09.2019 and comprises 4 prior art documents. Of the 4, 3 were patent applications and 1 was a periodical article. Also, 2 documents (i.e., patent documents) were used for both novelty and inventive step and 2 documents (patent and periodical article each) were used only for inventive step. A single patent document, i.e., WO2016049069, was used as a prior art document in both the present application and WO'354. Also, all 4 prior art documents used in the TPO of the present application were also used in 2 other Enanta applications WO'044 and WO'051.
Date of Filing of TPO	The TPO was filed on 25.09.2019.
National Phase as of 07.10.2022	No national phase entries

TPO No.	38
Appl. No.	PCT/US2018/034441: WO2018218051
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018218051
Applicants	Enanta Pharmaceuticals, Inc.
Priority Date	25.05.2017
Details	The application claims compounds with a parent Markush structure which inhibit the apoptosis signal-regulating kinase 1 (ASK-1), which is associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease and cardiovascular disease. More specifically, ASK-1 has been associated with hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The parent Markush structure comprises a 6 + 6 bicyclic fused ring wherein one of the 6 membered rings is a piperidine ring (saturated ring containing a single nitrogen atom) and the other 6 membered ring fused to it may be either a phenyl or pyridine ring. The phenyl/pyridine ring of the bicyclic ring is attached to an amide group which is further attached to a heteroaryl ring containing up to 3 nitrogen atoms which itself is further substituted (R1, R2). The piperidine ring of this bicyclic ring system is also further substituted on the nitrogen atom (R3) (claim 1 of WO'051). Compounds derived from the above parent Markush structure act on an identical target ASK-1 and are claimed for the purpose of treating disorders/diseases relating to liver dysfunction as in the previous applications WO'354, WO'044 and WO'042. Also, the parent Markush structure and compounds claimed in the present application WO'051 are similar to the Markush structures claimed in the other three applications. However, the closest structural similarity can be found with the Markush structure of WO'042 which comprises a central phenyl/pyridine ring fused to an unsaturated six membered ring containing up to 2 nitrogen atoms; whereas in WO'051 the central phenyl/pyridine ring is fused to a saturated analogue of an identical six membered ring (i.e., piperidine; containing a single nitrogen atom).
Claims	The application has 28 claims (1 independent and 27 dependent claims), of which 14 are secondary claims wherein 2 claims are for formulation, 1 is for use and 11 for method of treatment. Of the 19 Markush structures, 1 is the primary Markush structure (Formula I) and 18 are derivative Markush structures. Of the 18 derivative Markush structures, 2 are Markush structures (XIIa-XIIb) belonging to Formula XII, 2 are Markush structures (XIIIa-XIIIb) belonging to Formula XIII, 2 are Markush structures (XIVa-XIVb) belonging to Formula XIV and another 2 are Markush structures (XVa-XVb) belonging to Formula XV. The applicant claims 600 specific compounds and pharmaceutically acceptable salt forms thereof. There is one further claim which claims 364 specific compounds. But, as per the trend of subsequent applications, these 364 should be a subset of the 600 specific compounds previously claimed. This has not been verified by cross-checking each of the compounds.
ISR	The ISR comprises 3 documents, all of them listed to describe only the general state of the art and not considered to be of particular relevance (A). For all 4 of the Enanta applications, the ISR has been authored by the same ISA; and for three of these applications (i.e., WO'042, WO'044 and WO'051) which comprise a central fused ring in the scaffold, the prior art documents listed in the ISR are identical. However, at the time of filing the TPO for WO'051, the ISR was available, unlike with the previous described application WO'044, and one of the documents (US 8378108 by Glead Sciences Inc.) listed in the ISR has been used as a prior art document for the TPO (WO version of the patent, i.e., WO2011008709).

TPO	The TPO was filed on 25.09.2019 and comprises 4 prior art documents. Of the 4, 3 were patent applications and 1 was a periodical article. Also, 2 documents (i.e., patent documents) were used for both novelty and inventive step and 2 documents (patent and periodical article each) were used only for inventive step. A single patent document, i.e., WO2016/049069, has been used as a prior art document in both the present application and WO'354. Also, all 4 prior art documents used in the TPO of the present application were also used in 2 other Enanta applications WO'044 and WO'042.
Date of Filing of TPO	The TPO was filed on 25.09.2019.
National Phase as of 07.10.2022	No national phase entries

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<tr><td>TPO No.</td><td>44</td></tr>
<tr><td>Appl. No.</td><td>PCT/EP2018/071156: WO2019025600</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019025600</td></tr>
<tr><td>Applicants</td><td>Sandoz AG, Switzerland</td></tr>
<tr><td>Priority Date</td><td>03.08.2017</td></tr>
<tr><td>Details</td><td>The application claims sofosbuvir hydrate, more precisely the monohydrate form, for the treatment of HCV and pharmaceutical compositions thereof. It is the NS5B polymerase inhibitor of the hepatitis C virus.</td></tr>
<tr><td>Claims</td><td>The application has 16 claims, 1 independent and 15 dependent claims. This is a secondary application, so all 16 claims are secondary claims, mainly for the crystalline form of the hydrate compound – 6 claims for the hydrate, 9 claims for compositions, 1 claim for the process thereof. The hydrate is characterised using XRPD, fourier transform infrared spectrum, differential scanning calorimeter. There are 2 claims for use of the compound – 1 of which is for preparation of the pharmaceutical composition and 1 is for use of treatment of viral infections, HCV.</td></tr>
<tr><td>ISR</td><td>The ISR/WOSA/IPRP were published, with the European Patent Office, Rijswijk, Netherlands, being the ISA. The ISR listed 5 prior art documents, 4 of which were general documents and 1 document was against the novelty claim of the applicants (but was published after the priority date but prior to the filing date of the application).</td></tr>
<tr><td>TPO</td><td>The TPO used 4 prior art documents, 1 of which was an ISR document. Two documents used in the TPO challenged the inventive step and 2 challenged both inventive step and novelty of the claims in the application. Three of the prior art documents were periodicals and 1 was a patent document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 3.12.2019.</td></tr>
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<tr><td>EPO</td><td>03.03.2020</td><td>2018748923</td><td></td></tr>
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TPO No.	51
Appl. No.	PCT/US2018/052239: WO/2019/060740
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019060740
Applicants	Riboscience LLC
Priority Date	21.09.2017
Details	The application claims combinations of nucleoside derivatives as inhibitors of HCV replicon RNA replication. In particular, the application is concerned with the use of combinations of cytidine and uridine pyrimidine nucleoside derivatives as inhibitors of subgenomic hepatitis C virus RNA replication and pharmaceutical compositions containing such compounds. The applicant alleges a synergistic effect for the claimed combination. The applicant claims modified forms of a known anti-HCV drug sofobuvir; wherein Formula II comprises an identical nucleobase uridine; and nucleobase in Formula II is cytidine (replacement of one oxo group of uridine with an amine group). Further minor modifications have also been carried out on the sugar moiety attached to the nucleobase; and also on the phosphoramidate prodrug portion of the scaffold in both of the claimed Markush structures.
Claims	The application has 37 claims (5 independent and 32 dependent claims), wherein all 37 of the claims are for various forms (specifically prodrugs), 36 are secondary claims, 1 claim is for formulation, 35 are for method of treatment and all the secondary claims are also combination claims. The application is primarily directed at methods of treatment with a combination of prodrugs of nucleoside analogues, i.e., cytidine and uridine analogues and pharmaceutically acceptable salt forms thereof. The prodrugs are depicted by 2 Markush structures, i.e., Formulae I and II represent prodrugs of nucleoside analogues of cytidine and uridine respectively. First, the formulae claimed show minor changes in the substituents attached to the sugar moiety of the nucleoside (at 2' and 4' position). Due to the possibility of various substituents being attached at 2' and 4' position of the sugar moiety, the parent molecule itself will differ. Second, 1 of the independent claims is directed to 15 specific compounds, i.e., prodrugs of cytidine nucleoside analogues. This application has, therefore, been marked as a basic molecule application. The secondary method of treatment claims of the application relate to 2 Markush structures of prodrugs of cytidine and uridine nucleoside analogues. The secondary method of treatment claims also relate to 19 specific compounds, i.e., 15 cytidine nucleoside analogues (and their stereoisomers) and 4 uridine nucleoside analogues. Though the application claims stereoisomers for each of the specific 15 cytidine nucleoside analogues, the stereoisomers are not counted as separate compounds. The application also has an independent claim for the same 15 cytidine nucleoside analogues and their stereoisomers. Of the 5 independent claims, 3 are method of treatment claims, 1 is a composition claim (relating to the claimed combination) and 1 is a claim for specific compounds, i.e., prodrugs of cytidine analogues. The 3 independent method of treatment claims are for treating HCV with a combination of prodrugs of cytidine and uridine analogues (n=1), and in further combination with NS3A HCV protease inhibitors (n = 1) and NS5B HCV polymerase inhibitors (n = 1). There is only 1 formulation claim for the combination of prodrugs of cytidine and uridine nucleoside analogues. One dependent claim (claim 32) seems to have been erroneously drafted as a method of treatment claim instead of a composition claim. For the purpose of this analysis, this claim has not been counted as a composition claim. Thirty-six of the 37 claims are secondary claims (method of treatment or composition) re prodrugs of cytidine and uridine nucleoside analogues. One claim is for the prodrugs of cytidine nucleoside analogues. Of the 35 method of treatment claims, 31 are for a combination of prodrugs of cytidine and uridine analogues and 4 are for further combination with NS3A HCV protease inhibitors or NS5B HCV polymerase inhibitors. Thirty-six of the 37 claims are combination claims wherein combinations of prodrugs of cytidine (Formula I) and uridine (Formula II) nucleoside derivatives are claimed. Some of the claims are for combination with further therapeutic agents. Only 1 claim, which is for specific cytidine nucleoside analogues (claim 37), is not a combination claim.

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<tr><td>ISR</td><td>The ISR comprises 3 documents, all of them listed to describe only the general state of the art and not considered to be of particular relevance (A). However, the ISA notes that in light of one of the documents listed in the ISR (i.e., US8334270B2; Sofia et al.), the claimed invention lacks unity of invention as it does not provide a contribution over the existing prior art.</td></tr>
<tr><td>TPO</td><td>The TPO was filed on 21.01.2020 and comprises 2 prior art documents. Of the 2 documents, 1 was a patent application and the other a book chapter. Both the prior art documents were used for both novelty and inventive step. A table of comparison of structures disclosed in prior art (WO 2014/186637) and the structures claimed in the application was uploaded as an additional document.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 21.01.2020.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><td>Canada</td><td>11.03.2020</td><td>3075645</td><td></td></tr>
<tr><td>Singapore</td><td>17.03.2020</td><td>11202002431S</td><td></td></tr>
<tr><td>Israel</td><td>18.03.2020</td><td>273398</td><td></td></tr>
<tr><td>Japan</td><td>19.03.2020</td><td>2020538752</td><td></td></tr>
<tr><td>China</td><td>20.03.2020</td><td>201880061322.3</td><td>Published 22.05.2020</td></tr>
<tr><td>New Zealand</td><td>20.03.2020</td><td>762823</td><td>Published 27.03.2020</td></tr>
<tr><td>Republic of Korea</td><td>16.04.2020</td><td>1020207011082</td><td>Published 22.05.2020</td></tr>
<tr><td>EPO</td><td>21.04.2020</td><td>2018859097</td><td></td></tr>
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TPO No.	57
Appl. No.	PCT/US2018/054574: WO/2019/071105
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019071105
Applicants	Spring Bank Pharmaceuticals, Inc.
Priority Date	05.10.2017
Details	The application claims a crystalline form of SB9200 (also known as inagravirsoproxil) that is diastereomerically pure and stable at certain conditions, i.e., the Rp form of SB9200 and its hemi-tartrate salt. It also claims certain specific pharmaceutically acceptable salts thereof (i.e., hemi-tartrate salt, oxalate salt, citrate salt and fumarate salt), and compositions thereof and methods of using them. SB9200 is under clinical trials for treatment of HBV and HCV. It appears that Spring Bank has discontinued development of inarigivir to treat hepatitis B after the death of a patient (https://www.clinicaltrialsarena.com/news/spring-bank-stops-inarigivir-hbv/). It further appears that Spring Bank has suspended development of inarigivir for HIV, but is still exploring or licensing it for HCV and also planning its clinical trials as an adjuvant therapy for COVID-19 infections (https://adisinsight.springer.com/drugs/800038150).
Claims	The application has 87 claims (8 independent and 79 dependent claims), wherein all 87 claims are secondary claims, 20 of the claims are for various forms, 55 are for formulation, 7 are for method of treatment, 35 are for combination and 10 are "other" claims. Of the 20 claims for forms, 5 are product by process claims. The applicant claims the Rp form of SB9200 and the Rp form of the hemi-tartrate salt of SB9200 and characterises them using XRPD and ^{P} NMR. It also claims the hemi-tartrate salt, oxalate salt, citrate salt and fumarate salt of SB9200. Of the 55 claims for formulations, 12 are for compositions of Formula I, 13 are for Formula III, 27 are for combination of SB9200 with tenofovir or its prodrugs, and 3 are for solid oral dosage form. In the claims for compositions comprising the combinations, the applicant makes distinct claims for composition, particulate composition and pharmaceutical composition of the aforementioned combinations. In some of the formulation claims, the applicant characterises the composition as free from chemical impurities and lists the impurities, including the S-isomer. Of the 35 combination claims, 28 are drafted as claims for formulations (compositions or oral solid dosage form) and 7 are for method of treatment using the claimed compositions. Of the 10 "other" claims, 5 are process claims and 5 are product by process claims, the product being the Rp form. The product by process claims, therefore, overlap with the claims for the crystalline forms.
ISR	The ISR comprises 3 documents, all of them listed to describe only the general state of the art and not considered to be of particular relevance (A). However, the ISA (the ISA for the present application, WO'740 and the Enanta applications above is the same entity) notes that in light of one of the documents listed in the ISR (i.e., Coughlin et al.), the claimed invention lacks unity of invention as it does not provide a contribution over the existing prior art.
TPO	The TPO was filed on 05.02.2020 and comprises 5 prior art documents. Of the 5, 2 are patent applications and 3 are book chapters. One additional patent document was filed with 1 of the patent documents. None of the books were uploaded.Two documents were used for both novelty and inventive step, and 3 documents were used only for inventive step.
Date of Filing of TPO	The TPO was filed on 05.02.2020.
National Phase as of 07.10.2022	No national phase entries

PART C: Case Summaries – TB Applications

TPO No.[1]	2
Appl. No.[2]	PCT/SG2017/050553: WO2018084809
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018084809
Applicants	Nanyang Technological University, Schweizerisches Tropen- und Public Health-Institut and Universitat Basel Vizerektorat Forschung
Priority Date	02.11.2016
Details	The application is for the method of treating or preventing various mycobacteria deficient for or expressing cytochrome bd oxidase or a disease resulting from such infection. It claims the use of a compound capable of inhibiting cytochrome bc1 of the respiratory electron transport chain in combination with a therapeutic agent capable of inhibiting cytochrome bd oxidase. It specifically claims four such mycobacteria and three diseases, tuberculosis, leprosy and buruli ulcer.
Claims	The application has 16 claims, all of which are secondary claims, that is, they are all method of treatment claims. There are 2 Markush structures containing an imidazopyridine and an imidazothiazole scaffold and 11 specific compounds, including Q203, with a couple of claims for the combination of the drug with other drugs, and wherein the method kills the mycobacterium. The applicant also includes method of treatment with combinations of the claimed compounds with an additional therapeutic agent capable of inhibiting cytochrome bd oxidase. It specifically claims a combination with "quinolone compounds, Aurachin, nitric oxide (NO) donors such as PA-824, antibiotics LL- Z1272, Gramicidin S, and derivatives thereof". Interestingly, the WOSA points out that because the priority document did not disclose method of treatment with combination, the priority claim is invalid for the combination claims (claims 9 to 16).
ISR	The ISR had about 9 documents, comprising 5 documents and an additional 2 documents (published after the priority date, but before the filing date) that challenged the novelty of the drug, and 2 general documents.
TPO	The TPO had about 10 documents, 2 of which were ISR documents. The TPO had 1 document that dislodged the novelty of the claims in the application, with 3 documents bringing forth the lack of inventive step and 6 documents that disclosed the lack of novelty and/or inventive step of the claims made in the application. The TPO used 7 articles published in periodicals and 3 patent documents.
Date of Filing TPO	04.03.2019
National Phase as of 07.10.2022[3]	No national phase entries

[1] TPO No. refers to publisher's internal reference number
[2] Appl. No. provides information on the International Application No. and the Publication Number
[3] National phase as of 07.10.2022 reflects information provided on WIPO's patentscope database as at that date. However, this data is dynamic and may not provide accurate information on the actual status of the patent application.

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<tr><td>TPO No.</td><td>3</td></tr>
<tr><td>Appl. No.</td><td>PCT/IB2017/057225: WO2018092089</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018092089</td></tr>
<tr><td>Applicants</td><td>GlaxoSmithKline Intellectual Property Development Limited</td></tr>
<tr><td>Priority Date</td><td>18.11.2016</td></tr>
<tr><td>Details</td><td>This application discloses and claims heterocyclic amides that inhibit RIP1 kinase and methods of making and using the same. It relates to developing a potent, selective, small molecule inhibitor which would block RIP1-dependent cellular necrosis and thereby provide a therapeutic benefit in diseases or events associated with danger-associated molecular patterns (DAMPs), cell death and/or inflammation.</td></tr>
<tr><td>Claims</td><td>The application has 32 claims (6 independent claims and 26 dependent claims), of which 15 are secondary claims wherein 4 deal with formulation, 9 with uses, 2 with method of treatment and 2 with combination. Of the 4 formulation (pharmaceutical composition) claims, 2 overlap with the combination claims. Both the combination claims are drafted as formulation claims. There are 2 Markush structures and 3 specific compounds in the claims comprising a core of a 5-membered ring, 4,5-dihydro-1H-pyrazole ring which connects through nitrogen N1 to a piperidine ring through a carbonyl group. The application claims compounds for RIP1 kinase mediated diseases, including bacterial and viral infections. Though TB is mentioned in the description, it is not specifically claimed. The compounds are claimed specifically for treatment of other RIP1 mediated diseases such as ulcerative colitis, rheumatoid arthritis and psoriasis.</td></tr>
<tr><td>ISR</td><td>The ISR has 2 documents, both of which deal with the general state of the art which is not considered to be of particular relevance and therefore does not attack the novelty or inventive step of the molecule.</td></tr>
<tr><td>TPO</td><td>The TPO has 7 documents, none of which are ISR documents. It has 1 document that attacks the novelty of the claims and 3 additional documents attacking both novelty and inventive step. Additionally, 3 documents have disclosed the lack of novelty and/or inventive step of the claims made in the application. The TPO uses 5 articles published in periodicals and 2 patent documents.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 18.03.2019.</td></tr>
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<tr><td>Appl. No.</td><td>PCT/GB2017/053787:WO2018109504</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018109504</td></tr>
<tr><td>Applicants</td><td>Louise Golding et al.</td></tr>
<tr><td>Priority Date</td><td>16.12.2016</td></tr>
<tr><td>Details</td><td>The application relates to novel ionophores comprising bicyclic or tricyclic nitrogen containing N-oxide functionalised heterocycles, methods for their preparation and their medical use, in particular as anti-neoplastic and anti-infective agents. The application indicates that these compounds will have enhanced membrane penetration.</td></tr>
<tr><td>Claims</td><td>The application has 45 claims (1 independent and 44 dependent), of which 11 are secondary claims pertaining to formulation (8 claims), uses (6 claims) and 1 for the method of treatment. Of the 8 formulation (composition) claims, 1 is specifically for a composition per se, 6 claim use of the composition (apart from the claimed compounds) and 1 claims method of treatment using the formulation (apart from the claimed compounds). There are 11 claims for the combinations. Of the 11 combination claims, 3 are specifically for combinations per se. The remaining 8 claims are for formulation, use and method of treatment which claim both the claimed compounds as combinations. The claims contain 10 Markush structures with 490 specific compounds comprising either bicyclic or tricyclic nitrogen containing aromatic core where one or both of the nitrogen atoms are in the form of N-oxide. Of these 10 Markush structures, 5 are unique structures and 5 are corresponding variants of each of these 5 unique structures. Apart from TB, the application claims use for treatment of various types of cancers, bacterial and fungal infections.</td></tr>
<tr><td>ISR</td><td>The ISR had 11 documents, of which 10 documents and 1 additional document (published after the priority date, but before the filing date) directly attack the novelty of the application and 7 of these also cover the general state of the art.</td></tr>
<tr><td>TPO</td><td>The TPO had 8 documents, 1 of which was an ISR document. Of these, 6 documents have been used to dislodge novelty and 2 for attacking both novelty and inventive step. The TPO used 6 articles published in periodicals and 2 patent documents.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 16.04.2019.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><td>United States of America</td><td>14.06.2019</td><td>16469948</td><td>Published 26.03.2020
Granted 29.06.2021</td></tr>
<tr><td>EPO</td><td>16.07.2019</td><td>2017817848</td><td></td></tr>
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TPO No.	5
Appl. No.	PCT/IB2017/058326: WO2018116260
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018116260
Applicants	Yuria-Pharm Limited Liability Company
Priority Date	22.12.2016
Details	The application claims isonicotninylhydrazones as anti-tuberculosis agents. The primary compound claimed is a slightly modified analogue of isoniazid. Clinical trials were conducted for a pharmaceutical formulation containing this molecule as the primary compound for activity against MDR-TB.
Claims	The application has 17 claims (1 independent and 16 dependent claims), all of which are secondary claims for formulation.
ISR	The ISR had 5 documents, all of which target the inventive step and none for dislodging the novelty of the application.
TPO	The TPO had 8 documents, which included 1 ISR document. Of these 8 documents, 1 was exclusively for attacking novelty, 4 for both novelty and inventive step, and 3 only for inventive step. The prior art documents comprised 7 articles published in periodicals and 1 patent document.
Date of Filing TPO	The TPO was filed on 22.04.2019.
National Phase as of 07.10.2022	No national phase entries

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<tr><td>TPO No.</td><td>18</td></tr>
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<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018151681</td></tr>
<tr><td>Applicants</td><td>Nanyang Technological University and National University of Singapore</td></tr>
<tr><td>Priority Date</td><td>15.02.2017</td></tr>
<tr><td>Details</td><td>The application relates to pyrimidine compounds and compositions for treating tuberculosis. These compounds have been proposed to target the F1 domain of F-ATP synthase. Inhibition of ATP synthase in the mycobacteria leads to shutting off the supply of cellular energy, thereby causing cell death. The application claims pyrimidine compounds alone and in combination with bedaquiline or 6-chloro-2-ethyl-N-[[4-[4-[4-(trifluoromethoxy)phenyl]piperidin-1-yl]phenyl]methyl]imidazo[1,2-a]pyridine-3-carboxamide (Q203) or a combination thereof.</td></tr>
<tr><td>Claims</td><td>The application has 25 claims (2 independent and 23 dependent), of which 17 are secondary claims. There are 3 formulation claims, 7 claims for uses, 2 claims for method of treatment, 6 claims for combinations and 7 “other” claims. Of the 3 formulation claims, 2 overlap with use claims and all 3 claims are for combination. Of the 7 claims for use, 2 overlap with pharmaceutical formulation claims and 3 overlap with combination claims. Of the 2 method of treatment claims, 1 overlaps with a combination claim. Of the 6 combination claims, 1 overlaps with the use claims, 1 overlaps with method of treatment claims and 1 of the claims is for a kit.
Of the 7 “other” claims, 6 are process claims and 1 claim is for a kit.</td></tr>
<tr><td>ISR</td><td>The ISR had 11 documents, of which 10 attacked novelty and 1 was a general state of the art document.</td></tr>
<tr><td>TPO</td><td>The TPO had 6 documents and 1 of these was an ISR document. Of these 6 documents, 4 dislodged novelty and an additional 2 documents attacked both novelty and inventive step. The TPO prior art consisted of 4 articles published in periodicals and 2 patent documents.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 17.06.2019.</td></tr>
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<tr><td>United States of America</td><td>14.08.2019</td><td>1648973</td><td>Published 23.07.2020
Granted 03.08.2021</td></tr>
<tr><td>India</td><td>11.09.2019</td><td>201917036557</td><td>Published 15.11.2019</td></tr>
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<tr><td>Russian Federation</td><td>16.09.2019</td><td>2019128534</td><td>Published 16.03.2021
Withdrawn 11.10.2021</td></tr>
<tr><td>China</td><td>14.10.2019</td><td>201880025012.6</td><td>Published 29.11.2019</td></tr>
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<tr><td>Appl. No.</td><td>PCT/EP2018/054860: WO2018158280</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018158280</td></tr>
<tr><td>Applicants</td><td>Janssen Science Ireland Unlimited Co.</td></tr>
<tr><td>Priority Date</td><td>01.03.2017</td></tr>
<tr><td>Details</td><td>The application claims a combination of known anti-TB drugs, i.e., PZA + bc1 inhibitor (more specifically Q203). It also claims a further combination with other antibacterial agents.</td></tr>
<tr><td>Claims</td><td>The application has 16 claims (1 independent and 15 dependent), all of which are secondary claims. Of these, 2 claims pertain to formulation, 2 claims are for dosage forms, 5 claims for use, 2 claims are for treatments, all 16 for combinations, and there are 2 “other claims”. Of the 16 combination claims, 2 overlap with the formulation claims, 2 overlap with dosage claims, 5 overlap with use claims, 2 overlap with method of treatment claims and 2 of the claims are process claims. The 2 “other claims” are process claims. The diseases claimed are specifically TB (including MDR, latent TB) and mycobacterial infections.</td></tr>
<tr><td>ISR</td><td>The ISR had 2 documents, of which 1 attacked the novelty and the other was a general state of the art document.</td></tr>
<tr><td>TPO</td><td>The TPO had 6 documents, out of which 1 was referred in the ISR. Of these 6 documents, 3 documents dislodged novelty of the application and the other 3 challenged both novelty and inventive step. The TPO used 4 articles published in periodicals and 2 patent documents.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 01.07.2019.</td></tr>
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<tr><td>Japan</td><td>30.08.2019</td><td>2019547409</td><td></td></tr>
<tr><td>Philippines</td><td>02.09.2019</td><td>12019502002</td><td></td></tr>
<tr><td>United States of America</td><td>03.09.2019</td><td>16490677</td><td>Published 31.01.2020</td></tr>
<tr><td>Brazil</td><td>10.09.2019</td><td>112019017901</td><td></td></tr>
<tr><td>Eurasian Patent Organization</td><td>24.09.2019</td><td>201991997</td><td>Published 31.01.2020</td></tr>
<tr><td>Ukraine</td><td>30.09.2019</td><td>A201910076</td><td>Published 10.01.2020</td></tr>
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<tr><td>Republic of Korea</td><td></td><td>1020197025379</td><td>Published 25.10.2019</td></tr>
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<tr><td>Applicants</td><td>Merck Sharp & Dohme Corp.</td></tr>
<tr><td>Priority Date</td><td>20.03.2017</td></tr>
<tr><td>Details</td><td>The application relates to oxazolidinone compounds for inhibiting growth of mycobacterial cells as well as a method of treating mycobacterial infections by Mycobacterium tuberculosis. The application also claims administering a therapeutically effective amount of an oxazolidinone and/or a pharmaceutically acceptable salt thereof, or a composition comprising such compound and/or salt.</td></tr>
<tr><td>Claims</td><td>The application has 20 claims (2 independent and 18 dependent), of which 9 are secondary claims. There are 8 claims for formulation, 1 claim for use, 7 claims for method of treatment and 2 claims for combination. Of the 8 formulation claims, 1 claim is for a composition per se and 7 overlap with method of treatment claims as they claim method of treatment with the compound as well as composition. All 7 method of treatment claims claim method of treatment with both the compound as well as composition. The method of treatment claims overlap with combination claims. Both combination claims overlap with or are drafted with method of treatment claims. There are no claims for combination per se. The application claims 1 Markush structure with 23 specific compounds. Apart from the specific claim for the treatment of tuberculosis and resistant tuberculosis, the application also claims treatment for various bacterial infections.</td></tr>
<tr><td>ISR</td><td>The ISR had 1 document which attacks the novelty of the application.</td></tr>
<tr><td>TPO</td><td>The TPO had 5 prior art documents which were different from the ISR document. All these documents dislodged both novelty and inventive step. The TPO had 3 articles published in periodicals and 2 patent documents.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 22.07.2019.</td></tr>
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<tr><td>Applicants</td><td>Institute of Materia Medica, Chinese Academy of Medical Sciences</td></tr>
<tr><td>Priority Date</td><td>28.03.2017</td></tr>
<tr><td>Details</td><td>The application claims nitrogen containing heterocycle substituted benzoxazine oxazolidinone compounds, preparation method of these compounds and the use in the preparation of a drug for treating Mycobacterium tuberculosis. It also claims stereoisomers, pharmaceutically acceptable salts thereof, and a pharmaceutical composition comprising the compound disclosed in the application.</td></tr>
<tr><td>Claims</td><td>The application has 16 claims (1 independent and 15 dependent), of which there are 3 secondary claims, 2 claims for formulation, 1 claim for use and 1 other claim. Of the 2 formulation claims, 1 is for composition per se and 1 overlaps with the use claim which claims use of the compounds and compositions thereof. The 1 other claim is a process claim. The claims contain 9 Markush structures with 36 specific compounds. Of the 9 Markush structures, 1 is the primary Markush structure and 8 are derivative Markush structures. Of the 8 derivative Markush structures, 2 are isomers of the primary Markush structure, 3 are derivatives of one such isomer and 3 are derivatives of the second such isomer. Claim 12 sets out a relatively limited number of possible substituents for some of the Markush structures.</td></tr>
<tr><td>ISR</td><td>The ISR had 2 documents, both of which deal with the general state of the art which is not considered to be of particular relevance and therefore does not attack the novelty or inventive step of the molecule.</td></tr>
<tr><td>TPO</td><td>The TPO had 5 documents, none from the ISR. Of these documents, 1 attacked inventive step and the rest attacked both novelty and inventive step. The TPO contained 2 articles published in periodicals and 3 patents.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 29.07.2019.</td></tr>
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<tr><td>United States of America</td><td>27.09.2019</td><td>16498876</td><td>Published 24.06.2021
Granted 17.05.2022</td></tr>
<tr><td>Russian Federation</td><td>28.10.2019</td><td>2019134197</td><td>Granted 15.03.2021</td></tr>
<tr><td>India</td><td></td><td>201917043636</td><td>Published 10.01.2020</td></tr>
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TPO No.	34
Appl. No.	PCT/EP2018/061615: WO2018206466
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018206466
Applicants	GlaxoSmithKline Intellectual Property Development Limited
Priority Date	08.05.2017
Details	The application claims sanfetrinem, a pharmaceutically acceptable salt or ester prodrug thereof for use in the treatment of tuberculosis, either alone or in combination with beta-lactamase inhibitors and other agents. This is an application for a new use of a known compound, and its known prodrug (sanfetrinem cilexetil). Sanfetrinem is a beta-lactam containing compound which inhibits bacterial cell wall synthesis.
Claims	The application has 27 claims (9 independent and 18 dependent), all of which are secondary claims. Of these, 1 claim is for formulation, 6 for salt forms, 18 claims for use, 9 claims for the method of treatment and 7 claims pertaining to combination. All the claims (except the 9 method of treatment claims) are drafted as compounds/composition/ combinations for use as the application claims a new use for a known compound. Of the 6 claims for specific forms, 2 claims are for the ester prodrug of sanfetrinem, 2 claims are for sanfetrinem cilexetil and 2 claims are for the sodium salt of sanfetrinem. Of these 6 claims, 3 are drafted as method of treatment claims. The claims generally claim the compounds for use in the treatment of a disease resulting from a mycobacterial infection, mycobacterial infection, mycobacterium tuberculosis infection and also specifically for use in treatment of tuberculosis disease.
ISR	The ISR had 8 documents, of which 1 attacked novelty and 7 were general state of the art documents.
TPO	The TPO had 8 documents, 1 of which was an ISR document. Of these 8 documents, 1 document attacked inventive step and 7 dislodged novelty and inventive step of the application. All these 8 documents were articles published in periodicals.
Date of Filing TPO	The TPO was filed on 09.09.2019.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Canada	18.10.2019	3060396	
Australia	21.10.2019	2018265192	Published 07.11.2019
China	07.11.2019	201880030277.5	Published 06.03.2020
Japan	07.11.2019	2019561315	
United States of America	08.11.2019	16611908	Published 17.09.2020 Granted 22.02.2022
Brazil	19.11.2019	112019023322	Refused 18.01.2022
EPO	09.12.2019	2018721053	Granted 27.07.2022
Russian Federation	09.12.2019	2019139864	Published 09.06.2021 Granted 12.10.2021
Serbia	01.08.2022	P-2022/0731	Granted 31.08.2022
India		201917045452	Published 13.12.2019
Republic of Korea		1020197032729	Published 10.01.2020

TPO No.	47
Appl. No.	PCT/EP2018/072143: WO2019034700
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019034700
Applicants	GlaxoSmithKline Intellectual Property Development Limited and BioVersys AG
Priority Date	16.08.2017
Details	The application claims spiroisoxazoline compounds and their use in treatment of mycobacterial infections or treatment of diseases caused by mycobacterium such as tuberculosis, primarily to potentiate the action of ethionamide. More specifically, it claims a compound very similar to SMARt-420, a known spiroisoxazoline compound for use as ethionamide booster in the treatment of TB.
Claims	The application has 22 claims (1 independent and 21 dependent), of which 13 are secondary claims. The application has 1 claim for formulation, 5 claims for uses, 2 claims for method of treatment, and 5 claims for combination. Of the 5 claims for use, 4 are drafted as claiming the compound or its pharmaceutically acceptable salt for use. The application generally claims treatment of mycobacterial infection or disease caused by infection with mycobacterium. It specifically claims treatment of *Mycobacterium tuberculosis* infection and tuberculosis.
ISR	The ISR had 6 documents, and all dealt with the general state of the art which is not considered to be of particular relevance and therefore does not attack the novelty or inventive step of the molecule.
TPO	The TPO had 5 documents, of which 1 was an ISR document. Of these 5 documents, 2 attacked inventive step and 3 dislodged both novelty and inventive step. The TPO used 3 documents published in periodicals and 2 patent documents.
Date of Filing TPO	The TPO was filed on 16.12.2019.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Australia	30.01.2020	2018317804	Published 20.02.2020
Singapore	04.02.2020	11202000988R	
Israel	09.02.2020	272562	
New Zealand	10.02.2020	761518	Published 28.02.2020
Canada	12.02.2020	3072838	
Japan	14.02.2020	2020530727	
Mexico	14.02.2020	MX/a/2020/001808	Published 24.11.2020 Granted 19.07.2022
Philippines	14.02.2020	12020500339	
Thailand	14.02.2020	2001000850	
United States of America	14.02.2020	16639192	Published 04.02.2021 Granted 22.02.2022
China	17.02.2020	201880053326.7	Published 10.04.2020

	Brazil	27.02.2020	112020003192	
	Republic of Korea	11.03.2020	1020207007144	Published 21.04.2020
	EPO	16.03.2020	2019752171	Granted 29.09.2021
	Russian Federation	16.03.2020	2020109677	Published 16.09.2021
	Serbia	15.12.2021	P-2021/1543	Granted 31.01.2022

TPO No.	48
Appl. No.	PCT/EP2018/072205: WO2019034729
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019034729
Applicants	GlaxoSmithKline Intellectual Property Development Limited
Priority Date	17.08.2017
Details	The application appears to specifically claim a preclinical compound, GSK839, a tetrazole benzene sulfonamide, which is identified by the Working Group for New TB Drugs as a pipeline compound.
Claims	The application has 26 claims (1 independent and 25 dependent), of which 15 are secondary claims. There is 1 claim for formulation, 7 claims for uses, 2 claims for treatment, and 5 claims for combination. Of the 7 claims for use, 6 are drafted as claiming the compound or its pharmaceutically acceptable salt for use. The application generally claims treatment of mycobacterial infection or disease caused by infection with mycobacterium. It specifically claims *Mycobacterium tuberculosis* infection and tuberculosis.
ISR	The ISR had 6 documents and all dealt with the general state of the art which is not considered to be of particular relevance and therefore does not attack the novelty or inventive step of the molecule.
TPO	The TPO had 4 documents, of which 1 was an ISR document. Of these, 2 documents attacked inventive step and the other 2 documents dislodged both novelty and inventive step. The TPO made use of 3 articles published in periodicals and 1 patent document.
Date of Filing TPO	The TPO was filed on 17.12.2019.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Australia	31.01.2020	2018317812	Published 20.02.2020
Canada	12.02.2020	3072854	
Japan	14.02.2020	2020508427	
United States of America	14.02.2020	16639163	Published 23.07.2020 Granted 27.07.2021
China	17.02.2020	201880053320.X	Published 10.04.2020
Brazil	27.02.2020	112020003247	
Republic of Korea	11.03.20202	1020207007186	Published 22.04.2020
EPO	17.03.2020	2018755815	Granted 23.06.2021
Russian Federation	17.03.2020	2020110818	Published 17.09.2021
Serbia	26.08.2021	P-2021/1076	Granted 30.09.2021

TPO No.	55
Appl. No.	PCT/EP2018/077222: WO2019068910
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019068910
Applicants	Quretech Bio Ab and Washington University in St. Louis
Priority Date	05.10.2017
Details	The application relates to ring-fused thiazolino 2-pyridone compounds and, in particular, combinations of such ring-fused thiazolino 2-pyridones with other known anti-TB agents for treating various types of tuberculosis infections.
Claims	The application has 46 claims (2 independent and 44 dependent), of which there are 45 secondary claims. Of these, there are 2 claims for formulation, 5 claims for salt forms, 9 claims for use, 4 claims for method of treatment, 45 claims for combination and 3 other claims. There are 2 independent claims, 1 for combination and 1 for specific compounds. All claims except 1 (claim 46) are drafted as combination claims wherein parent/derived Markush structures of Formula I (imidazopyridines; acting on cytochrome b subunit of the bc1 complex) and Formula II (ring-fused thiazolino 2-pyridone compounds) are claimed in combination with each other and also further with other known anti-TB agents for the treatment of infections caused by mycobacteria. However, 1 independent claim is directed to 34 specific ring-fused thiazolino 2-pyridone (Formula II) compounds. Therefore, this application is being treated as a basic molecule application. The Markush structures are claimed as part of the combination claims and not separately as Markush structures per se. Of the 11 Markush structures, 3 are for imidazopyridines, of which 1 is a primary Markush structure (Formula I) and 2 are derivative Markush structures. Of the 11 Markush structures, 8 are ring-fused thiazolino 2-pyridone structures, of which 1 is a primary Markush structure (Formula II) and 7 are derivative Markush structures. Of the 7 derivative Markush structures, 2 are directly derived from Formula II (Formula IIa and IIb), 2 (Formula IIIa and IIIb) specifically claim various nicotinic hydrazide salt forms of Formula IIa and IIb, and the other 3 (Formula IV, IVa, IVb) specifically claim Markush structures derived from Fomula II bonded with a nicotinamide moiety. Two additional derivative structures (Formula IIa51 and Formula IVa5; claims 4 and 8) have not been counted as separate Markush structures because they differ from their parent Markush structures (Formula IIa and Formula IVa) only in terms of their stereochemistry. Thirty-four specific ring-fused thiazolino 2-pyridone (Formula II) compounds are claimed in the independent claim. In a combination claim, 87 specific ring-fused thiazolino 2-pyridone (Formula II) compounds (which include the 34 mentioned above) are claimed. Of the 5 claims for forms, 3 are claims for the nicotinic hydrazide salt forms of compounds of Formula II and 2 are claims for stereoisomers of certain derivative Marksush structures of Formula II. As regards the 3 claims for the salt forms, 2 broad claims (claims 1 and 2) include within them the nicotinic hydrazide salt form specifically and therefore are counted as claims for “forms”. One (claim 5) specifically claims Markush structures (Formula IIIa and IIIb) for different nicotinic hydrazide salt forms wherein the compounds differ in the substitution of various anionic groups (A-) on the parent Markush structure. Of the 9 use claims, 4 are drafted as use claims per se and 5 are drafted as claims to combination for use. Of the 3 “other” claims, 1 claim is a combination wherein the claimed drug is profiled in a test and 2 claims are for the claimed combination in a kit (apart from composition).
ISR	The ISR had 3 documents, of which 1 document and an additional document (published after the priority date, but before the filing date) attacked the novelty of the application and 1 document was a general state of the art document.
TPO	The TPO had 3 documents, of which 1 was an ISR document. All the TPO documents attacked both novelty and inventive step. The TPO made use of 1 document published in a periodical and 2 patent documents.

Date of Filing TPO	The TPO was filed on 05.02.2020.
National Phase as of 07.10.2022	

Office	Entry Date	National Number	National Status
Japan	31.03.2020	2020518682	
United States of America	11.04.2020	16652829	Published 08.10.2020 Granted 28.09.2021
China	17.04.2020	201880067818.1	Published 05.06.2020
Philippines	05.05.2020	12020550567	
EPO	06.05.2020	2018785905	
Russian Federation	06.05.2020	2020113346	Published 09.11.2021
Republic of Korea		1020207010849	Published 09.06.2020

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<tr><td>TPO No.</td><td>64</td></tr>
<tr><td>Appl. No.</td><td>PCT/IB2019/051934: WO2019175737</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019175737</td></tr>
<tr><td>Applicants</td><td>University of Notre Dame Du Lac</td></tr>
<tr><td>Priority Date</td><td>12.03.2018</td></tr>
<tr><td>Details</td><td>The application claims imidazopyridine and pyrazolopyridine compounds wherein carbon hydrogen bonds have been replaced with isotopic carbon-deuterium bonds, syntheses thereof, compositions thereof, and methods of using such compounds and compositions for killing and/or inhibiting the growth of M. tuberculosis and/or M. avium. In this application, deuterated imidazopyridine and pyrazolopyridine compounds are broadly claimed for the treatment of tuberculosis mycobacterial and non-tuberculosis mycobacterial infection, without mentioning the specific diseases.</td></tr>
<tr><td>Claims</td><td>The application has 11 claims (2 independent and 9 dependent), all of which are secondary claims. The application has 4 claims for formulation and 3 claims for method of treatment. The application is not considered as an application for basic molecule as all the compounds claimed are deuterated forms of known imidazopyridine compounds and the process of deuteration is known to a person skilled in the art. The secondary claims of the application relate to 4 Markush structures. Of the 4 Markush structures, 2 have an imidazopyridine core [wherein 1 Markush structure has the core and substituents deuterated (A deut) and the other Markush structure has the linker too deuterated] and 2 structures have a pyrazolopyridine core [wherein 1 Markush structure has the core and substituents deuterated (B deut) and the other Markush structure has the linker too deuterated]. The application claims 130 specific deuterated compounds of certain known compounds, wherein H is replaced with D at various positions and substituents. These include deuterated forms of known drugs such as Q203 and TB-47. However, as all compounds are deuterated analogues of known compounds, and the process of deuteration itself is known, the number of specific compounds is counted as 0. Of the 4 formulation claims, 1 is a composition claim per se and the other 3 are method of treatment of infection caused by mycobacterium by administration of the claimed compounds or composition.</td></tr>
<tr><td>ISR</td><td>The ISR had 2 documents. Both these documents attacked the inventive step of the application.</td></tr>
<tr><td>TPO</td><td>The TPO had 9 documents, all of which attacked the inventive step of the application. The TPO used 3 documents published in periodicals, 5 patent documents and 1 book reference.</td></tr>
<tr><td>Date of Filing TPO</td><td>The TPO was filed on 30.03.2020.</td></tr>
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<tr><th>Office</th><th>Entry Date</th><th>National Number</th><th>National Status</th></tr>
<tr><td>United States of America</td><td>11.09.2020</td><td>16980230</td><td>Published 14.01.2021</td></tr>
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PART D: Case Summaries: Applications claiming HIV, HCV and TB treatments

TPO No.[1]	6
Appl. No.[2]	PCT/IB2017/058015: WO/2018/116108
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018116108
Applicants	GlaxoSmithKline Intellectual Property Development Limited
Priority Date	20.12.2016
Details	The application discloses IDO (indoleamine dioxygenase) inhibitor compounds derived from a scaffold comprised of a pyridine core and pharmaceutically acceptable salts thereof, their pharmaceutical compositions, their methods of preparation, and methods for their use in the prevention and/or treatment of diseases.
Claims	The application has 16 claims (2 independent and 14 dependent), of which 9 are secondary claims wherein 2 are for formulation, 2 are for use and 6 for method of treatment. Of the 2 formulation claims, 1 overlaps with a method of treatment claim as the composition is claimed for treatment. The application claims a single Markush structure with the core being pyridine ring substituted at positions 2 and 3 with an amine group, wherein the amine itself is further substituted and also includes an acid group substitution at position 5. A single compound has also been claimed specifically; having this pyridine core wherein the amine at position 2 is substituted with an alkyl chain of 3 carbon atoms and a tetrahydropyran ring and the amine at position 3 is substituted with another pyridine ring; and an acidic functional group substitution at position 5. The application claims compounds/pharmaceutical composition containing these compounds for treating chronic viral infections such as HIV and HCV and bacterial infections such as TB by modulating activity of IDO.
ISR	The ISR has 2 documents, of which 1 was listed for novelty (X) and also listed for inventive step (Y). The other ISR document was published after the priority date of the present application but before the international filing date (P) and was listed only for inventive step (Y).
TPO	The TPO was filed on 23.04.2019 and comprised 6 prior art documents. Of the 6 documents, only 1 was uploaded to the WIPO website. Five of the 6 documents were patent applications and 1 was a periodical article. Four documents were used for both novelty and inventive step, and 2 were used only for inventive step. In the TPO, 2 of the documents used had a publication date after the priority date of the present application (P documents) but before the international filing date. Of the two P documents, 1 document was used for both novelty and inventive step and 1 document was used for only inventive step.
Date of Filing of TPO	The TPO was filed on 23.04.2019.
National Phase as of 07.10.2022[3]	**Office**: United States of America; **Entry Date**: 25.05.2019; **National Number**: 16464795; **National Status**: Published 24.10.2019 Granted 29.09.2020

1 TPO No. refers to publisher's internal reference number

2 Appl. No. provides information on the International Application No. and the Publication Number

3 National phase as of 07.10.2022 reflects information provided on WIPO's patentscope database as at that date. However, this data is dynamic and may not provide accurate information on the actual status of the patent application.

	Japan	18.06.2019	2019532923	
	EPO	22.07.2019	2017825965	Withdrawn 02.03.2021

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<tr><td>TPO No.</td><td>7</td></tr>
<tr><td>Appl. No.</td><td>PCT/IB2017/058014: WO/2018/116107</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018116107</td></tr>
<tr><td>Applicants</td><td>GlaxoSmithKline Intellectual Property Development Limited</td></tr>
<tr><td>Priority Date</td><td>20.12.2016</td></tr>
<tr><td>Details</td><td>The application discloses IDO (indoleamine dioxygenase) inhibitor compounds derived from a scaffold comprised of a pyridine core and pharmaceutically acceptable salts thereof, their pharmaceutical compositions, their methods of preparation, and methods for their use in the prevention and/or treatment of diseases.</td></tr>
<tr><td>Claims</td><td>The application has 19 claims (2 independent and 17 dependent), of which 9 are secondary claims wherein 2 claims are for formulation, 2 are for use and 6 for method of treatment. Of the 2 formulation claims, 1 overlaps with a method of treatment claim as the composition is claimed for treatment. The application claims a single Markush structure with the core being pyridine ring substituted at positions 2 and 3 with an amine group, wherein the amine itself is further substituted and also includes an acid group substitution at position 5. (The Markush structures claimed in WO’107 and WO’108 are identical.) A single compound has also been claimed specifically; having this pyridine core wherein the amine at position 2 is substituted with an alkyl chain of 3 carbon atoms and a tetrahydropyran ring and the amine at position 3 is substituted with a thiadiazole ring (the only difference in the compounds claimed in both WO’107 and WO’108 is the presence of a different heteroaryl ring at this position); and an acidic functional group substitution at position 5. The application claims compounds/pharmaceutical composition containing these compounds for treating chronic viral infections such as HIV and HCV and bacterial infections such as TB by modulating activity of IDO.</td></tr>
<tr><td>ISR</td><td>Even though the Markush scaffolds claimed in both WO’107 and WO’108 are identical, there is no overlap in the ISR documents across both the applications. The ISR for the present application has 4 documents, of which 2 were published after the priority date (P documents) but before the international filing date. Of these 2 documents, 1 was listed for both novelty and inventive step (X) and the other document was listed to describe only the general state of the art and is not considered to be of particular relevance (A). Of the remaining 2 documents, 1 was an X document and the other an A document.</td></tr>
<tr><td>TPO</td><td>The TPO was filed on 23.04.2019 and comprised 6 prior art documents. Of the 6 documents, only 1 was uploaded to the WIPO website. Of the 6 documents used in the TPO, 5 were patent applications and 1 was a periodical article. Also, 5 documents were used for both novelty and inventive step and 1 was used only for inventive step. In the TPO, 2 of the documents used had a publication date after the priority date of the present application (P documents) but before the international filing date. Both the P documents were used to assail novelty and inventive step. The prior art documents used across WO’107 and WO’108 were identical.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 23.04.2019.</td></tr>
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16.04.2020
Granted
26.01.2021</td></tr>
<tr><td>Japan</td><td>18.06.2019</td><td>2019533010</td><td></td></tr>
<tr><td>EPO</td><td>22.07.2019</td><td>2017825965</td><td>Withdrawn
16.03.2021</td></tr>
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<tr><td>TPO No.</td><td>39</td></tr>
<tr><td>Appl. No.</td><td>PCT/IB2018/054762: WO2019003143</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019003143</td></tr>
<tr><td>Applicants</td><td>GlaxoSmithKline Intellectual Property Development Limited</td></tr>
<tr><td>Priority Date</td><td>28.06.2017</td></tr>
<tr><td>Details</td><td>The application claims compounds with a Markush structure which modulate indoleamine 2,3-dioxygenase (IDO1), which is associated with chronic viral infections such as HIV, HCV and HBV, autoimmune disorders, neurodegenerative disorders and chronic bacterial infections such as tuberculosis.</td></tr>
<tr><td>Claims</td><td>The application has 16 claims, 1 independent and 15 dependent claims consisting of 1 Markush structure claim. There are 9 secondary claims, of which 1 is a formulation claim, 2 are claims for use and 6 are claims for methods of treatment. The compounds claimed as indoleamine modulators are used for the treatment of HIV, HCV and TB, and for diseases like Parkinson’s disease, Huntington’s disease and prosthetic joint infection.</td></tr>
<tr><td>ISR</td><td>The ISR/WOSA/IPRP were published, with the European Patent Office, Rijswijk, Netherlands, being the ISA. The ISR listed 3 documents, comprising 2 which dislodged the novelty claims in the application (1 of them being a document published after the priority date, but before the filing date of the application) and 1 other document (E document).</td></tr>
<tr><td>TPO</td><td>The TPO filed 4 prior art documents, none from the ISR. All 4 documents dislodged the inventive step arguments of the claims in the application. 1 prior art document used was a periodical article and 3 were patent documents. It is interesting to note that the scaffolds claimed in the application were similar to the scaffolds and compounds claimed in WO’108 and WO’107 – for which TPOs were filed earlier.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 28.10.2019.</td></tr>
<tr><td>National Phase as of 07.10.2022</td><td>
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<tr><td>Canada</td><td>11.12.2019</td><td>3066973</td><td></td></tr>
<tr><td>Japan</td><td>26.12.2019</td><td>2019572171</td><td></td></tr>
<tr><td>China</td><td>27.12.2019</td><td>201880043633.7</td><td>Published 11.02.2020</td></tr>
<tr><td>Brazil</td><td>31.12.2019</td><td>112019027363</td><td>Withdrawn 21.12.2021</td></tr>
<tr><td>EPO</td><td>28.01.2020</td><td>2018749513</td><td>Published 06.05.2020 Withdrawn 08.06.2021</td></tr>
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<tr><td>Appl. No.</td><td>PCT/IB2018/058389: WO/2019/087028</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019087028</td></tr>
<tr><td>Applicants</td><td>GlaxoSmithKline Intellectual Property Development Limited</td></tr>
<tr><td>Priority Date</td><td>30.10.2017</td></tr>
<tr><td>Details</td><td>The application claims compounds with a Markush structure comprising a spirocyclic core which modulate indoleamine 2,3-dioxygenase (IDO1), which is associated with chronic viral infections such as HIV, HCV and HBV, autoimmune disorders, neurodegenerative disorders and chronic bacterial infections such as tuberculosis.</td></tr>
<tr><td>Claims</td><td>The application has 14 claims (1 independent and 13 dependent claims), wherein 9 are secondary claims. Of the 9 secondary claims, 7 are for formulation, 2 are for use and 6 are method of treatment claims. Of the 7 claims for formulation, 1 is for composition per se and the other 6 claims are for the dependent method of treatment claims comprising administration of the claimed composition for treatment of diseases/ conditions by modulation of IDO activity. Of the 6 method of treatment claims, 2 specifically characterise the disease/condition to be treated in terms of biomarkers of IDO activity. The application broadly claims treatment of conditions such as cancer, chronic viral and bacterial infections and neurological disorders, and also specifically claims method of treatment of diseases related to these conditions such as HBV, HCV, tuberculosis and Parkinson’s disease via modulation of IDO activity. Thus, the number of diseases is given as > 10.

Of the 2 claims for use, 1 claim is drafted as “compound or salt for use” and the other claim is drafted as a claim for use of “compound or salt for manufacture of medicament for treating diseases”.</td></tr>
<tr><td>ISR</td><td>The ISR comprises 3 documents, all of them listed to describe only the general state of the art and not considered to be of particular relevance (A). Also, one of the A documents was published after the priority date of the present application but before the international filing date (P).</td></tr>
<tr><td>TPO</td><td>The TPO was filed on 02.03.2020 and comprises 5 prior art documents. Of the 5 documents, 4 are patent applications and 1 is a periodical article. Also, 2 documents were used for both novelty and inventive step and 3 documents were used only for inventive step. One of the patent documents in the prior art (WO 2019/078968), used to assail both novelty and inventive step, was published after the priority date of the present application but before the international filing date (P, X). In the TPO, the 1 additional document uploaded is a periodical document (Arrumugam et al.) to support a periodical document cited (Mbongue et al.) for which a note was written.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 02.03.2020.</td></tr>
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<tr><td>Canada</td><td>23.04.2020</td><td>3080100</td><td></td></tr>
<tr><td>Japan</td><td>28.04.2020</td><td>2020523977</td><td></td></tr>
<tr><td>China</td><td>29.04.2020</td><td>201880070747.0</td><td>Published 09.06.2020</td></tr>
<tr><td>EPO</td><td>02.06.2020</td><td>2018807124</td><td>Withdrawn 03.05.2022</td></tr>
<tr><td>Brazil</td><td>24.09.2020</td><td>112020008490</td><td>Withdrawn 19.04.2022</td></tr>
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TPO No.	62
Appl. No.	PCT/US2018/061117: WO2019099564
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019099564
Applicants	Children's Medical Center Corporation and Dana-Farber Cancer Institute, Inc
Priority Date	14.11.2017
Details	The application is a basic molecule application as well as a biologic application for HIV, HCV and TB. It claims imidazopyrimidine compounds and their derivatives as enhancers or modifiers of an immune response and is thus useful in treating and/or preventing diseases, as adjuvants in a vaccine for various diseases (e.g., proliferative disease, inflammatory disease, autoimmune disease, infectious disease or chronic disease), or as stand-alone anti-infective or immune response modifying agents. It also claims pharmaceutical compositions, kits, methods and uses including or using the claimed compounds. The diseases listed include HIV, HCV and TB as well as several other diseases such as influenza, cancer, allergy, HPV, HBV, smallpox, yellow fever, mumps, etc. The mechanism of action of the claimed compounds is immune response enhancing/ modifying activity as well as stand-alone anti-infective activity. In the description, the applicant discloses that commercial libraries were screened for activation of human immune cells and adjuvant activity and that the SAR of known imidazopyrimidine compounds was studied for the generation of the claimed compounds present in the pharmaceutical composition/vaccine of the present application.
Claims	The application has 67 claims, of which 1 is an independent claim and the remaining 66 are dependent claims. It claims 3 Markush structures and 38 specific compounds. Of the 3 Markush structures, 1 is a primary Markush structure and 2 are derivative Markush structures. However, the derivative Markush structures are not numbered specifically. The applicant also specifically disclaims 6 compounds in 1 of the claims. From the description, it appears that these compounds were part of the imidazopyrimidine compounds that were screened by the applicant. The application claims the imidazopyrimidine compounds as well as their pharmaceutically acceptable salts. There are 52 secondary claims, of which 52 are formulation claims, 2 are dosage claims, 3 are use claims, 46 are method of treatment claims, 51 are combination claims and 1 is an "other" claim. Of the 52 claims for formulation, 2 are for pharmaceutical composition per se. All the 46 method of treatment claims, 3 use claims and 1 "other" claim all relate to either the claimed compounds or the claimed compositions. Thus, all the secondary claims have been counted as formulation claims too. The 2 dosage claims, which disclose frequency of dosing, of the claimed composition have been drafted as method of treatment claims. The 1 "other" claim relates to a kit comprising the claimed compound or the claimed pharmaceutical composition. Of the 3 claims for use, 2 are drafted as use of compound/pharmaceutical composition as medicament (also specifically as immunomodulator); 1 claim is drafted as use of compound/pharmaceutical composition for treating diseases.

	All 46 method of treatment claims relate to the claimed compounds, compositions thereof or where the claimed compound is an adjuvant in a vaccine. Of these, 28 claims relate to the treatment of various diseases/conditions or protection against a range of pathogens (claims 18-45). Two claims relate to frequency of dosing, 1 claim relates to route of administration, 12 claims relate to targeted patient, condition and time of administration. Two claims relate to administration of the claimed composition as a prophylactic (n = 1) and as combination therapy (n = 1). One claim relates to method of enhancing an immune response in a subject. Of the 51 claims for combination, 1 is drafted as a composition claim per se and another is drafted as a method of treatment claim wherein the claimed composition is administered as part of combination therapy. All the secondary claims (except 1 formulation claim) impliedly include a reference to the claimed combination and have therefore been counted as combination claims too. The application broadly claims method of treatment with claimed compounds/ pharmaceutical compositions thereof of various conditions such as proliferative, inflammatory, autoimmune, viral, bacterial and paediatric infections and specifically lists certain diseases, including influenza, HIV, HCV and TB.
ISR	The ISR, WOSA and IPRP have been published; the USPTO is the ISA. The ISR cites 5 documents, of which 2 are X documents, 1 is a Y document and 2 are A documents. In the ISR, one of the documents listed for novelty (X) was also listed for inventive step (Y). The search strategy has been separately published.
TPO	Two TPOs were filed. The first TPO cites 6 documents. Of these 6 documents, 3 are used to assail inventive step and 3 are used to assail both novelty and inventive step. Two of these documents are periodicals and 4 are patent documents. In the first TPO, 7 further/additional documents (5 periodical prior art documents and 2 patent documents) were cited along with the main documents cited for which notes were written. Of the 7 additional documents, (i) 2 additional periodical articles each were cited in support of a periodical article and a patent document (n = 4), (ii) 1 additional periodical article was cited in support of a patent document, and (iii) 1 additional patent document each was cited in support of 2 patent documents (n = 2). A second TPO with a note on 1 patent document (which was used as an additional/ supporting document in the first TPO) was also filed on the same day. “Additional comments” were also filed with this TPO. In the description, the applicant discloses and admits that commercial libraries were screened for activation of human immune cells and adjuvant activity and that the SAR of known imidazopyrimidine compounds was studied for the generation of the claimed compounds present in the pharmaceutical composition/vaccine of the present application. Thus, 1 of the additional documents is an “additional comment” which highlights the admissions by the applicant in the description to point out that the claimed imidazopyrimidine compounds lack inventive step.
Date of Filing of TPO	The TPO was filed on 16.03.2020.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
Japan	14.05.2020	2020526527	
United States of America	14.05.2020	16754171	Published 04.08.2022
Republic of Korea	12.06.2020	1020207016955	Published 22.07.2020
EPO	15.06.2020	2018879326	
China	30.06.2020	201880084871.2	Published 13.11.2020

TPO No.	63
Appl. No.	PCT/US2018/061135: WO2019099578
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019099578
Applicants	Children's Medical Center Corporation and Dana-Farber Cancer Institute, Inc
Priority Date	14.11.2017
Details	The application is a biologic application for HIV, HCV and TB. The application claims compositions comprising an antigen and imidazopyrimidine compound for enhancing human immune response and/or as adjuvants in vaccines. It also claims methods of enhancing immune response in a subject by administering the imidazopyrimidine compounds per se. The diseases listed include HIV, HCV and TB as well as several other diseases such as influenza, cancer, allergy, HPV, HBV, smallpox, yellow fever, mumps, etc. The mechanism of action of the claimed compounds is immune response enhancing activity. In the description, the applicant discloses that commercial libraries were screened for activation of human immune cells and adjuvant activity and that the SAR of known imidazopyrimidine compounds was extensively studied for the generation of compounds present in the pharmaceutical composition/vaccine of the present application.
Claims	This application claims pharmaceutical compositions/vaccine containing imidazopyrimidine compounds and an antigen. This application was filed on the same day as WO2019099564 by the same applicant (for which TPO #62 above was filed). The descriptions of both the applications are almost identical. However, the 6 compounds specifically disclaimed in WO2019099564 have been specifically claimed in the pharmaceutical compositions and method of treatment claims of the present application. The application has 143 claims, of which 7 are independent claims and 136 are dependent claims. Of the 7 independent claims, 2 are formulation claims, 3 are method of treatment claims and 2 are use claims. All 143 claims relate to either pharmaceutical composition, method of treatment and use of imidazopyrimidine compounds as an adjuvant along with an antigen or method of enhancing immune response with imidazopyrimidine compound per se. Therefore, this is primarily a secondary application. The application does not claim the Markush structures per se. However, the secondary claims (formulation and method of treatment claims) relate to 3 Markush structures and 42 specific imidazopyrimidine compounds (or their salts). Of the 3 Markush structures, 1 is a primary Markush structure (Formula I) and the other 2 are derivative Markush structures. The 2 derivative Markush structures are not numbered specifically. There are 47 formulation claims, 2 use claims, 94 method of treatment claims and 131 combination claims. Of the 47 formulation claims, 1 independent claim is for a composition comprising an antigen and an imidazopyrimidine compound, 13 dependent claims list the antigens for the claimed composition, 16 dependent claims define the Markush structures or the imidazopyrimidine compounds for the claimed composition, and 13 dependent claims further define the composition itself (i.e., conjugation of imidazopyrimidine compound to the antigen; adsorption onto alum, vaccine and possible second adjuvants). The second independent formulation claim relates to a vaccine comprising an antigen and

	an imidazopyrimidine compound as an adjuvant and 3 dependent claims further define the vaccine composition, including adjuvant system. Of the 2 use claims, 1 is for use of an imidazopyrimidine compound as an adjuvant in a vaccine and the second claim is for use of an imidazopyrimidine compound to enhance immune response in a subject. Of the 94 method of treatment claims, 82 claims relate to method of enhancing immune response with a composition comprising imidazopyrimidine compound and an antigen (wherein specific antigens and imidazopyrimidine compounds along with other adjuvants are claimed), 1 claim relates to method of vaccinating a subject with the claimed composition or vaccine, 1 claim relates to method of treating a disease with the claimed composition or vaccine and 10 claims relate to a method of enhancing immune response by administration of the claimed imidazopyrimidine compounds alone. Apart from the 2 use claims claiming use of imidazopyrimidine compounds as adjuvants and enhancing immune response and 10 method of treatment claims for enhancement of immune response by administration of imidazopyrimidine compounds alone, all the other claims (i.e., n = 131) have been considered as combination claims. With respect to diseases, the application broadly claims method of treatment with claimed compounds/pharmaceutical compositions thereof of various conditions such as proliferative, inflammatory, autoimmune, viral, bacterial and paediatric infections and specifically lists certain diseases, including influenza, HIV, HCV and TB. Therefore, the number of diseases is counted as > 10.
ISR	The ISR, WOSA and IPRP have been published; the USPTO is the ISA. The ISR cites 9 documents, of which 7 are X documents, 1 is a Y document and 1 is an A document. In the ISR, one of the documents listed for novelty (X) was also listed for inventive step (Y). The search strategy has been separately published.
TPO	The TPO cites 7 documents. Of these 7 documents, 3 are used to assail inventive step and 4 are used to assail both novelty and inventive step. Of these 7 documents, 3 are periodicals, 3 are patent documents and 1 is a book. Five additional documents were cited in the TPO. Of these, 1 was a book chapter to support another book chapter itself; 1 patent document each was cited in support of a periodical article and a patent document (i.e., n = 2); and 1 periodical article was cited in support of a patent document. As mentioned earlier, 1 document, i.e., “additional comments”, was also uploaded along with the TPO. “Additional comments” were filed along with the TPO pointing out how the imidazopyrimidine compounds claimed in the composition and method of treatment claims are not novel (previously known compounds) or lack inventive step. Given the commonality of the descriptions of WO2019099564 and this application, 2 patent documents (i.e., WO2012088411 and WO2006033703) were used as common prior art documents for both these TPOs.
Date of Filing of TPO	The TPO was filed on 16.03.2020.

National Phase as of 07.10.2022

Office	Entry Date	National Number	National Status
United States of America	13.05.2020	16763847	Published 10.09.2020
Japan	14.05.2020	2020526547	
Republic of Korea	12.06.2020	1020207016958	Published 22.07.2020
EPO	15.06.2020	2018878690	
China	13.07.2020	201880086316.3	Published 25.08.2020

PART E: Case Summaries: Applications claiming HIV and TB treatments

TPO No.[1]	60
Appl. No.[2]	PCT/US2018/057126: WO/2019/084020
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019084020
Applicants	Gilead Sciences, Inc.
Priority Date	24.10.2017
Details	The application claims treatment of a patient co-infected with a viral disease (HIV or HBV) and tuberculosis with a combination of tenofovir alafenamide fumarate (TAF) and an antimycobacterial agent, more specifically rifampicin.
Claims	The application has 31 claims (2 independent and 29 dependent claims); wherein all 31 are secondary claims. All 31 are also combination, method of treatment and dosage claims. Of the 31 claims, 3 are specifically for formulation. All the claims are for method of treatment for treating a patient with a viral condition (HIV or HBV) co-infected with TB with a combination of TAF and an anti-mycobacterial agent, more specifically rifampicin. One of the independent claims is for a combination of TAF and anti-mycobacterial agent. The second independent claim is for a combination of TAF, bictegravir and emtricitabine in combination with rifampicin. The 3 formulation claims are the method of treatment claims claiming treatment with a single tablet; of these, 2 claims also refer to the doses of the therapeutic agents. Both the independent claims refer to the dosage and/or dose and therefore, all 31 claims are counted as dosage claims too. Of these dosage claims, the 2 formulation claims specifically refer to the doses. Thirteen method of treatment claims characterise the pharmacokinetic parameters, i.e., TAF and TFV exposure.
ISR	The ISR comprises 5 documents. One of them is listed to describe only the general state of the art and not considered to be of particular relevance (A) and 4 of them are listed as Y documents, wherein the claimed invention cannot be considered to involve an inventive step when the said document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
TPO	The TPO was filed on 24.02.2020 and comprises 7 prior art documents. Of the 7 documents, 1 is a patent application, 5 are periodical articles and 1 is an “other” prior art document. Also, 1 document was used only for novelty, 1 was used for both novelty and inventive step and 5 documents were used only for inventive step. In the TPO, the 1 "other" prior art document used is a report of a conference proceeding. An additional document was uploaded to establish the date of the report. The US Department of Health and Human Services (DHHS) guidelines are referred to as a supporting document. However, it was not uploaded. The 1 document used to assail only novelty is a PX document, a report of a conference proceeding.
Date of Filing of TPO	The TPO was filed on 24.02.2020.
National Phase as of 07.10.2022[3]	

Office	Entry Date	National Number	National Status
EPO	25.05.2020	2018800413	Withdrawn 19.12.2020

[1] TPO No. refers to publisher’s internal reference number

[2] Appl. No. provides information on the International Application No. and the Publication Number

[3] National phase as of 07.10.2022 reflects information provided on WIPO’s patentscope database as at that date. However, this data is dynamic and may not provide accurate information on the actual status of the patent application.

PART F: Case Summaries: Applications claiming HIV and HCV treatments

TPO No.[1]	28
Appl. No.[2]	PCT/US2018/024288: WO2018183171
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018183171
Applicants	Bristol-Myers Squibb Company
Priority Date	27.03.2017
Details	The compounds in the application are substituted isoquinoline derivatives as immunomodulators, used for the treatment of cancer and infectious diseases, HIV, HCV, etc. The compounds are inhibitors of protein PD-1 and PD-L1 and CD80/PD-L1 protein interactions.
Claims	There are a total of 15 claims, of which 1 has a Markush structure, while there are 5 specific compounds claimed. One specific compound has been listed twice, as two of its isomeric forms have also been claimed. Fourteen claims are dependent on one claim. There is one formulation claim and 9 method of treatment claims, 2 of which overlap with the 2 combination claims.
ISR	The ISR/WOSA/IPRP were published, with the European Patent Office, Rijswijk, Netherlands, being the ISA. Two prior art documents were listed in the ISR – one document that affected the novelty of the application and the same document was also listed as a general document.
TPO	The TPO contained both the ISR documents and 1 additional document – totalling 3 prior art documents, 2 of which would affect the novelty and inventive step, whereas 1 prior art document was used that affects the inventive step claimed in the application. The 3 prior art documents used were prior patent applications.
Date of Filing of TPO	The TPO was filed on 29.07.2019.
National Phase as of 07.10.2022[3]	

Office	Entry Date	National Number	National Status
Japan	26.09.2019	2019553088	
China	27.09.2019	201880022254.X	Published 15.11.2019
United States of America	17.09.2019	16499009	Published 11.06.2020 Granted 29.06.2021
Republic of Korea	23.10.2019	1020197031232	Published 03.12.2019
EPO	28.10.2019	2018716873	

1 TPO No. refers to publisher's internal reference number

2 Appl. No. provides information on the International Application No. and the Publication Number

3 National phase as of 07.10.2022 reflects information provided on WIPO's patentscope database as at that date. However, this data is dynamic and may not provide accurate information on the actual status of the patent application.

TPO No.	30
Appl. No.	PCT/US2018/027969: WO2018195075
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018195075
Applicants	Aquinnah Pharmaceuticals, Inc.
Priority Date	19.04.2017
Details	The application makes claims of compounds, compositions used for modulation of TDP-43 inclusion formation and stress granules in cells, used in the treatment of HIV, HCV and other diseases such as neurogenerative, musculoskeletal, ophthalmological diseases or disorders, cancer, etc.
Claims	The application has 51 claims, of which 1 is an independent claim and 50 are dependent claims. The application claims a patent on 4 Markush structures (1 main formula and 3 derived from the main Markush) and 22 specific compounds. There are 23 secondary claims, all of which are for formulation; 22 claims are also for use of the compounds. The secondary claims are also characterised by the mechanism of action, that is, modulation of TDP-43 inclusion formation and stress granules.
ISR	The ISR/WOSA/IPRP were published, with USPTO being the ISA. There were 4 documents listed in the ISR, of which 3 were general documents and 1 was a document affecting the novelty – though published after the priority date of the application, but before the filing date.
TPO	The TPO used only 1 of the ISR documents and added another 3 documents as prior art challenging the inventive step and the novelty claims in the application. One document was used only for inventive step and 3 documents were used for both novelty and inventive step challenges. All 4 documents used as prior art were patent documents.
Date of Filing of TPO	The TPO was filed on 19.08.2019.
National Phase as of 07.10.2022	No national phase entries

TPO No.	32
Appl. No.	PCT/IB2018/052936: WO2018198084
Link to Appl.	https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018198084
Applicants	Lupin Limited
Priority Date	27.04.2017
Details	The application claims cyclic di-nucleotide compounds with tricyclic nucleobases, their tautomeric forms, stereoisomers, pharmaceutically acceptable salts, and their combination with suitable medicament, by the use of STING modulators, for the treatment of HIV, HCV and cancer, among other diseases.
Claims	There are 25 claims, which consist of 2 independent claims and 23 dependent claims. The application contains 3 Markush structures and about 30 specific compounds. The application claims the salt forms, the tautomeric, stereoisomeric forms, and its pharmaceutically accepted hydrate, solvate, or its prodrug. There are about 12 secondary claims, of which 4 are claims for formulations, 2 claims are for the use of the compounds, and 6 claims are for method of treatment. There are 3 claims for the combination of the compounds, and all 3 are drafted as composition claims – thus overlapping with the formulation claims.
ISR	The ISR/WOSA/IPRP were published, with the European Patent Office, Rijswijk, Netherlands, being the ISA. The ISR quoted 4 prior art documents, of which 3 were general documents and 1 was a document affecting novelty of the application, though it was published after the priority date but prior to the filing date of the application. The document affecting the novelty of the claims in the application was also listed as a general document.
TPO	The TPO used 1 of the ISR documents and 3 additional documents that would affect the inventive step and the novelty of the application. The document used after the priority date would affect both novelty and inventive step. The TPO used 1 periodical article and 3 patent documents as prior art documents to challenge the claims in the application.
Date of Filing of TPO	The TPO was filed on 27.08.2019.
National Phase as of 07.10.2022	No national phase entries

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<tr><td>Appl. No.</td><td>PCT/US2018/052180: WO2019060692</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019060692</td></tr>
<tr><td>Applicants</td><td>Chimerix, Inc.</td></tr>
<tr><td>Priority Date</td><td>21.09.2017</td></tr>
<tr><td>Details</td><td>The application claims crystalline hemihydrate forms of an antiviral compound which is claimed for antiviral infections, including norovirus, HIV and HCV. The claimed compound appears to be a derivative, a CMX-521, which is presently being developed for treatment of norovirus. It is a secondary application, and no mechanism of action has been disclosed. Crystallisation conditions using water activity as a parameter have been claimed. It may be noted that as per Adis Insight, CMX-521 is tagged as DNA-directed RNA polymerase modulators, nucleoside reverse transcriptase inhibitors and polymerase inhibitors.</td></tr>
<tr><td>Claims</td><td>The application has 43 secondary claims, of which 15 are independent claims and 28 are dependent claims. There are 2 formulation claims, 21 claims of the crystalline form of the compounds (1 of which is a claim of the hemihydrate form of compound A, and 6 are claims of forms of compounds B to G), 4 claims for the use of the compounds and 3 claims for method of treatment. There are 13 process claims too in the application.</td></tr>
<tr><td>ISR</td><td>The ISR/WOSA/IPRP were published, with the European Patent Office, Rijswijk, Netherlands, being the ISA. The ISR has only 1 document against the novelty claims of the application.</td></tr>
<tr><td>TPO</td><td>The TPO used 3 prior art documents, none from the ISR. Two of the documents in the prior art were for inventive step and one was for both inventive step and novelty. Two of the documents used in the TPO were periodical articles and 1 was a book.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 21.01.2020.</td></tr>
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<tr><td>Appl. No.</td><td>PCT/CN2018/106983: WO2019057158</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019057158</td></tr>
<tr><td>Applicants</td><td>Jiangsu Hengrui Medicine Co., Ltd and Shanghai Hengrui Pharmaceutical Co., Ltd</td></tr>
<tr><td>Priority Date</td><td>22.09.2017</td></tr>
<tr><td>Details</td><td>The application claims compounds and pharmaceutical compositions containing fused heteroaryl derivatives acting as TLR-7 agonists for the treatment of many viral diseases, HIV, HCV, HPV, HBV, SARS, Zika virus, cancer, etc.</td></tr>
<tr><td>Claims</td><td>The application has 26 claims, 2 independent and 24 dependent. The claims contain 10 Markush structures, with 8 specific compounds, and 9 secondary claims. The tautomer, racemate, enantiomer, diastereomer or mixtures of the compounds are also claimed. One claim is for a formulation, 5 are for the use of the compounds, and 3 are other claims for process.</td></tr>
<tr><td>ISR</td><td>The ISR/WOSA/IPRP were published, with the China State Intellectual Property Office being the ISA. The ISR has 6 prior art documents, 2 of which are against the novelty, and 4 are general documents against claims of the application.</td></tr>
<tr><td>TPO</td><td>The TPO annexed only 1 document, not from the ISR. The TPO, however, refers to 2 documents of the ISR (1 general and 1 novelty-challenging document) in the note. The TPO referred to only 1 periodical document, but along with it, filed an additional periodical document. The prior art was against the novelty and inventive step claims of the application.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 22.01.2020.</td></tr>
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24.04.2020
Granted
23.08.2022</td></tr>
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<tr><td>Appl. No.</td><td>PCT/US2018/053871: WO2019070643</td></tr>
<tr><td>Link to Appl.</td><td>https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019070643</td></tr>
<tr><td>Applicants</td><td>Bristol-Myers Squibb Company</td></tr>
<tr><td>Priority Date</td><td>03.10.2017</td></tr>
<tr><td>Details</td><td>The application claims macrocyclic peptides which inhibit the PD-1/PD-L1 and PD-L1/CD80 protein/protein interaction, and thus are useful for the amelioration of various diseases, including cancer and infectious diseases, like HIV, HCV, HBV, herpes virus, influenza, etc.</td></tr>
<tr><td>Claims</td><td>There are 16 claims, 1 independent and 15 dependent. One claim has a Markush structure, whereas there are 12 secondary claims. All 12 secondary claims are method of treatment claims, and 4 are claims for combinations.</td></tr>
<tr><td>ISR</td><td>The ISR/WOSA/IPRP were published, with the European Patent Office, Rijswijk, Netherlands, being the ISA. The ISR has only 1 document against the novelty claims of the application.</td></tr>
<tr><td>TPO</td><td>The TPO referred to 2 prior art documents, none from the ISR. One document was against only inventive step and the other was against both novelty and inventive step. One document was a patent document and the other was a book.</td></tr>
<tr><td>Date of Filing of TPO</td><td>The TPO was filed on 03.02.2020.</td></tr>
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<tr><td>United States of America</td><td>03.04.2020</td><td>16753666</td><td>Published 17.09.2020</td></tr>
<tr><td>EPO</td><td>04.05.2020</td><td>2018793327</td><td></td></tr>
<tr><td>Republic of Korea</td><td></td><td>1020207012116</td><td>Published 27.05.2020</td></tr>
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ANNEX 2
Case Studies

Table of Contents

Case Studies: TB drugs

Case Study 1: BVL-GSK098 in combination with ETH/PTO as oral treatment for pulmonary TB

TPO No.:	47
Name of Drug:	BVL-GSK098
Chemical Class:	Amidopiperidine
Molecular Formula:	C12H14F6N2O2
IUPAC Name:	4,4,4-trifluoro-1-(3-(trifluoromethyl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-8-yl) butan-1-one
Name of Target:	Mycobacterial transcriptional regulator
Mechanism of Action:	Booster for anti-TB compounds activated via the EthA pathway
Clinical Trials:	Phase I completed
Application No.:	PCT/EP2018/072143: WO2019034700
Applicants:	GlaxoSmithKline Intellectual Property Development Limited and BioVersys AG
Application Published on:	21.02.2019
Application Filed on:	15.08.2018
Priority Date:	16.08.2017
Summary:	This application relates to compounds of Formula (I) used in therapy of mycobacterial infections, such as tuberculosis.
Keywords:	tuberculosis, GSK, basic molecule, ethionamide booster

Background

A structural analogue of isoniazid (used in the treatment of TB), called ethionamide, is used for the treatment of multidrug-resistant TB. It belongs to a class of organic compounds known as pyridines and its derivatives. These compounds contain the pyridine ring, which is a six-membered aromatic heterocycle that consists of one nitrogen and five carbon atoms. The alternate parent compounds of this class of drugs are thioamides, heteroaromatic compounds, etc.

Spiro-heterocycles are prevalent in plants and animal domains and have been used extensively in the pharmaceutical industry and organic chemistry. Among the heterocycles, the isoxazoles have a broad biological spectrum, including antibacterial, anti-cancer, etc., and therefore are used in medicines. Spiro isoxazoline compounds are also useful in the treatment of TB. It is important to note that introduction of fluorine atoms in biologically active molecules is known to dramatically modify several parameters, such as acidity, basicity, delivering its drug-like properties, lipophilicity, metabolic stability and bioavailability of molecules. Thus, fluorine atoms are used in pharmaceutical science.

Patent application WO2019034700 (WO'700)

This application claims a patent for a compound called BVL-GSK098 in combination with ethionamide (ETH)/ prothionamide (PTO) as an oral treatment for tuberculosis. The compound BVL-GSK098 interferes with the system that controls the gene activity in the TB bacteria, and thus helps in boosting the impact of ETH, thereby also allowing for a reduction in the dose of ETH. The compound consists of a structure that is a spiroisoxazoline fused to a piperidine ring via a single carbon, and the nitrogen of the piperidine ring is attached to a carbonyl group which is further substituted with a fluorine group, and discloses an increase in ethionamide activity against TB. The application also claims the salt forms of the compound, and use in combination with anti-TB or anti-viral drugs.

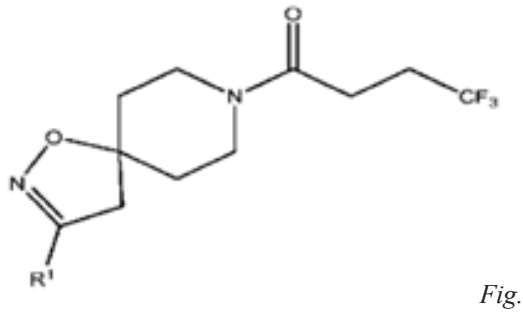

Fig. 1

The claimed compound is used as a transcriptional modulator for boosting ETH and lowering the dose, to overcome MDR-TB infections. The application, WO'700, has about 22 claims for compounds with a spiroisoxazoline scaffold for the treatment of TB.

Importance of the drug

BVL-GSK098 has been developed through an extensive lead optimisation programme with collaborators from the University of Lille. Low doses of the compound fully restore and boost activity of anti-TB drugs to kill *Mycobacterium tuberculosis*, including MDR strains. The drug has the potential in future to be placed in the universal TB treatment regimen, including overcoming MDR-TB with improved safety, time to cure and relapse rates.[19]

The drug has completed GLP toxicology studies and in vitro and in vivo efficacy in animal models against MDR-TB, including overcoming pre-existing resistance mechanisms in *Mycobacterium tuberculosis* by employing bioactivation pathways for ETH. It has completed Phase I trials in humans. The development of this drug is being supported by the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) through a grant of 6.92 million euros.[20] It was previously financially supported by the Wellcome Trust, and since May 2019 has been supported by the IMI2 JU.

In 2019, the US FDA gave a Qualified Infectious Disease Product (QIDP) designation to this compound in fixed combination with ETH for treatment of pulmonary TB.[21] This makes the drug eligible for FDA priority review, fast-track designation and a five-year extension of market exclusivity upon approval.[22] The World Health Organization also considers ETH important in TB treatment, especially for MDR-TB.[23]

BioVersys is a private Swiss pharmaceutical company that focuses on small molecules acting on bacterial targets, especially antimicrobial resistance. It is developing BVL-GSK098 under its Transcriptional Regulator Inhibitory Compound (TRIC) platform in collaboration with GlaxoSmithKline (GSK), the Pasteur Institute Lille and a consortium of the University of Lille.

Why was a TPO filed for this application?

A TPO was filed on 16.12.2019 that cited five prior art documents while referring to a total of eight prior art documents. There was a need to file the TPO as the ISR referred to six prior art documents that were cited as general documents of no particular relevance. Unfortunately, the WOSA referred to all the claims (claims 1 to 22) in the application as novel and inventive.

19 "Boosting ethionamide efficacy and lowering the dose with a small molecule transcriptional modulators, to overcoming MDR-TB infection and define new place for Ethionamide in 1st-line TB treatments", app.dimensions.ai

20 TRIC-TB project, available at https://www.imi.europa.eu/projects-results/project-factsheets/tric-tb

21 https://www.imi.europa.eu/news-events/newsroom/regulatory-decision-gives-boost-development-potential-new-tb-drug

22 "BioVersys: First patients dosed in Phase 1 clinical trial on multidrug-resistant tuberculosis infections", available at https://www.swissbiotech.org/listing/bioversys-announces-first-subjects-dosed-in-phase-1-clinical-trial-of-bvl-gsk098-4/

23 https://www.who.int/docstore/gtb/publications/mdrtb/PDF/who.tb.99.260.pdf

Focus on the TPO

The TPO[24] referred to: (1) US2015/0344498 that disclosed spiroisoxazoline compounds for mycobacterial infections. The document disclosed an identical core and substitution patterns to those of compounds claimed in WO'700, with a difference in only one of the substitutions, on compounds that are known to have anti-mycobacterial activity. Thus, the document challenged the novelty and inventive step of the claims of application WO'700. (2) A periodical article – Blondiaux, N. et al. (along with supplementary tables) – disclosed the structure of SMARt-420, the most active compound of the spiroisoxazoline series, its mechanism of action, its substitutions, that could be further explored. The document challenged the novelty and inventive step of the claims of WO'700. Interestingly, this prior art document was disclosed in the ISR, but was also used in the TPO, along with the supplementary material, to show lack of novelty and/or inventive step of the claims in WO'700. (3) Rubin, E.J., a periodical article which discussed the mechanism of action of the SMARt-420 compound and the potential revival of ethionamide. The document challenged the inventive step of WO'700. (4) US2008/0269271 disclosed substituted spiro compounds for producing medicaments as pain relievers. The spiro compounds disclosed in this prior art document are very similar to those claimed in WO'700, with identical core substitution patterns. The document was used to challenge the novelty and inventive step of the claims of WO'700. (5) Three periodical articles were referred to in the citation of Yale, H. (1959) that reviewed the studies and the value of the trifluoromethyl group of compounds as anti-infective and anti-TB too. The TPO also referred to Kumar et al. (2012) and Ramprasad et al. (2016) who explored trifluoromethyldiaminisoquinazoline and the enhanced anti-tubercular activity of trifluoromethyl analogues, respectively. The documents challenged the inventive step of WO'700.

The TPO brought to the fore prior art documents that disclose the isoxazoline ring fused via a single carbon to the piperidine ring, with substitutions on the nitrogen, including the fluorine group substitutions, and the efficient increase in ETH activity on mycobacteria. The prior art discloses the use of such compounds against MDR-TB. It also discloses the spiroisoxazoline compounds to be administered with other antibiotics. Interestingly, the document cited in the ISR and also used in the TPO discloses SMARt-420 spiroisoxazoline compounds, and its combination with ethionamide effective against all ETH-resistant, MDR, XDR (extensively resistant) isolates. The substitution patterns of these compounds have also been revealed in the prior art. Prior art documents showing the use of the trifluoromethyl group and its therapeutic value in anti-infectives, and its use in anti-tubercular studies were also cited in the TPO.

Thus, the TPO analysed that the application lacked novelty and/or inventive step, and does not deserve a patent. The applicants have used known compounds with known and obvious substitution patterns, known processes, known to be useful in therapy and treatment of TB that may be combined with other anti-TB or antibiotic drugs.

National phase

This application has already entered the national phase in many countries, including Australia, Brazil, Canada, China, European Patent Office, Israel, India, Japan, Mexico, Republic of Korea, Russian Federation, Singapore, etc[25] and published in: AU2018317804, CN110997680, SG11202000988R, KR1020200041344, EP3668879, JP2020531575, BR112020003192, US20210032268, IL272562, NZ761518, CO20200001506, CA3072838, CL2020000362, IN202017006478, MXMX/a/2020/001808, TH2001000850, RU2020109677, etc. [26]

Impact of the TPO

The European Patent Office has taken cognisance of the TPO, and has uploaded the prior art used in the TPO. It has also asked the applicants if they would want to comment on the TPO.[27] It is important that the patent offices in other countries too take cognisance of the prior art cited in the TPO while examining the application.

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24 Available at https://patentscope.wipo.int/search/docs2/pct/WO2019034700/pdf/R2vWeEMpXdf6BBWVUCPZDsIPeChSWGjX6gq8LL9LtyJ8A1Nkoo0XxMs1MXSSVR21BvRstjXh1l5681F66MvixHwrq4GrYdP1RjoWFPRbVShKxnnAEqwAytFtwyieA_Db?docId=id00000051743598

25 https://patentscope.wipo.int/search/en/nationalphase.jsf

26 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019034700&tab=FAMILY

27 https://patentscope.wipo.int/search/en/detail.jsf?docId=EP297165592&tab=NATCOLLDOCUMENTS

Conclusion

This drug will enter Phase II clinical trials. It has been largely funded through public funds, and has been developed in collaboration with private parties and a university. The applicants have used compounds that are known and obvious to a person skilled in the art. An application for a patent appears to be unwarranted and should be opposed.

Further, the drug, if found to be safe and efficacious, ought not to be highly priced either, as it has been funded and developed with the help of public institutions that have used public money. Therefore, one needs to not only keep a watch on the progress of the clinical trials on this drug, but also constantly check the national phase status, and oppose patents on this application. Reference could be made to the TPO filed that is listed along with the ISR, WOSA and other documents.

Case Study 2: Q203 – Telacebec and its analogues

TPO Nos.:	2, 20 and 55
Name of Drug:	Telacebec (Q203)[28]
Chemical Class:	Imidazopyridine amide
Molecular Formula:	C29H28ClF3N4O2
IUPAC Name:	6-chloro-2-ethyl-N-(4-(4-(4-(trifluoromethoxy)phenyl)piperidin-1-yl)benzyl) imidazo[1,2-a]pyridine-3-carboxamide
Name of Target:	qcrB subunit of the cytochrome bc1 complex
Mechanism of Action:	Depletion of adenosine triphosphate (ATP) synthesis of *M. tuberculosis*
Clinical Trials:	Phase II[29]
Importance of Drug:	Pipeline MDR-TB drug, with promising results in Phase I and II clinical trials that were completed by September 2019[30]
Summary:	Drug Q203 for treatment of MDR-TB, and its use in combination with other anti-TB drugs
Keywords:	tuberculosis, Nanyang University, Janssen Sc., Quretech, Qurient, Q203, telacebec

Applications linked to this drug for which TPOs were filed

Application No.	*Applicants*	*Application Published on*	*Application Filed on*	*Priority Date*
PCT/SG2017/050553: WO2018084809	Nanyang Technological University, Schweizerisches Tropen- und Public Health-Institut and Universitat Basel Vizerektorat Forschung	11.05.2018	02.11.2017	02.11.2016
PCT/EP2018/054860: WO2018158280	Janssen Sciences Ireland UC	07.09.2018	28.02.2018	01.03.2017
PCT/EP2018/077222: WO2019068910	Quretech Bio and Washington University in St. Louis	11.04.2019	05.10.2018	05.10.2017

Background

After the discovery of streptomycin in 1943, treatment for tuberculosis and prevention of drug resistance required a combination of at least three effective drugs – streptomycin, aminosalicyclic acid and isoniazid. Since then, for many decades further treatment regimens for TB received very little research focus. At the same time, there was a significant increase in the number of MDR strains of *Mycobacterium tuberculosis*, and better drugs are required to treat not only TB but also MDR-TB.

Drug Q203,also called telacebec, developed as an orphan drug, has been tried in Phase I and II trials in humans. The drug target, the qcrB subunit of the cytochrome bc1 complex, is the electron transfer complex capable of energy transduction (prevents the bacterium from multiplying by disrupting its ability to generate energy).[31] The mechanism of action of Q203 in *M. tuberculosis* has been attributed to decreased biosynthesis of intracellular adenosine triphosphate, thereby leading to cell death regardless of the replication status of the bacteria.

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28 See https://www.newtbdrugs.org/pipeline/compound/telacebec-q203

29 Clinical Trial Phase 2: https://clinicaltrials.gov/ct2/show/NCT03563599

30 See https://www.treatmentactiongroup.org/wp-content/uploads/2019/12/pipeline_tb_treatment_lm_final.pdf
Trials are underway for combination of Q203 with other TB drugs. No other drug in the current TB pipeline belongs to this class (ibid).

31 See https://www.newtbdrugs.org/pipeline/clinical

Combinations of pyrazinamide (PZA) and cytochrome bc1 inhibitor, such as Q203, have demonstrated potent activities in reducing TB. It is being tried in combination with other anti-TB drugs too, such as clofazamine, bedaquiline, etc. Trials have shown the activity of Q203 against MDR- and XDR-TB isolates that makes Q203 an important compound for the treatment of MDR- and XDR-TB given in combination with other anti-TB drugs.

Structure and history of Q203

It is interesting to note that the drug has been developed in collaboration with various institutes and has also been licensed to various companies. As seen in the table above, the applications for patents have been filed by different companies.

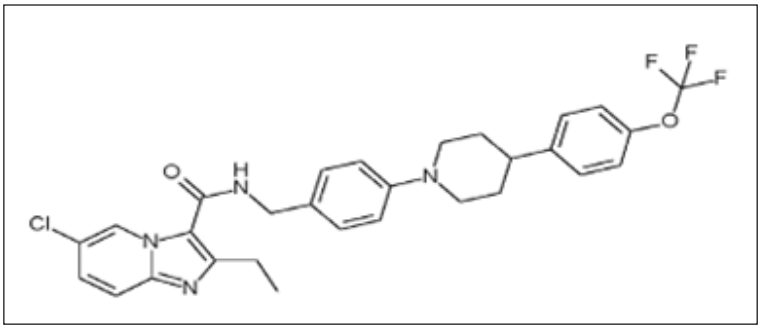

Fig. 1

Timeline of development of Q203

- **2013:** An article written by Kevin Pethe et al., "Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis", was published in *Nature Medicine*. The lead author was from Institut Pasteur Korea, while the other co-authors were from the Novartis Institute of Tropical Diseases, various universities in France, the United States, Singapore and the Republic of Korea, and Qurient. Institut Pasteur Korea licensed Q203 to Qurient Co. Ltd. (Republic of Korea).[32]
- **2014:** Russian biotechnology company Infectex acquired a licence from Qurient Co. Ltd.[33] Infectex conducted successful Phase I trials to assess the safety, tolerability and pharmacokinetics of ascending doses of Q203 in single use in healthy volunteers.[34]
- **2015:** The US FDA designated Q203 for MDR-TB as an orphan drug.[35]
- **2016:** The US FDA approved Phase-Ib study for Q203.
- **May 2018:** Phase I trials for Q203 were completed.[36]
- **July 2018:** Phase II trials were conducted.
- **September 2019:** Phase II trials were completed.[37]

Patent applications have been filed for Q203, its analogues, and for its formulations, combinations, etc. There are several documents, including patent documents such as WO2011113606, WO2012143796 (treatment of inflammation), WO2015014993, WO2017001660 and WO2017001661, that disclose compounds that may be useful in the inhibition of cytochrome bc1 activity. The patent applications are from various companies and countries. However, here we discuss the three applications with regard to the drug Q203 for which TPOs were filed.

Patent applications on Q203

a. Patent application PCT/SG2017/050553: WO2018084809

The application claims method of treating or preventing mycobacterial infections of a large number of mycobacteria deficient for or expressing cytochrome bd oxidase or a disease resulting from such infection. It claims the use of a compound capable of inhibiting cytochrome bc1 of the respiratory electron transport chain in combination with a therapeutic agent capable of inhibiting cytochrome bd oxidase. The application has 16 claims, all of which are secondary claims, i.e., they are all method of treatment claims. Two Markush structures containing an imidazopyridine and animidazothiazole scaffold and 11 specific compounds, including Q203, are claimed. There are also a couple of claims for the combination of the drug with other drugs, and wherein the method kills

[32] See http://www.ip-korea.org/RTV/story.php#none
[33] See http://infectex.ru/en/news/maxwell-biotech-venture-funds-portfolio-company-infectex-acquires-exclusive-rights-to-qurients-tuberculosis-drug-q203/
[34] See https://clinicaltrials.gov/ct2/show/NCT02530710
[35] See http://www.ip-korea.org/community/events_view.php?board=news&seq=2040
[36] See https://clinicaltrials.gov/ct2/show/NCT02858973
[37] See https://clinicaltrials.gov/ct2/show/NCT03563599

the mycobacterium. The application specifically claims four such mycobacteria and three diseases, tuberculosis, leprosy and buruli ulcer. The applicant also includes methods of treatment with combinations of the claimed compounds with an additional therapeutic agent capable of inhibiting cytochrome bd oxidase. It specifically claims a combination with "quinolone compounds, Aurachin, nitric oxide (NO) donors such as PA-824, antibiotics LL-Z1272, Gramicidin S, and derivatives thereof".

Why was a TPO filed for this application?

The ISR had about nine documents; seven documents – five documents and an additional two documents (published after the priority date, but before the filing date) challenged the novelty and inventive step of the compound claimed in the application, and there were two general documents. Interestingly, the WOSA pointed out that because the priority document did not disclose method of treatment with combination, the priority claim was invalid for the combination claims (claims 9 to 16). The WOSA also stated that claims 1 to 16 are directed towards therapeutic methods, which are excluded under the PCT rules, and the patentability of the claims would be dependent on the formulation of the claims in the national phase.

A TPO was filed on 04.03.2019. The TPO referred to 10 documents, two of which were also cited in the ISR. The importance of this drug in the treatment of TB and MDR-TB was one of the main reasons for filing the TPO.

Focus on the TPO

The TPO referred to: (1) WO2011113606 that dislodged the novelty of the claims in the application, as it disclosed anti-infective compounds that were identical or analogues of the compounds claimed in the application. (2) WO2011057145 that disclosed imadozolpyridine compounds for the treatment of tuberculosis and other infections. This citation challenged the novelty and inventive step of the application. (3) WO2017049321 that disclosed some of the compounds in the application. As the WOSA mentioned that the priority date of 02.11.2016 was not available for claims 9 to 16, this prior art had relevance for the determination of novelty. (4 to 10) Kang et al., Pethe, Kevin et al., Forte, Elena et al., Arora et al., Ko & Choi, Ishaque, M. et al., and Scherr, N. et al. were periodical articles cited in the TPO that challenged the novelty and/or inventive step of the claims in the application.

The TPO and the ISR together contain about 17 documents that challenge the novelty and inventive step claims of the application. The prior art documents disclosed not only identical structure, the core of the compounds claimed, but also the substitution patterns that are claimed in the application. The prior art also disclosed the use of the compounds for various mycobacterium diseases, including TB, etc. The structure and properties of the compound Q203 and its role in inhibiting cytochrome bc1 or cytochrome bd complex were disclosed in the prior art. The prior art also disclosed combining the said compound with other antibacterial agents. Thus, the prior art challenges the novelty and inventive step of the claims in the application.

National phase

The application has not entered the national phase in any country yet.

b. Patent application PCT/EP2018/054860: WO2018158280

This application is for a combination therapy for treatment of bacterial and mycobacterial diseases, including those caused by pathogenic bacteria. It primarily is related to tuberculosis, though it broadly claims the combination for treatment of bacterial infections too. It claims combination of the compound Q203 with other anti-TB drugs, such as pyrazinamide, delamanid, rifampicin, isoniazid, clofazimine, bedaquiline, etc.

The application has 16 claims for combination of known anti-TB drugs with Q203. It claims a further combination with other antibacterial agents. The applicant also claims formulation, dosage and process claims. Claims have been made for the use of the compound in treatment and method of treatment too.

Why was a TPO filed for this application?

The WOSA noted that some jurisdictions such as the European Patent Office do not allow patents on the use of the compound in medical treatment, but allow claims on the product. The ISR contained two documents, one of which was the patent document WO2017001660 (WO'660) that brought out the lack of novelty and inventive

step of the application, as it disclosed the use of cytochrome bc1 inhibitors in combination with one or more antibacterial agents, including PZA, bedaquiline, clofazimine, rifampicin, isoniazid, etc. It was felt that the drug is important, and the combinations with other known anti-TB drugs for treatment of TB and MDR-TB would not only be obvious but also known, and that this needed to be brought out through the TPO. Further, the TPO would bring out some additional prior art documents that were not cited in the ISR/WOSA.

Focus on the TPO

The TPO was filed on 01.07.2019, and cited six documents, of which three disclosed the lack of inventive step and three disclosed the lack of novelty and/or inventive step of the claims in the application.[38] The TPO referred to: (1) Zumla et al. that provides the overview to combination therapy for treatment of TB and the WHO recommendations for the same, and describes the treatment regimen with PZA combined with other anti-tubercular drugs, such as bedaquiline, pretomanid, etc. The TPO cited Zumla et al. to challenge the novelty and the inventive step claims of the application. (2) Gualoano et al. that explains that the standard regimen for treating MDR-TB is combination therapy, and thus combining PZA with Q203 and other drugs is neither novel nor inventive. (3) WO'660 that discloses combining pharmaceutical compositions containing cytochrome bc1 inhibitors along with known antibacterial agents, and thus shows that the claims are obvious to a person skilled in the art. (4) Lamprecht et al. that explains energy metabolism targeting combinations for TB, and reports testing antimycobacterial activity of a combination of BDQ, CFZ and Q203. (5) Zhang et al. that explains the synergistic activity of combining drugs like BDQ that cause defects in energy production, with PZA. (6) WO2016073524 that describes combination treatment for TB.

Interestingly, on 12.08.2019, the applicant responded to the TPO stating that though PZA is used in treatment of TB, the combination of PZA and bc inhibitor (Q203) gave an unexpected synergistic effect which could not be predicted in the prior art cited, and that such synergistic results had not been disclosed, and therefore, there was evidence of inventive step. However, the prior art used in the TPO did disclose the synergistic effect, and combinations as stated in the application were not only revealed in the prior art cited but would also be obvious to a person skilled in the art.

National phase

The application has entered into national phase in several countries, including the European Patent Office, India, Japan, Republic of Korea, Philippines, Brazil, etc.[39] As on 25.03.2021, this application was published in these countries as KR1020190121315, EP3589323, VN1201905277, US20200016154, EA201991997, CN110831630, JP2020509040, BR112019017901, PH12019502002, IN201927039062 and UAA201910076.

Impact of the TPO

The European Patent Office listed the TPO and the documents cited in it, along with the ISR documents, and the reply of the applicant to the TPO. Yet, the European Search Report is a duplicate of the ISR, and does not take into account the TPO.[40] It is therefore imperative that some interventions take place in the patent offices where the applications have been filed.

c. Patent application PCT/EP2018/077222: WO2019068910

The application is for a combination of Q203 with anti-TB drugs and antibacterial drugs such as rifampicin, pyrazinamide, ethambutol, bedaquiline, ethionamide, delamanid, pretomanid, etc. for the treatment of TB, and other bacterial infections. The compound is a ring-fused thiazolino 2-pyridones (the compound of Formula II), in combination with anti-TB drug that inhibits the cytochrome b subunit of the bc1 complex (encoded with gene *qcrB*) in *Mycobacterium tuberculosis*.

[38] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018158280&tab=PCTDOCUMENTS&_cid=P21-KMPWC1-60586-1

[39] https://patentscope.wipo.int/search/en/nationalphase.jsf

[40] https://patentscope.wipo.int/search/en/detail.jsf?docId=EP280242201&tab=NATCOLLDOCUMENTS

The application has 46 claims that contain 12 Markush structures, though all 46 are secondary claims. There are about 87 specific compounds that have been claimed. About 38 claims are for the combination of the compounds, one claim is for formulation, one claim is for the salt form, and there are four claims each for use of the combined compounds and method of treatment.

Why was a TPO filed for this application?

The ISR cited three documents, one of which was a novelty-attacking document, that is, WO2014185853 (WO'853); one was dated after the priority date of the application but prior to the filing date, that is, WO2017175182; and one was a general document on design and synthesis of triazole functionalised ring-fused 2-pyridones as antibacterial. The combination of the drug Q203 with other anti-TB drugs is important and therefore it was important to file the TPO.

Focus on the TPO

The TPO was filed on 05.02.2020.[41] It cited three documents, only one of which was already cited in the ISR: (1) Quretech's earlier application, WO'853, for compounds and methods of treatment of Chlamydia infections. It disclosed ring fused thiazolino 2-pyridones that are being used in the present application as anti-infective agents for the treatment of tuberculosis. (2) WO2015014993 disclosed compounds as anti-infective agents, particularly anti-TB. The core and type of substituents reported in this prior art document essentially covered compound Q203, which has been claimed in the present application. (3) Pethe et al. disclosed the structure of Q203 and its mechanism of action of inhibiting cytochrome bc1 to treat TB. The TPO cited each of these documents to urge that the claims of the present application thus lacked novelty and inventive step.

National phase

As on 09.03.2021, the application has been filed in at least five countries, China, Japan, Korea, the EPO and the Russian Federation.[42] As of 26.03.2021, the application has been published in about eight countries as CN111246848, KR1020200066315, EP3691619, US20200316036, JP2020536085, JP2020518682, IN202017015684 and RU2020113346.

Impact of the TPO

The TPO has been listed in the documents at the EPO. However, it is not reflected in the EPO report on the application. The US examination report contained a very detailed analysis of the application, and included the prior publications by the applicant, two of the documents from the TPO and the documents from the ISR. However, it is not clear if the TPO was used by the USPTO for conducting the search. The USPTO has a document which is a "non-final rejection" of most of the claims of the applicant. The Japanese application referred to the ISR, but not the TPO.

Conclusion

The drug Q203 is an important candidate for MDR- and XDR-TB treatment. This drug has entered human clinical trials and has the potential to be a useful therapy against TB, including MDR-TB, among many other mycobacterium diseases. Unfortunately the extent of evergreening patent applications filed on this drug may prevent its generic production and supply for many years. In each of the applications above, the claims were found to lack novelty or inventive step or both. It is imperative that the TPOs be recognised and the patent offices in various countries should take cognisance of them.

41 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019068910&_cid=P21-KMPWED-61345-1
42 https://patentscope.wipo.int/search/en/nationalphase.jsf

Case Study 3: Sanfetrinem cilexetil (GV-118819X)

TPO No.:	34
Name of Drug:	Sanfetrinem cilexetil (GV-118819X)
Other Names:	Sanfetrinem (GV-104326X)
Chemical Class:	Beta-lactam antibiotic
Molecular Formula:	C23 H33 NO8 (sanfetrinemcilexetil)
IUPAC Name:	1-cyclohexyloxycarbonyloxyethyl(1*S*,5*S*,8*aS*,8*bR*)-1-(1*R*)-1-hydroxyethyl-5-methoxy-2-oxo-5,6,7,8,8*a*,8*b*-hexahydro-1*H*-azeto[1,2-b]isoindole-4-carboxylate[43]
Name of Target:	Penicillin binding protein 1a
Mechanism of Action:	Cell wall inhibitor
Clinical Trials:	Phase 2a trials have been planned for 2021[44]
Application No.:	PCT/EP2018/061615: WO2018206466
Applicant:	GlaxoSmithKline Intellectual Property Development Limited
Application Published on:	15.11.2018
Application Filed on:	04.05.2018
Priority Date:	08.05.2017
Summary:	This application claims sanfetrinem cilexetil and its combination with other known anti-TB drugs, beta-lactamase inhibitors and anti-HIV compounds for the treatment of tuberculosis.
Keywords:	sanfetrinem, sanfetrinem cilexetil, GV-104326X, GV-118819X

Background

Sanfetrinem cilexetil is an oral prodrug (hexetil ester prodrug) of sanfetrinem, which is a tricyclic beta-lactam antibiotic developed by GSK in the 1990s.[45,46] Sanfetrinem was identified in a screen of ca. 2,000 beta-lactams for its activity against intracellular *M. tuberculosis* H37Rv.[47] The hexetil portion of the scaffold undergoes rapid hydrolysis by carboxylesterases to a number of products including the parent compound (trinem antibiotic), acetaldehyde and cyclohexanol in vitro and in vivo.[48] Although Phase 2 trials have been conducted for the drug, further development was halted reportedly due to commercial considerations.[49] While plans for a Phase 2a clinical study for its activity against M. tb have been announced, it is unclear whether this study has been launched yet.[50]

43 "Sanfetrinemcilexetil", available at https://pubchem.ncbi.nlm.nih.gov/compound/Sanfetrinem-cilexetil

44 "Sanfetrinem", available at https://www.newtbdrugs.org/pipeline/compound/sanfetrinem

45 "Sanfetrinem", available at https://www.newtbdrugs.org/pipeline/compound/sanfetrinem

46 Access to Medicine Foundation, "Antimicrobial Resistance Benchmark 2020", available at https://accesstomedicinefoundation.org/media/uploads/downloads/5e270aa36821a_Antimicrobial_Resistance_Benchmark_2020.pdf

47 Garcia et al., "Sanfetrinem, repurposing an oral beta-lactam with intracellular activity for the treatment of tuberculosis", TBScience 2019, The Union Conference, 50th Union World Conference on Lung Health Oral Communication, available at https://araid.es/en/content/sanfetrinem-repurposing-oral-beta-lactam-intracellular-activity-treatment-tuberculosis

48 Oliver J, Naidoo A, Vandin L, Pugnaghi F, Gatehouse D and Comelli R, "Carboxylesterases, a key factor in evaluating potential genotoxicity of Trinem antibiotics", *Mutagenesis*, 2000; 15(1): 45-55, doi:10.1093/mutage/15.1.45

49 Ibid.

50 Ibid.

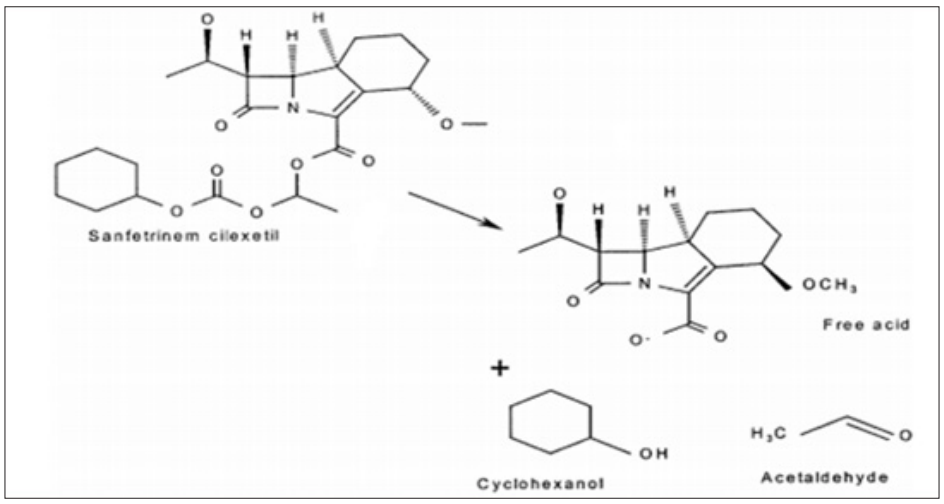

Fig. 1: Conversion of the parent drug to its active form and formation of by-products. Reproduced from Oliver et al., "Carboxylesterases, a key factor in evaluating potential genotoxicity of Trinem antibiotics", Mutagenesis*, 2000; 15(1):45-55, Figure 1, p. 46.*

Chemical Structure

As stated earlier, the parent compound sanfetrinem belongs to the broad family of beta-lactam antibiotics. More specifically, they can be classified as carbapenems, wherein the backbone of carbapenems comprises a beta-lactam ring fused to a five-membered ring (very similar to the penicillin backbone; however, in carbapenem a carbon atom is present at the C1 position instead of a sulphur atom as in penicillin).

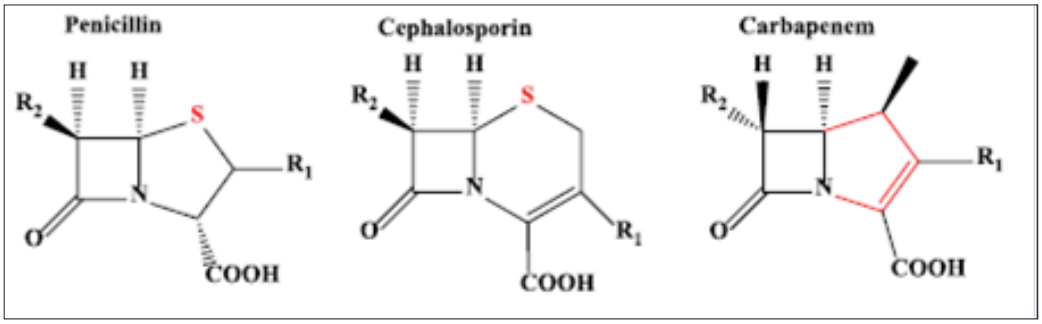

Fig. 2: Basic carbapenem backbone present in sanfetrinem. Reproduced from Papp-Wallace et al., "Carbapenems: past, present, and future", Antimicrobial Agents and Chemotherapy*, 2011; 55(11): 4943-4960, Figure 2(F), p. 4945.*

It is known that carbapenems possess a broad spectrum of activity, are potent against both gram-positive and gram-negative bacteria, and are relatively resistant to hydrolysis by most beta-lactamases. Sanfetrinem is a tricyclic beta-lactam wherein O-CH3 substituted cyclohexyl ring is fused to a known carbapenem backbone (see Fig. 1). As of 2011, sanfetrinem was known to enter phagocyctes and have potential to kill intracellular pathogens.[51] It is to be noted that M. tb is also an intracellular pathogen that thrives inside the phagosome of the host's macrophage.[52]

[51] Papp-Wallace KM, Endimiani A, Taracila MA and Bonomo RA, "Carbapenems: past, present, and future", *Antimicrob. Agents Chemother*., 2011; 55(11): 4943-4960, doi:10.1128/AAC.00296-11

[52] Gengenbacher M and Kaufmann S, "*Mycobacterium tuberculosis*: success through dormancy", *FEMS Microbiology Reviews*, 2012; 36(3): 514-532, doi:10.1111/j.1574-6976.2012.00331.x

Patent application WO2018206466 (WO'466)

WO'466 is an application filed by GSK wherein a known parent compound sanfetrinem, its salt forms (specifically sodium) and its ester prodrugs have been claimed for the treatment of a new indication, i.e., repurposing/revival of an older compound (new use application). The compounds claimed in this application, i.e., sanfetrinem and sanfetrinem cilexetil (hexetil prodrug), both have been disclosed in literature since the 1990s for the treatment of conditions/disorders associated with both gram-positive and -negative bacteria.

Despite the compounds being already known for the treatment of bacterial infections, the applicant claims sanfetrinem, its salt forms (specifically sodium salt) and prodrugs (specifically sanfetrinem cilexetil) for use in the treatment of diseases resulting from mycobacterial infection (specifically M. tb) (claims 1 to 9). Apart from the claims for the parent compound and its forms, the application also claims method of treatment of diseases resulting from mycobacterial infection with these claimed compounds (claims 10 to 18), the use of the claimed compounds in the manufacture of medicament for use in the treatment of tuberculosis, a mycobacterial infection or disease resulting therefrom (claim 19), pharmaceutical compositions comprising the parent compound or its various forms for such use (claim 20) and combination of these compounds with other known anti-TB drugs (one claim specifically for amoxicillin clavulanate), beta-lactamase inhibitors (one claim specifically for clavulanic acid/clavulanate) and anti-HIV compounds (claims 21 to 27).

As detailed below, beta-lactam antibiotics, specifically carbapenems, alone or in combination with known anti-TB agents and beta-lactamase inhibitors, have already been repurposed and explored and its combinations with other agents are known to have synergistic activity for the treatment of tuberculosis. Combination of these compounds with known therapeutic agents is also obvious as combination therapy is the cornerstone for treatment of conditions such as HIV and TB due to the emergence of resistance.

Why was a TPO filed for this application?

The ISR lists one "X" and seven "A" documents. The ISA refers to three of these documents in the WOSA. As per the WOSA, the subject matter disclosed in these documents is not sufficient to assail novelty and/or inventive step for claims 1 to 25.

(i) The ISR lists as an "X" document a patent document, i.e., WO2016046845 (WO'845), which discloses orally administered stealth nanoparticles for the improvement of poorly available therapeutic agents. It claims combination of carbapenem antibiotic (including sanfetrinem) with a beta-lactamase inhibitor (including clavulanic acid). In light of this, the WOSA notes that claims 26 and 27 are not novel.

However, WO'845 also claims a pharmaceutical composition comprising sanfetrinem alone. It also claims pharmaceutical compositions comprising sanfetrinem for the purpose of treating bacterial infections.

(ii) The ISR lists seven documents as "A" documents which define the general state of the art and can be considered as not of particular relevance.

One of these "A" documents cited by the ISA in the WOSA is a periodical article by Wivagg et al., which discloses treatment of tuberculosis with existing beta-lactams alone or in combination with a beta-lactamase inhibitor (meropenem+clavulanate). It also discloses that M. tb possesses a strong and unusual beta-lactamase. It also notes that some degradation-resistant beta-lactams such as carbapenems have had some efficacy against M. tb.

The WOSA indicates that an improved alternate beta-lactam (as the applicant has disclosed that the minimum inhibitory concentration (MIC) of sanfetrinem is lower than other carbapenems when used as monotherapy), its forms alone or as part of combination therapy has been claimed in the present application, which thus involves inventive step.

However, the ISA does not consider that the applicant is merely switching one carbapenem for another and exploring a similar battery of tests to confirm the anti-tuberculosis activity of sanfetrinem, a known carbapenem. Testing an alternative compound having an identical structural backbone for the same activity is obvious to a person skilled in the art. Further, Wivagg et al. also disclose combination therapy with a beta-lactamase inhibitor.

(iii) Another "A" document cited by the ISA in the WOSA is a periodical article by Tamura et al., which discloses that sanfetrinem cilexetil has high stability to many beta-lactamases and states that it has a broad spectrum of activity against gram-positive and -negative bacteria. Mycobacteria are considered gram-positive bacteria structurally, due to the absence of a true outer membrane and presence of a thick layer of peptidoglycan, and also share some characteristics of gram-negative bacteria such as having porins in their outer lipid layer and not retaining Gram stain.[53] Thus, a compound such as sanfetrinem cilexetil proven to have activity against various strains of gram-positive and -negative bacteria and specifically tested for upper respiratory infection would have been explored for tuberculosis by a person skilled in the art.

The WOSA states that improved effectiveness of sanfetrinem as compared with other carbapenems (when used as monotherapy) for treatment of TB could not have been expected. However, the ISA does not appear to acknowledge that sanfetrinem itself is a second-generation carbapenem; its features such as high stability against beta-lactamases of various bacteria, good pharmacokinetic behaviour of sanfetrinem cilexetil in mice and low MIC values (comparable to or lower than other carbapenems; Tables 2 and 3 of Tamura et al.) indicate that this compound, on testing against mycobacterial isolates, may exhibit desired biological effect.

The following patent documents cited by the ISR are not discussed in the WOSA:

(i) The ISR cites two patent documents – EP 2085084 and EP 2135871 – as "A" documents. Both these patent documents disclose Markush scaffolds for both sanfetrinem and sanfetrinem cilexetil and claim these compounds for the treatment of bacterial infections.

(ii) The ISR further cites a patent document, i.e., WO2016128949, which discloses a Markush scaffold having a backbone similar to carbapenem compounds for the treatment of mycobacterial infections.

(iii) The ISR cites a periodical review article by Bush and Macielag, which reviews in general beta-lactam antibiotics and beta-lactamase inhibitors.

(iv) The ISR further cites a periodical article by Braggio et al., which reports the role of intestinal and liver metabolism in converting sanfetrinem cilexetil to its active form. It discloses that such an ester sidechain prodrug was synthesised after an extensive search for a suitable prodrug, and also states that this prodrug had increased oral bioavailability when compared with the parent drug sanfetrinem.

It may be noted that many of these documents bring to the fore the knowledge that the compounds claimed in the present application were already disclosed in prior art for the treatment of bacterial infections, both alone and in combination with beta-lactamase inhibitors. A gap not covered by the documents in the ISR is the combination of such a beta-lactam antibiotic with other known anti-TB and anti-HIV agents. Another shortcoming of the WOSA is not acknowledging the lack of inventive step in claiming use of a known beta-lactam antibiotic for treatment of infections caused by mycobacteria (as repurposing of beta-lactams for treatment of TB is already known).

Focus on the TPO

Eight prior art documents – all of them periodical articles – were referred to in the TPO; one of these periodical articles was already cited in the ISR and WOSA. Of these eight periodical articles, one was used for assailing inventive step and all the others were used for assailing both novelty and inventive step.

(i) The TPO refers to Tamura et al. (1998), which was cited in the ISR and already discussed in the WOSA. As discussed above, even though Tamura et al. disclose the structure of sanfetrinem cilexetil and its activity against gram-positive and -negative bacteria, the WOSA still listed it as an "A" document instead of a "Y" document. The TPO points out that, in light of the disclosures of Tamura et al., claims 1 to 20 of the present application lack novelty and/or inventive step.

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[53] Da Silva PB, Campos DL, Ribeiro CM, da Silva IC and Pavan FR, "New antimycobacterial agents in the pre-clinical phase or beyond: recent advances in patent literature (2001-2016)", *Expert Opinion on Therapeutic Patents*, 2017; 27(3): 269-282, doi: 10.1080/13543776.2017.1253681

(ii) The TPO cites a periodical article by Kurz and Bonomo (2012), which reviewed on all fronts whether beta-lactams and beta-lactamase inhibitors can effectively be used to treat M. tb infection. They detailed the mechanisms by which resistance against beta-lactams occurs and noted that a reduction in mycobacterial burden was seen by a combination of amoxicillin (beta-lactam) and beta-lactamase inhibitors. They also gave a summary of the data of different beta-lactam antibiotics against three clinical strain collections of M. tb that included MDR- and XDR-TB. They observed that different studies showed that the addition of beta-lactamase inhibitors improved the activity of beta-lactams. The TPO points out that, in light of the disclosures of Kurz and Bonomo, claims 1 to 20 (use of a known beta-lactam sanfetrinem for TB), 21 to 23 (combination of beta-lactam with other antibiotics including amoxicillin clavulanate), and 26 and 27 (combination of beta-lactam with beta-lactamase inhibitors) lack novelty and/or inventive step.

(iii) The TPO also cites a periodical article by Dincer et al. (2004), who investigated the in vitro efficacy of various beta-lactam and beta-lactamase inhibitor combinations against M. tb, particularly in MDR clinical isolates. They reported that monotherapy with beta-lactams such as cefepime and meropenem alone, i.e., without the presence of a beta-lactamase inhibitor, has also shown activity against M. tb. They stated that combination of beta-lactam with a beta-lactamase inhibitor could be an alternative choice of treatment and prove a useful method of treatment in developing and low-income countries where waiting out the process of drug discovery and lead optimisation of new molecules is not feasible. The TPO points out that, in light of the disclosures of Dincer et al., claims 1 to 23, 26 and 27 of the present application lack novelty and/or inventive step.

(iv) The TPO cites a periodical article by Diacon et al. (2016), who reported that a combination of a carbapenem such as meropenem with amoxicillin-clavulanic acid resisted hydrolysis by beta-lactamase and showed synergistic anti-tuberculosis activity. They disclosed that due to the long record of safety of beta-lactams in wide-ranging patient populations including those living with HIV, patients with highly resistant TB can be treated with commercially available beta-lactam combinations as a rescue regimen. Diacon et al. also noted that anti-TB agents have to be evaluated for safety and efficacy in combination with other anti-TB and antiretroviral agents. Thus, as Diacon et al. disclosed combination with other anti-TB and anti-HIV agents, the TPO points out that all claims lack novelty and/or inventive step.

(v) The TPO cites a periodical article by Rulas et al. (2015), who reported the development of a dehydropeptidase I (DHP-I) deficient murine model TF3157 which allowed a closer reproduction of human blood pharmacokinetic profiles of beta-lactams in mice. They showed how beta-lactam combinations gave rise to significant and robust reduction in CFU (colony forming units) levels in the lungs of DHP-I deficient mice, with faropenem-medoxomil (faropenem is also a carbapenem like sanfetrinem) having the highest efficacy followed by meropenem. The authors postulated that the murine model developed could be used for the systematic in vivo characterisation of old and novel beta-lactams as antitubercular leads and for selection and eventual inclusion of safe and efficacious beta-lactam drug components in clinical regimens. The applicant in WO2018206466 used the same murine model developed by Rulas et al. and performed in vivo characterisation of sanfetrinem cilexetil and its sodium salt. It is obvious to a person skilled in the art to screen other existing beta-lactams for anti-TB activity using the same DHP-I deficient murine model. The TPO argues that, in light of the disclosures of Rulas et al., claims 1 to 23, 26 and 27 lack novelty and/or inventive step.

(vi) The TPO cites Pagliotto et al. (2016), a periodical article which reported the anti-TB activity of traditional first-line anti-TB drugs in combination with amoxicillin (a beta-lactam) and clavulanate (a beta-lactamase inhibitor) and the synergy shown by such combinations. The TPO also cites a periodical article by Gonzalo and Drobniewski (2013), which also reported on the use of a combination of one or two beta-lactams and a beta-lactamase inhibitor in the treatment of MDR- and XDR-TB and also the synergy exhibited by these combinations. These documents were used to show that a combination of beta-lactam and beta-lactamase inhibitors with or without other proven anti-TB agents had previously exhibited synergistic effect. The TPO points out that the applicant has only changed the beta-lactam in the previously explored combination and explored the synergistic effect of another known sanfetrinem (or its various forms) with other anti-TB agents and beta-lactamase inhibitors, and that this is obvious to a person skilled in the art. Summarily, the TPO points out that in light of the disclosures of Pagliotto et al. and Gonzalo and Drobniewski, claims 1 to 23, 26 and 27 (excluding claims 24 and 25 for combination with anti-HIV agents) lack novelty and/or inventive step.

(vii) The TPO also cites a periodical article by Lowther et al. (1997), which reported combinations of sanfetrinem with antimicrobial agents, including amoxicillin/clavulanate and antivirals/antiretrovirals (e.g., zidovudine, acyclovir). As this document mainly relates to combination of sanfetrinem with other therapeutic compounds (treatment of TB was not disclosed), the TPO pointed out that claims 21 to 25 lack inventive step.

Thus, though the content of the seven documents cited in the ISR was noted by the ISA as not being sufficient to deem lack of novelty and/or inventive step, the TPO by referring to eight prior art periodical documents (one periodical article, i.e., Tamura et al., was cited in both the ISR and the TPO) shows how the applicant has merely claimed new use, i.e., repurposing/revival of older drug, of sanfetrinem (a known beta-lactam and carbapenem), its sodium salt and its known prodrug sanfetrinem cilexetil for treatment of infections caused by mycobacteria (although the drug has already been previously broadly claimed for treatment of bacterial infections) and its combination with other known beta-lactamase inhibitors, anti-TB and anti-HIV agents, and that these claims lack novelty and/or inventive step.

It is hoped that these documents will aid patent offices in their determination of novelty and inventive step of the claims for the known compound sanfetrinem and its forms for treatment of diseases resulting from mycobacterial infections, specifically M. tb.

National phase

As of 07.04.2021, this application has entered the national phase in eight countries/jurisdictions, i.e., Australia, Canada, China, EPO, India, Japan, Republic of Korea and the Russian Federation.

As of 07.04.2021, this application has been published as AU2018265192, CA 3060396, CN201880030277.5, EP2018721053, IN201917045452, JP2019561315, KR1020197032729 and RU2019139864. WIPO Patentscope also lists BR112019023322 and US20200289462 as patent family members.

Impact of the TPO

The European Patent Office has taken cognisance of the TPO and has uploaded the prior art cited in the TPO. The EPO has issued a communication to the applicant enclosing the TPO and informing the applicant that it may comment on it. In the communication from the Examining Division to the applicant, the EPO cites the TPO and states that Lowther et al. cited in the TPO will be taken into account in the proceedings before the Examining Division. It states that the other documents cited in the TPO are not more relevant than documents already on file and do not change the assessment of novelty and inventive step given in the WOSA; nonetheless it refers to Kurz and Bonomo as reaching the same disclosure as Wivagg et al. (an ISR document). Though the Examining Division notes the arguments in the TPO about the disclosures in the other documents cited in the TPO, it states that the skilled person could not have had a reasonable expectation of success and could not have expected an improved effectiveness compared with carbapenems when used as a monotherapy.

During prosecution before the US Patent and Trademark Office in US20200289462, on 14.01.2021, the applicant filed the documents cited in the TPO as part of its Supplemental Information Disclosure Statement; the Applicant stated that their inclusion “should not be construed as an admission that any particular cited document is effective prior art or that it discloses or renders obvious any aspect of the claimed invention”. The USPTO does not appear to have taken note of the TPO. Interestingly, on 08.11.2019, the applicant amended the claims to delete the claims for the compounds and pharmaceutical compositions thereof. The claims under prosecution are all method of treatment claims for treating tuberculosis with sanfetrinem or its prodrug sanfetrinem cilexetil or the sodium salt, either alone or in combination with other anti-tuberculosis agents and antiretroviral agents.

Other patent applications

There are other applications claiming sanfetrinem and its various forms. A few of them are listed below:

(1) WO2009095387 (applicant: Lek Pharmaceuticals D. D.): This application claims a Markush scaffold which discloses sanfetrinem and its various forms (i.e., ester prodrug and salt forms) for the treatment of bacterial infections.[54]
(2) WO2011012715 (applicant: Ascendis Pharma): This application claims biodegradable PEG based hydrogel for sanfetrinem cilexetil among many other drugs.[55]
(3) WO1992003437 (applicant: Glaxo S.P.A): This application claims sanfetrinem cilexetil for the treatment of bacterial infections.[56]
(4) WO1994021637 (applicant: Glaxo S.P.A): This application claims process for preparation of sanfetrinem cilexetil.[57]

[54] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2009095387
[55] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2011012715
[56] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1992003437
[57] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1994021637

Case Study 4: Bictegravir

TPO Nos.:	45, 46
Name of Drug:	Bictegravir
Other Names:	BIC, GS-9883
Chemical Class:	Integrase inhibitors
Molecular Formula:	C21H18F3N3O5
IUPAC Name:	(1*S*,11*R*,13*R*)-5-hydroxy-3,6-dioxo-*N*-[(2,4,6-trifluorophenyl)methyl]-12-oxa-2,9-diazatetracyclo11.2.1.0^{2,11}.0^{4,9}hexadeca-4,7-diene-7-carboxamide
Name of Target:	HIV integrase
Mechanism of Action:	HIV integrase inhibitors plus nucleoside reverse transcriptase inhibitor (NRTI)
Clinical Trials:	Approved drug
Summary:	The applications claim compositions and combination of bictegravir and NRTIs and method of treating and preventing HIV with the claimed combination.
Keywords:	bictegravir, emtricitabine, lamivudine, integrase inhibitors, nucleoside reverse transcriptase inhibitors

Applications linked to this drug for which TPOs were filed:

Application No.	*Applicants*	*Application Published on*	*Application Filed on*	*Priority Date*
WO2019030625	ViiV Healthcare Co.	14.02.2019	02.08.2018	09.08.2017
WO2019030626	ViiV Healthcare Co.	14.02.2019	08.02.2018	09.08.2017

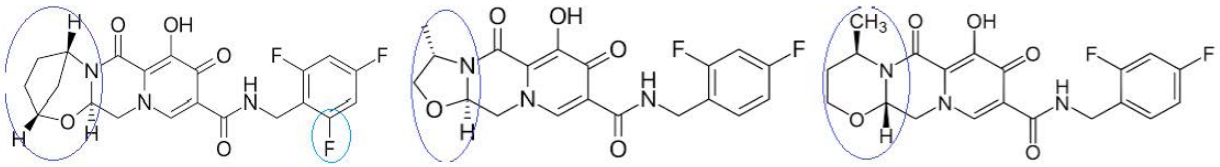
Background

Bictegravir (BIC) is an HIV integrase strand transfer inhibitor (INSTI). BIC is structurally derived from an earlier compound dolutegravir where the oxazine ring of dolutegravir has been replaced with an oxazepine ring in BIC. In vitro and early clinical trial results for BIC were presented in the summer of 2016 at the ASM Microbe conference which was held in Boston, USA (16-20 June). The in vitro antiviral activity of BIC alone and in combination with tenofovir alafenamide, emtricitabine (FTC) and darunavir was also reported.[58]

Chemical structure

BIC is the third integrase inhibitor approved for use belonging to the class of carbamoyl pyridones. The structure of BIC comprises a three-ring fused system; the previously approved compounds belonging to this class, i.e., cabotegravir and dolutegravir, differ only in terms of (i) the terminal ring of the fused ring system (oxazole in the case of cabotegravir and oxazine in the case of dolutegravir; however, these ring systems are all closely associated and contain one oxygen atom) and (ii) the number of fluorine atoms.

[58] Highleyman L, "New integrase inhibitor bictegravir looks promising in early studies", 6 July 2016, NAM aidsmap, available at https://www.aidsmap.com/news/jul-2016/new-integrase-inhibitor-bictegravir-looks-promising-early-studies



Oxazepine ring in bictegravir | Oxazole ring in cabotegravir | Oxazine ring in dolutegravir

Fig. 1: Structural difference between approved integrase inhibitors

Approval and licensing status

As of 2018, bictegravir is available as part of a fixed dose combination under the tradename Biktarvy. Biktarvy tablets (comprising 50 mg BIC + 200 mg FTC + 25 mg tenofovir alfenamide) have been approved for use by the US FDA (February 2018) and the European Medicines Agency (June 2018). The recommended dose is one tablet per day.[59, 60] In September 2017, the Medicines Patent Pool (MPP) signed a licensing agreement with Gilead Sciences for BIC.[61]

Patent litigation

In early 2018, ViiV Healthcare filed patent infringement litigation against Gilead Sciences, Inc. over BIC in the United States and Canada. The United States case relates to US patent No. 8,129,385 and was filed in the US District Court for the District of Delaware. The case before the court is currently pending. The Canadian case related to Canadian patent No. 2,606,282 (primary patent broadly claiming compounds belonging to the class of carbamoyl pyridones and specifically claiming dolutegravir) and was filed in the Canadian Federal Court in Toronto.[62] On 6 April 2020, the Federal Court dismissed ViiV's action, holding that BIC sodium did not fall within the scope of the claims of Canadian patent No. 2,606,282.[63, 64, 65]

Patent applications on bictegravir

While Gilead Sciences, Inc. is marketing the fixed dose combination of BIC, FTC and tenofovir alfenamide, ViiV Healthcare has filed secondary patent applications covering a combination of bictegravir and lamivudine (also known as 3TC, an analogue of FTC; NRTI class).

a. Patent application WO2019030625

WO'625 is a secondary application by ViiV Healthcare and claims method for treating or preventing HIV in a patient using a combination of BIC (INSTI) and 3TC (NRTI) or a pharmaceutical composition thereof as well as compositions comprising these compounds. Apart from method of treatment claims claiming co-administration of the claimed combination in separate and single dosage form (initial 3 claims), WO'625 also claims combination

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59 Biktarvy Label, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf

60 EMA, "Biktarvy (bictegravir / emtricitabine / tenofovir alafenamide): An overview of Biktarvy and why it is authorised in the EU", EMA/277223/2018, EMEA/H/C/004449, available at https://www.ema.europa.eu/en/documents/overview/biktarvy-epar-medicine-overview_en.pdf

61 Medicines Patent Pool, "Bictegravir", available at https://medicinespatentpool.org/licence-post/bictegravir-bic/

62 GSK Press Release, "ViiV Healthcare files patent infringement litigation against Gilead Sciences Inc. over bictegravir", 7 February 2018, available at https://www.gsk.com/en-gb/media/press-releases/viiv-healthcare-files-patent-infringement-litigation-against-gilead-sciences-inc-over-bictegravir/

63 Frontini M, "Federal Court Resolves Patent Infringement Action By Summary Trial", 22 April 2020, available at https://www.dww.com/articles/federal-court-resolves-patent-infringement-action-by-summary-trial

64 Berenbaum A, "Federal Court dismisses ViiV's action for patent infringement re: Gilead's BIKTARVY following summary trial on claim construction", 10 May 2020, available at https://www.jdsupra.com/legalnews/federal-court-dismisses-viiv-s-action-60975/

65 *ViiV Healthcare Company v. Gilead Sciences Canada, Inc.*, 2020 FC 486, available at https://decisions.fct-cf.gc.ca/fc-cf/decisions/en/item/468790/index.do

of the two drugs (and their salt forms) (claim 8), pharmaceutical composition comprising the two compounds (or their salts) and specific doses of the compounds (75 mg of BIC and 300 mg of 3TC) (claims 4, 5, 9) and also kit for co-administration (claims 6,7). Thus, essentially the application claims the combination of these two drugs and their salt forms. However, both the drugs claimed in this application, i.e., BIC and 3TC, are already known drugs. Also, the United States Department of Health and Human Services (DHHS) guidelines for use of antiretroviral agents in HIV-1 infected adults and adolescents (available online on 14 July 2016, i.e., before the priority date of WO'625) recommend that antiretroviral agents are to be given as part of combination therapy and specifically advise use of two NRTIs with an INSTI to prevent resistance issues.[66]

Why was a TPO filed for this application?

The ISR of WO'625 lists two documents – a patent document WO2004089382 and a periodical article (Sax et al. (2017)) – as Y documents and the WOSA issued by the ISA opines that the claimed invention cannot be considered to involve an inventive step. The WOSA opines that all the claims possess novelty. Now, one of these two documents (Sax et al. (2017)) reports findings for clinical trials conducted for a combination regime of BIC administered with tenofovir alafenamide fumarate and FTC. Given the minor difference in the structures of FTC and 3TC (FTC has a fluorine atom on the cytidine nucleobase) and the common general knowledge that an INSTI is expected to be administered in combination with an NRTI, the novelty aspect could also have been covered. The ISR also lists a patent document by ViiV itself – WO2018051250 – as a PX document, i.e., the claimed invention cannot be considered to have novelty or inventive step in light of this document, which was published after the priority date but before the international filing date of the application, thus making it relevant only in countries where the law considers such documents to be state of the art. This PX document claims a triple combination of BIC, tenofovir alafenamide and 3TC (the present application differs only in the absence of tenofovir alafenamide in the combination claimed). Thus a search was conducted to check whether the claims of WO'625 could be assailed on the ground of novelty too, apart from the PX document.

Focus on the TPO

The TPO cites a patent document and three periodical articles as prior art. The patent document was cited to point out the lack of novelty of the claims and the periodical articles were cited to point out the lack of inventive step of the claims. One of the periodical articles was also cited in the ISR.

The patent document cited as prior art – WO2014100323 – is the primary patent application which specifically claims the structure of BIC and discloses that BIC can be administered in combination with known NRTIs such as 3TC and FTC. It also discloses pharmaceutical compositions containing such a combination and dosage form. It further discloses the range in which BIC can be present in a composition. In light of WO'323, the TPO points out that claims 1 to 5 and 8 to 11 of WO'625 too lacked novelty and/or inventive step (the ISR and WOSA only cover inventive step for these claims).

The TPO cites three periodical articles to point out the lack of inventive step in the combination claimed. Ford et al. (2017) disclose that FTC and 3TC are interchangeable clinically and can be substituted for each other. Tsiang et al. (2016) disclose that synergy was found for a two-drug combination of BIC and FTC. Sax et al. report that they searched for previous evidence of clinical trials involving BIC, dolutegravir and 3TC and then proceeded to conduct trials with BIC and a fixed dose combination of tenofovir alafenamide and FTC (again shows interchangeability of FTC and 3TC). The TPO points out that on the basis of the disclosures of these documents – combination of BIC and FTC and the interchangeability of FTC and 3TC – the claims for combination of BIC and 3TC lack inventive step (claims 1 to 11).

It may also be noted that though the WOSA issued by the ISA cites Sax et al. (Y document in the ISR) who disclose combination of BIC and FTC, it does not note the similarity in chemical structure and efficacy between FTC and 3TC. Again, the ISR and WOSA fail to note that synergism had already been found for dual combination of these drugs, i.e., BIC and FTC (Tsiang et al. (2016), not listed in the ISR). The WOSA also fails to note that WO'323 – the primary patent application on bictegravir – broadly discloses the subject matter claimed in WO'625.

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66 US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (last updated 14 July 2016), available at https://web.archive.org/web/20191201140941/https://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL003464.pdf

National phase

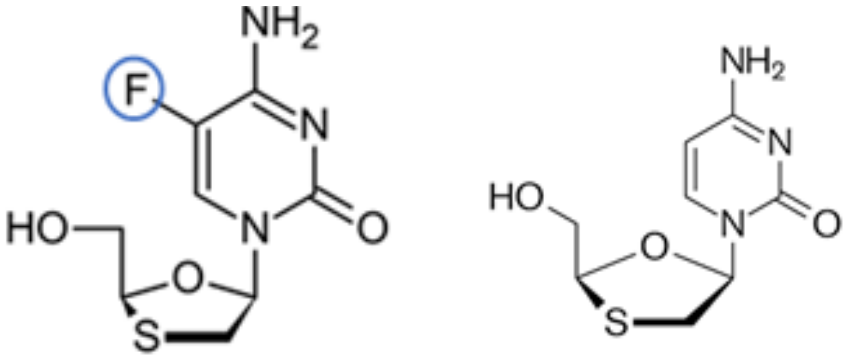
As of 7 April 2021, this application has entered the national phase in at least two countries/jurisdictions, i.e., European Patent Office and Japan.

WO'625 has been published as EP2018844317 and JP2020507085. While not listed as a national phase entry, WIPO Patentscope lists US20200246351 as a patent family member.

b. Patent application WO2019030626

WO'626 is also a secondary application by ViiV Healthcare and claims methods for treating or preventing HIV in a patient by administering BIC and FTC or their pharmaceutical compositions. This application too claims such method of treatment by co-administration in separate dosage forms or a single dosage form (claims 2 and 3), combination of the two drugs (and their salt forms) (claim 8), pharmaceutical composition comprising the combination of two compounds (or their salts) and specific doses of the compound (75 mg of BIC and 200 or 300 mg of FTC) (claims 4, 5) and also kit for co-administration (claims 6, 7).

It may be noted that the claims of WO'626 and WO'625 follow an identical template and claim a combination of BIC with a known NRTI. The only difference is that the NRTI claimed in WO'625 is 3TC and that claimed in WO'626 is FTC. However, it should be noted that FTC is also a known drug. The only structural difference between 3TC and FTC is the presence of a fluorine atom on the cytidine nucleobase in FTC. Given that antiretroviral therapy is routinely administered in combination to treat HIV, it was clear that patents granted to these applications – WO'625 and WO'626, which claim a combination of HIV INSTI with an NRTI – would pose barriers to access to medicines. Therefore, a need to file TPOs was felt.



1. Emtricitabine (FTC)
2. Lamivudine (3TC)

Fig. 2: Structural difference between emtricitabine and lamivudine

Why was a TPO filed for this application?

The ISR of WO'626 lists three documents – the same documents listed in the ISR of WO'625 and one additional patent document – as Y documents; the periodical article (Sax et al.) is also listed as an X document. The ISR of WO'626 also lists the same PX document listed in the ISR of WO'625 – WO2018051250. The WOSA issued by the ISA rightly opines that there is no inventive step involved in the claims of WO'626. However, even in light of Sax et al. (XY document in the ISR, which discloses treatment of HIV with a combination of BIC, tenofovir alafenamide and FTC), the WOSA opines that only claims 1 (method of treating HIV with BIC (or its pharmaceutical composition) and FTC (or its pharmaceutical composition)), 8 (combination of BIC or its salt and FTC or its salt) and 10 (composition, kit or combination for use in therapy) lack novelty. The WOSA opines that claims 2 to 7 and 9, which claim method of treatment in single and separate dosage forms, pharmaceutical composition containing specific doses of the drugs and kits for co-administration with the two agents, are novel. However, when method of treatment with these two agents is already known (in light of Sax et al), claims to the pharmaceutical composition and dosage form should not have been considered novel, as these drugs were already available individually as tablets (as administered in Sax et al.) and the concept of designing a dosage form is an essential part of formulation development and is routinely done. Thus, it was felt that in this application, all the claims lacked novelty in light of the X document.

Focus on the TPO

The TPO cites as prior art two patent documents and three periodical articles which were used to point out lack of both novelty and inventive step of the claims. One of the periodical articles was also cited in the ISR.

As this patent application, i.e., WO'626, differs from WO'625 only in terms of the NRTI being claimed in the combination with BIC, i.e., FTC instead of 3TC, three of the four prior art documents used in the TPO for WO'625 were also cited here. As these documents directly reveal combination of BIC and FTC, the fourth prior art document used for WO'625, i.e., Ford et al. (2017) (showing interchangeability of FTC and 3TC), was not included in this TPO.

Apart from these, two other documents – a patent document WO20170833304 and a periodical article by Hentig et al. (2017) – are also cited in the TPO for WO'626. Both these documents disclose a combination of BIC, tenofovir alafenamide and FTC for the purpose of treating HIV. WO'304 also discloses specific doses of BIC and FTC in the combination, type of pharmaceutical composition (e.g., single or multi-layer tablet) and kit containing claimed combination. As a three-drug regimen was found to be effective, it is also obvious for a person skilled in the art to test for a two-drug regimen. The WOSA issued by the ISA fails to take into account the disclosures of these prior documents, which reveal the same three-drug combination as Sax et al. and also disclose kits and pharmaceutical compositions, and specific doses of both drugs in the claimed combination of WO'626. The WOSA also fails to note that WO'323 broadly claims combination of BIC with known NRTIs and does not list Tsiang et al., which reports synergism for a combination of BIC and FTC. On the basis of these prior art documents, the TPO points out that claims for specific dose, dosage forms, pharmaceutical compositions and kits for the claimed combination also lack novelty.

National phase

As of 7 April 2021, this application has entered the national phase in at least two countries/jurisdictions, i.e., European Patent Office and Japan.

WO'626 has been published as EP2018843567 and JP2020506979. While not listed as a national phase entry, WIPO Patentscope lists US20200171039 as a patent family member.

Other secondary applications

Several other secondary applications have been filed on BIC by Gilead Sciences, Inc. and other companies. A TPO has also been filed for WO2019084020 (TPO No. 60; applicant: Gilead Sciences, Inc.), which claims administration of tenofovir alafenamide fumarate or combinations with TAF, including a three-drug combination of TAF, BIC and FTC twice daily, with an anti-mycobacterial agent for treatment of TB co-infection along with HIV; and WO2019144015 (TPO No. 66; applicant: Gilead Sciences, Inc.), which claims metabolites of BIC. The list below does not cover all the secondary applications on BIC. However, it does give an indication as to how secondary patents are being used to extend the monopoly of a clinically effective drug. The primary patent application of 2014 itself broadly covers polymorphs and combination therapy. However, even six years after the publication of the primary patent, applications are still being filed by the originator, Gilead Sciences, Inc., as well as other companies claiming synthesis of more stable polymorphs or solid forms having improved physicochemical properties. However, such studies are routinely conducted in the process of drug discovery or in the course of formulation development to check for issues relating to shelf life and toxicity.

- WO2015196137 (applicant: Gilead Sciences, Inc.): Claims crystalline forms (Forms I-VIII) of BIC [67]
- WO2017083304 (applicant: Gilead Sciences, Inc.): Claims pharmaceutical compositions of combination of BIC, TAF and FTC[68]
- WO2018005328 (applicant: Concert Pharmaceuticals, Inc.): Claims deuterated forms of BIC and pharmaceutically acceptable salts thereof[69]
- WO2018051250 (applicant: ViiV Healthcare Company): Claims combination of BIC, TAF and 3TC[70]

67 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015196137
68 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2017083304
69 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018005328
70 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018051250

- WO2019144015 (applicant: Gilead Sciences, Inc.): Claims metabolites of BIC, including compositions and salts thereof, which are useful in the prevention and/or treatment of HIV as well as analytical methods related to the administration of bictegravir (a TPO has been filed for this application)[71]
- WO2019154634 (applicant: Sandoz AG): Claims crystalline and solvate form of BIC sodium (a TPO has been filed for this application)[72]
- WO2019207602 (applicant: Mylan Laboratories Limited): Claims crystalline forms of BIC, amorphous BIC sodium, amorphous solid dispersion of BIC sodium with pharmaceutically acceptable carrier and processes for the preparation thereof[73]
- WO2020061163 (applicant: Gilead Sciences, Inc.): Claims method of preventing or treating HIV using a combination of BIC, either alone or in combination with one to three additional agents, including tenofovir alfenamide hemifumarate and FTC.[74]

Case Study 5: Rovafovir Etalafenamide (GS 9131)

TPO No.:	43
Name of Drug:	ethyl ((S)-((((2R,5R)-5-(6-amino-9H-purin-9-yl)-4-fluoro-2,5-dihydrofuran-2-yl)oxy)methyl)(phenoxy)phosphoryl)-L-alaninate; GS-9131; rovafoviretalafenamide
Chemical Class:	reverse transcriptase inhibitor
Molecular Formula:	C21H24FN6O6P
IUPAC Name:	ethyl (2S)-2-[[[(2R,5R)-5-(6-aminopurin-9-yl)-4-fluoro-2,5-dihydrofuran-2-yl]oxymethyl-phenoxyphosphoryl]amino]propanoate
Name of Target:	HIV nucleoside reverse transcriptase
Mechanism of Action:	Inhibition of HIV nucleoside reverse transcriptase
Clinical Trials:	Phase II trials (at the time of filing TPO); subsequently terminated
Application No.:	PCT/US2018/044415: WO2019027920
Applicant:	Gilead Sciences, Inc.
Application Published on:	07.02.2019
Application Filed on:	30.07.2018
Priority Date:	01.08.2017
Summary:	The application is a secondary application for two crystalline forms and amorphous forms of GS-9131 and the crystalline forms of two salts (phosphate salt and xinafoate salt) and of phosphate acetonitrile solvate.
Keywords:	NRTI, GS-9131, rovafoviretalafenamide

Background

WO 2019/027920 is a secondary application by Gilead Sciences, Inc., a pharmaceutical company for GS-9131, a nucleoside reverse transcriptase inhibitor (NRTI). NRTIs form the backbone of first-line antiretroviral treatment for people living with HIV with tenofovir forming part of the WHO's first-line recommended regimen.[75]

Clinical trials

At the time of filing the TPO, GS-9131 (a prodrug of GS-9148) was in Phase II clinical trials for the treatment of HIV which had commenced in or around 2018. Subsequently, it appears that Gilead Sciences, Inc. has terminated the Phase II trial in HIV-1 treatment-experienced patients "in Zimbabwe and Uganda and Zimbabwe due to failure of meeting targeted antiviral response".[76]

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71 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019144015
72 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019154634
73 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019207602
74 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020061163
75 See for e.g. WHO Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (2nd edition 2016), available at https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1 (last accessed on 26 September 2020).
76 https://adisinsight.springer.com/drugs/800016343 (last accessed on 25 September 2020)

Importance of drug

If approved, GS-9131 would be another addition to the class of HIV nucleoside reverse transcriptase inhibitors used for treatment of HIV. The description accompanying the patent application also describes it as being useful for the treatment of both HIV-1 and HIV-2 infections.[77]

Patent application WO2019027920

The application is a secondary patent application and claims crystalline forms (Forms I and II; claims 1 to 17) and amorphous forms (claim 53) of GS-9131 (a prodrug of GS-9148). It also claims two crystalline forms of the vanillate salt (Forms I and II; claims 1, 18 to 33), the crystalline form of the phosphate salt (claims 1, 34 to 40), the crystalline form of xinafoate salt (claims 1, 41 to 47) and the crystalline form of phosphate acetonitrile solvate (claims 1, 48 to 52). The solid state forms are characterised by one or more known techniques such as XRPD, DSC, TGA thermogram and dynamic vapour sorption isotherm.

It also claims pharmaceutical compositions of the claimed crystalline forms, either alone or in combination with other therapeutic agents, solid dosage forms (including single layer, multilayer and bilayer tablets) thereof and method of treating viral infections, such as HIV.

Why was a TPO filed for this application?

A TPO was filed for this application as it is a secondary patent application for an NRTI under development.

If approved, GS-9131 would be an addition to the class of NRTIs as it is reportedly active against both HIV-1 and HIV-2 and also exhibits *in vitro* activity against HIV-1 with NRTI-resistance patterns.[78] It is also reported to exhibit lower potential for renal accumulation and nephrotoxicity.[79] These are disadvantages known to be associated with tenofovirdisoproxil fumarate.[80]

As a secondary application, this would also extend the term of the patent monopoly. As admitted by Gilead Sciences, Inc. in the description accompanying the patent application, the basic compound was disclosed in WO 2006/015261 (filing date: 27 July 2005) and is thus known.

Interestingly, Gilead Sciences, Inc. has also previously filed an application specifically claiming the citrate, succinate and malonate salts of the compound and their crystalline structures, i.e. WO 2010/005986 (filing date: 7 July 2009).[81] As per Gilead Sciences, Inc., the citrate salt was previously identified as the most chemically stable form of GS-9131, but subsequently found to exhibit stability issues during storage.[82] As of the date of filing the TPO, GS-9131 was in Phase II clinical trials.

Due to the numerous salt forms or solvate forms claimed, the ISR cites lack of unity of invention and restricts its report and opinion to the claims for the crystalline forms of GS-9131 and various secondary claims relating to pharmaceutical compositions and method of treatment thereof. Therefore, it is silent on the various salt forms and their characterisation. The ISR cites WO 2010/005986 – the previous application for the salt forms – and opines that the claims relating to crystalline forms I and II of GS-9131 (claims 1 to 17 and 54 to 70) lack novelty. However, as mentioned above, it is silent on the novelty and inventive step of the crystalline forms of the salt and solvate forms claimed.

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77 WO 2019/027920, para 0007, available at https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019027920

78 Jules Levin, "GS-9131 is a Novel NRTI with Activity Against NRTI-Resistant HIV-1", Conference Reports for NATAP, February 2017, available at https://www.natap.org/2017/CROI/croi_88.htm

79 Cihlar et al., "Novel Nucleotide Human Immunodeficiency Virus Reverse Transcriptase Inhibitor GS-9148 with a Low Nephrotoxic Potential: Characterization of Renal Transport and Accumulation", *Antimicrobial agents and chemotherapy*, 2009; 53(1): 150–156; doi: 10.1128/AAC.01183-08.

80 Ray et al., "Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus", *Antiviral Research*, 2016; 125:63–70; doi: 10.1016/j.antiviral.2015.11.009.

81 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2010005986

82 WO 2019/027920, paras 0005–0006

Focus on the TPO

In order to ensure that patent offices have the benefit of prior art documents relating to all the claims, the TPO cited two documents to assail novelty and/or inventive step and eight documents to assail inventive step.The TPO cited three patent documents relating to GS-9131 (WO 2006/015261, WO 2010/005986 and WO 2012/159047) that disclose GS-9131 and its various salt forms (including organic salt forms) generally and the phosphate salt specifically. The TPO also cited the document cited in the ISR (WO 2010/005986) to point out how it discloses a salt screen to identify suitable salts of GS-9131 and their characterisation.

In support of the lack of inventive step, the TPO cited three periodical articles regarding salt formation and/or solid state chemistry (Sarma et al. (2016), Elder et al. (2010) and Huang and Tong (2004)). Two of the prior art documents disclose the state of the art regarding salt formation and their selection and the various studies of solid state chemistry (including crystallinity and polymorphism) that are routinely carried out on active pharmaceutical ingredients and salts thereof. The TPO pointed out how one of these periodical articles (Elder et al. (2010)) specifically discloses salt forms (such as xionfoate salt) that could be employed to develop a less soluble salt of an active pharmaceutical ingredient thus enabling extended release dosage forms as well as salt forms with longer and bulkier chains (such as xinofoate salt) to overcome palatability issues, if any.

The TPO cited a conference proceeding (White et al. (2017)) to show the known activity of GS-9131 against HIV-1 and HIV-2 and HIV-1 NRTI-resistant strains and their combination with other agents. It also cited a periodical article – Cihlar et al. (2008) – in support of this conference proceeding to show that combinations of GS-9131 with other therapeutic agents have been previously tested.

Further, the TPO cited two patent documents relating to tenofovir alafenamide (structurally similar to GS-9131) – WO 2015/040640 and WO 2018/144390, the latter of which is a PX document. The TPO cited a periodical article – Birkus et al. (2007) – in support of the structural similarity between the prodrug moieties of tenofovir alafenamide and GS-9131. One of these patent documents discloses (i) the phosphate and vanillate salts thereof and characterises the phosphate salt thereof and (ii) that the salts may be in the form of solvates, hydrates, etc. The TPO also pointed out that WO 2018/144390 – the PX document – discloses crystalline forms of tenofovir alafenamide as well as the vanillate and bis-xinofoate salts of tenofovir alafenamide and their alleged advantages, and characterises them.

The TPO also cited a patent document – US 8563530 – which discloses a compound belonging to the class of nucleoside phosphoramidates (with structural similarity to GS-9131), its hydrate, solvate and salt forms for the treatment of HCV infection and the characterisation of these forms.

Through these documents, the TPO attempts to show the existing knowledge regarding GS-9131 and its known activity and combination studies with various anti-HIV agents. It also points out the broad general disclosures in earlier patent documents relating to GS-9131 regarding pharmaceutically acceptable salt forms. To support the proposition that the claims lack inventive step, the TPO cites general periodical articles setting out the state of the art regarding salt formation, salt selection and solid state chemistry. It also cites patent documents relating to structurally similar drugs, including tenofovir alafenamide, that disclose and/or claim various salt forms and their characterisation. These include salt forms also now specifically claimed for GS-9131. It is hoped that these documents will aid patent offices in their determination of novelty and inventive step of the claimed crystalline forms as well as the salt forms of GS-9131.

National phase

As of 07-04-2021, this application has entered the national phase in the European Patent Office. It is published as EP2018755368. While AR112642 is not listed as a national phase entry, it is listed by WIPO Patentscope as a patent family member.

Impact of the TPO

The European Patent Office has issued a communication of its intent to grant a patent. The EPO does not appear to have taken note of the TPO. The amended claims of this EP application pertain only to the two crystalline forms of GS-9131 and pharmaceutical composition, dosage forms and use thereof.

Case Study 6: Compounds and pharmaceutical compositions useful as ASK-1 (Apoptosis Signal Regulating Kinase-1) inhibitors

TPO Nos.: 35, 36, 37 and 38
Name of Drug: Not Available (N/A)
Chemical Class: N/A
Molecular Formula: N/A
IUPAC Name: N/A
Name of Target: Apoptosis Signal Regulating Kinase-1 (ASK-1)
Mechanism of Action: ASK-1 inhibitors

Applications linked to this drug for which TPOs were filed:

Application No.	*Applicants*	*Application Published on*	*Application Filed on*	*Priority Date*
PCT/US2018/032579: WO2018209354	Enanta Pharmaceuticals, Inc.	15.11.2017	14.05.2018	12.05.2017
PCT/US2018/034429 : WO2018218044	Enanta Pharmaceuticals, Inc.	29.11.2018	24.05.2018	25.05.2017
PCT/US2018/034423: WO2018218042	Enanta Pharmaceuticals, Inc.	29.11.2018	24.05.2018	25.05.2017
PCT/US2018/034441: WO2018218051	Enanta Pharmaceuticals, Inc.	29.11.2018	24.05.2018	25.05.2017

Clinical Trials:
Summary: These multiple applications claim inhibitors of ASK-1, which is associated with liver disorders including chronic viral hepatitis and non-alcohol steatohepatitis (NASH).
Keywords: ASK-1 inhibitors
Note: WO'044, WO'042 and WO'051 are applications published on the same date i.e. 29.11.2018; and also have the same filing date i.e. 24.05.2018 and priority date 25.05.2017.

Background

These four applications relate generally to compounds and pharmaceutical compositions useful as ASK-1 (Apoptosis Signal Regulating Kinase-1) inhibitors and methods for their preparation and use. ASK-1 is a member of the large MAPK kinase kinase (MAP3K) family that activates downstream MAPKs, c-Jun N-terminal kinases (JNKs) and p38 MAPKs, and it plays a pivotal role in various stress responses, including cell death, differentiation, and production of inflammatory cytokines.[83]

[83] Hayakawa, R., Hayakawa, T., Takeda, K., & Ichijo, H. (2012). Therapeutic targets in the ASK1-dependent stress signaling pathways. *Proceedings of the Japan Academy. Series B, Physical and biological sciences*, 88(8), 434-453. https://doi.org/10.2183/pjab.88.434

Importance of drug

In all four of the applications, it is disclosed that ASK-1 has been associated with many liver disorders and diseases including chronic viral hepatitis and hepatic steatosis, including non-alcoholic fatty liver disease (NAFLD) and non-alcohol steatohepatitis (NASH). Apart from liver disorders, ASK-1 has been associated with autoimmune disorders, neurodegenerative disorders, inflammatory diseases, chronic kidney disease, cardiovascular disease, metabolic disorders, and acute and chronic liver diseases.

At the time of filing the TPOs, selonsertib (GS-4997), an ASK-1 inhibitor developed by Gilead Sciences, Inc., was under clinical trials for the treatment of NASH. Given the similarity in the structures and the possible importance of this class, these applications were considered to be relevant.

Patent applications on ASK-1 inhibitors

a. Patent application PCT/US2018/032579; WO2018209354

WO2018/218051 (WO'354) is a patent application by Enanta Pharmaceuticals, Inc. having 26 claims (one independent and 25 dependent claims); of these 13 are secondary claims wherein one claim is for formulation, one is for use, and 11 are for method of treatment. Of the 37 Markush structures claimed in the application, one is the primary Markush structure (claims 1 to 4) and the others are derivatives of this parent Markush structure. The 36 derivative Markush structures (claims 5 to 12) are classified into nine groups/families, each containing four variations (i.e. Formulae Ia to Id, IIa-1 to IIa-4, IIb-1 to IIb-4, IVa-1 to IVa-4, IVb-1 to IVb-4, Va-1 to Va-4, Vb-1 to Vb-4, VIa-1 to VIa-4, VIb-1 to VIb-4).

The parent Markush structure comprises a pyridine or phenyl ring which is substituted at position 2 with an amide group which is further attached to a five- or six-membered heteroaryl ring (A) which itself is further attached to a five-membered ring comprising two, three or four nitrogen atoms (R). The central pyridine or phenyl ring is also substituted at position 4 with an imidazole ring, which itself is further substituted (R3) and is also substituted at position 5 (R2).

However, it is to be noted that (a) the scope of the parent Markush structure claimed is very broad structurally and encompasses all the derivative Markush scaffolds (b) within the derivative Markush scaffolds, the differences between the structures are very minor (e.g. Ia and Ib only differ in the placement of the four nitrogen atoms within the five-membered ring attached to ring A).

Thus, it is clear that in WO'354, the applicant is trying to claim very specifically all possible Markush scaffolds and compounds that can be derived from a parent Markush scaffold. Even minor modifications in the placement and number of heteroatoms in a single aromatic ring have been specifically claimed. Using this strategy, the applicant has claimed 600 specific compounds and also pharmaceutically acceptable salt and esters of these claimed compounds. Such a strategy ensures that any other ASK-1 inhibitor developed within the scope of the broad parent scaffold would already have been claimed in WO'354. It also places unnecessary pressure on the patent office, which would be responsible for reviewing the broad scope of the parent Markush scaffold and also the specific compounds claimed within a single patent application.

Why was a TPO filed for this application?

The ISR lists two Y documents and three A documents. However, opinion has only been established with regard to claims 1 and 14 of the application in the ISR and WOSA wherein the WOSA notes that in light of the two Y documents, i.e. US 2011/0009410and US 2015/0005280, the subject matter claimed in WO'354 lacks inventive step. However, both these claims have been considered novel by the WOSA; thus a search was conducted to check whether the novelty aspect too could be covered for this application.

Focus on the TPO

The TPO refers to three documents, one of which is a periodical article (for inventive step) and the other two are patent documents (for novelty and/or inventive step).

Kawarazaki et al. disclose how ASK-1 plays an important role in cancer, cardiovascular, infectious (such as TB and HIV), neurodegenerative and metabolic disorders and can be a target and how ASK-1 inhibitors can be important for the purposes of treatment.

WO 2012/003387 (WO'387; applicant: Gilead Sciences, Inc.) claims a parent scaffold (formula I) with an identical substitution pattern and substituents as the parent scaffold claimed in WO'354. The only minor difference is that the present application claims R, the terminal substituent, as a five-membered ring containing not only two or three nitrogen atoms (i.e. imidazole and triazole respectively), but also four nitrogen atoms (i.e. tetrazole). However, R being imidazole and triazole (containing two and three nitrogen atoms in a five-membered ring respectively) have already been claimed in WO'387; further, it is obvious to also explore four nitrogen atoms in a five-membered ring at an analogous position. Thus, ASK-1 inhibitors claimed in the present application WO'354 have been derived from a scaffold already disclosed in WO'387 for the treatment of a broad range of diseases/conditions also disclosed in WO'387. In the TPO, claims 1 to 26 have been shown to lack novelty and/or inventive step in light of this document.

WO2016049069 (WO'069; applicant: Gilead Sciences Inc.) also claims a Markush scaffold (formula I) identical to the parent Markush scaffold claimed in the present application with the exception of the terminal substituent i.e. R being a tetrazole ring. However, in this application ASK-1 inhibitors have specifically been claimed for the treatment of liver disorders. This document has been cited in the European Search Report (national phase stage) and the Supplementary report as a document cited in the application itself.

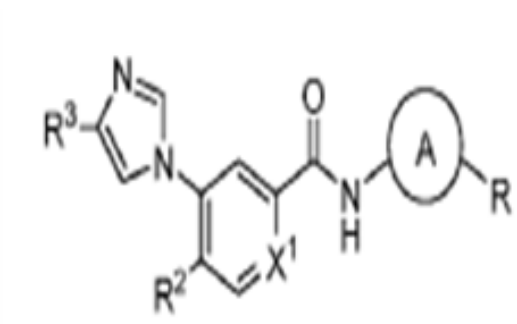


Fig. 1: Markush scaffold claimed in WO'354

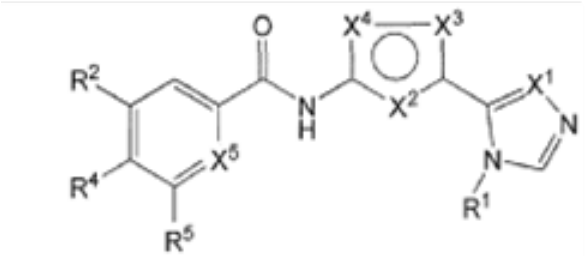


Fig. 2: Markush scaffold claimed in WO'387

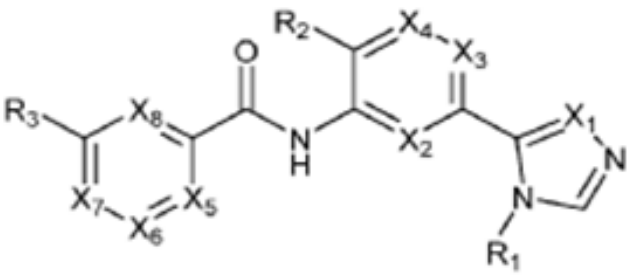


Fig. 3: Markush scaffold claimed in WO'069

(i) In Fig. 1, i.e. the parent Markush scaffold claimed in WO'354, the central pyridine or phenyl ring is substituted at position 4 with imidazole and at position 2 with an amide group which is further substituted with A, which is claimed to be a 5- or 6-membered heteroaryl ring. This has already been claimed in WO'387 and WO'069 respectively.

(ii) WO'387 and WO'069 (Figs. 2 and 3 respectively) already claim a central pyridine or phenyl or heteroaryl ring substituted at position 4 with a heteroaryl ring which includes imidazole (R2 and R3 in WO'387 and WO'069 respectively), wherein the heteroaryl ring itself may be further substituted at an analogous position as in Fig. 1.

(iii) As is seen on direct comparison, the substitution pattern across all the Markush scaffolds is identical.

(iv) In Fig. 1, i.e. the parent Markush scaffold claimed in WO'354, the R terminal ring (RHS of the structure) is claimed to be an imidazole, triazole or tetrazole ring (containing 2, 3 and 4 nitrogen atoms respectively). However, WO'387 and WO'069 claim an imidazole and triazole ring at an analogous position. It is obvious for a person skilled in the art to explore a closely related tetrazole ring (containing 4 nitrogen atoms) at an analogous position.

Thus, the TPO points out that an identical Markush scaffold and compounds derived therefrom have already been claimed as ASK-1 inhibitors and have also been claimed for the purposes of treating a range of medical disorders/ diseases including liver disorders.

National phase

WO'354 has entered national phase in seven countries and has been published in at least 11 countries as of 31.03.2021. The application has been published as AU2018266911, KR1020200007000, EP3621615, CN110869017, MYPI 2019006507, BR112019023449, JP2020519584, CA3063180, NZ759204, VN1/069958 and IN201947051124.[84]

Impact of the TPO

The European Patent Office has taken cognisance of the TPO, and has asked the applicant to comment on it if they wish to. However, apart from one document mentioned in the TPO, which is also mentioned in the application, the EP Search Report does not use the documents of the TPO.[85]

Note: While it has not been pointed out in the TPO, it may be noted that document WO'069 – one of the prior art documents cited in the TPO – is the primary application which claims compound selonsertib (GS-4997) for the treatment of NASH. However, clinical trials of this compound for the treatment of NASH and fibrosis have been terminated as of 29 June 2020 due to lack of efficacy.[86, 87] It remains to be seen if the compound may be useful as an anti-cancer agent or for other illnesses and conditions.

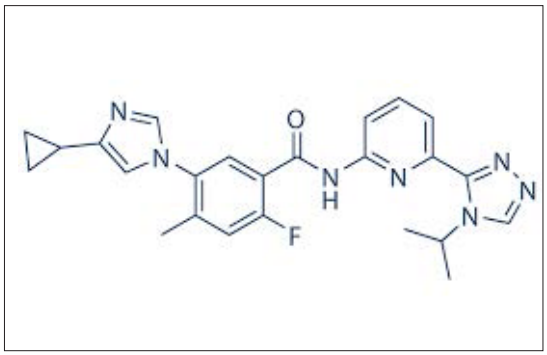
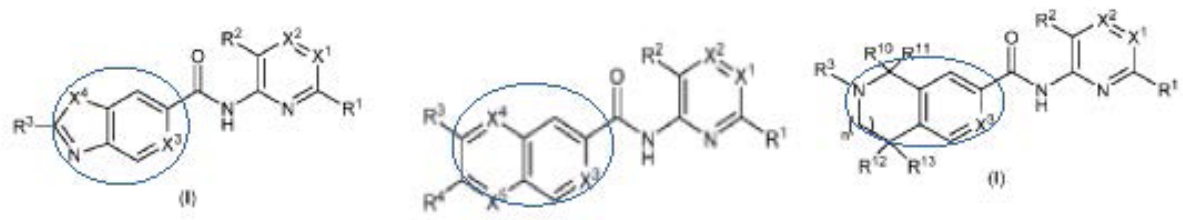


Fig. 4: Structure of selonsertib

b. Patent applications WO'044, WO'042 and WO'051

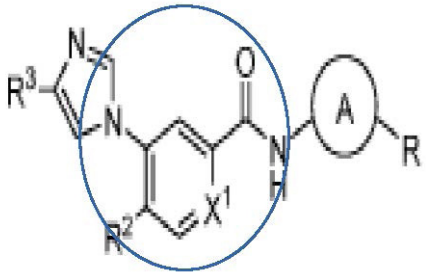
Key issues in the patent applications

Patent applications WO2018/218044 (WO'044), WO2018/218042 (WO'042) and WO2018/218051 (WO'051) are discussed together in this section due to very minor differences in the parent Markush structures claimed in these applications and because the prior art documents used in the TPOs are identical across all three applications. Also, the parent Markush scaffold claimed in these three applications can be considered derivatives of the parent scaffold claimed in WO'354 as the strategy employed in these three applications comprises fusion of a five- or six-membered ring with the central six-membered aryl or heteroaryl ring as opposed to substitution of this five- or six-membered ring on the central six-membered aryl or heteroaryl ring seen in WO'354 (see figure below).



Parent Markush scaffolds disclosed in WO'044, WO'0042 and WO'051 respectively (TPO Nos. 36-38)

84 https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018209354&tab=FAMILY&_cid=P12-KN04G5-38345-1
85 https://patentscope.wipo.int/search/en/detail.jsf?docId=EP290831295&tab=NATCOLLDOCUMENTS
86 https://clinicaltrials.gov/ct2/show/NCT03053050
87 https://www.fiercebiotech.com/biotech/gilead-s-selonsertib-flunks-another-nash-phase-3



Parent Markush structure disclosed in WO'354 (TPO: 35)

Fig. 5: Fusion strategy employed by Enanta Pharmaceuticals, Inc. in TPO Nos. 36, 37 and 38

i. WO2018218044 (WO'044; TPO No. 36): WO'044 is a patent application by Enanta Pharmaceuticals, Inc. having 30 claims (one independent and 29 dependent claims); of these, 14 are secondary claims wherein two claims are for formulation, one is for use, and 11 are for method of treatment. Of the 25 Markush structures, one is the primary Markush structure (Formula I) and 24 are derivative Markush structures. Of the 24 derivative Markush structures, eight are Markush structures (IIa-h) belonging to formula II and another four are Markush structures (IIIa-d) belonging to formula III.

The parent Markush structure comprises a 5+6 bicyclic fused ring wherein the five-membered ring may contain up to two heteroatoms and the six-membered ring may be either a phenyl or pyridine ring. The six-membered ring of the bicyclic ring is attached to an amide group which is further attached to a heteroaryl ring containing up to three nitrogen atoms which itself is further substituted (R1, R2). The five-membered ring of the bicyclic ring is also further substituted (R3).

Also, the parent Markush structure and compounds claimed in application WO'044 are similar to the parent Markush structures claimed in the other three Enanta Applications as shown above.

However, the closest structural similarity can be found with the parent Markush structure of WO'354 wherein the parent Markush structure comprises a central phenyl/pyridine ring (six membered ring) substituted with an imidazole ring which has been replaced in the present application with a bicyclic ring structure containing a phenyl/pyridine ring fused to an imidazole ring (or oxazole/thiazole rings) at an analogous position. Thus, the only difference between WO'044 and WO'354 is the fusion strategy for the central core of the scaffold employed by the applicant, which is obvious to a person skilled in the art.

Using this simple strategy of fusion instead of substitution, the applicant claims 738 specific compounds and pharmaceutically acceptable salts thereof in WO'044.

ii. WO2018218042 (WO'042, TPO No. 37): WO'042 is a patent application by Enanta Pharmaceuticals, Inc. having 36 claims (one independent and 35 dependent claims); of these, 14 are secondary claims wherein two claims are for formulation, one is for use, and 11 are for method of treatment. Of the 35 Markush structures, one is the primary Markush structure (formula I) and 34 are derivative Markush structures. Of the 34 derivative Markush structures, eight are Markush structures (IIa-h) belonging to formula II and another eight are Markush structures (IIIa-h) belonging to formula III.

The parent Markush structure comprises a 6+6 bicyclic fused ring wherein a six-membered aromatic ring containing up to two nitrogen atoms is fused to another six-membered ring (either a phenyl or pyridine ring). The phenyl/pyridine ring of the bicyclic ring is attached to an amide group which is further attached to a heteroaryl ring containing up to three nitrogen atoms which itself is further substituted (R1, R2). The other six-membered (containing up to two nitrogen atoms) ring of the bicyclic ring is also further substituted (R3 and R4).

However, the closest structural similarity can be found with the Markush structure of WO'044 wherein the scaffold also comprises a central phenyl/pyridine ring (six-membered ring). However, in WO'044 this central ring is fused to an imidazole ring (or oxazole/thiazole rings), a five-membered ring containing two nitrogen atoms, which has been replaced in WO'042 with a six-membered pyrimidine ring also containing two nitrogen atoms. Such replacement of related ring systems containing the same number of heteroatoms (in this case two nitrogen atoms) is routinely explored in lead discovery and development and is obvious to a person skilled in the art.

Thus, this application claims another variation of the parent Markush structure claimed in WO'354 and WO'044. In WO'044, the applicant has employed a strategy of fusion of the known core disclosed in WO'354 and in this application, the 5+6 fused bicyclic ring system claimed in WO'044 has been replaced with a closely related 6+6 fused bicyclic ring system. By employing a slight variation over application WO'044, i.e. by switching a 5+6 bicyclic core with a 6+6 core, the present applicant claims 1,440 compounds.

iii. WO2018218051 (WO'051; TPO No. 38): WO'051 is a patent application by Enanta Pharmaceuticals, Inc. having 28 claims (one independent and 27 dependent claims); of these, 14 are secondary claims wherein two claims are for formulation, one is for use, and 11 are for method of treatment. Of the 19 Markush structures, one is the primary Markush structure (formula I) and 18 are derivative Markush structures. Of the 18 derivative Markush structures, two are Markush structures (XIIa-XIIb) belonging to formula XII, two are Markush structures (XIIIa-XIIIb) belonging to formula XIII, two Markush structures (XIVa-XIVb) belonging to formula XIV and another two are Markush structures (Xva-Xvb).

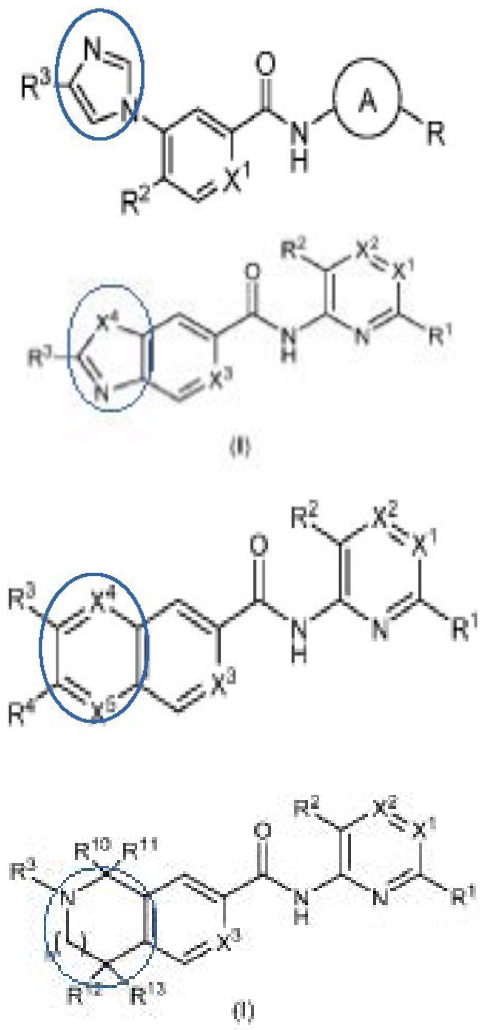
The parent Markush structure comprises a 6+6 bicyclic fused ring wherein one of the six-membered rings is a piperidine ring (saturated ring containing a single nitrogen atom) and the other six-membered ring fused to it may be either a phenyl or pyridine ring. The phenyl/pyridine ring of the bicyclic ring is attached to an amide group which is further attached to a heteroaryl ring containing up to three nitrogen atoms which itself is further substituted (R1, R2). The piperidine ring of this bicyclic ring system is also further substituted on the nitrogen atom (R3).

The closest structural similarity can be found with the Markush structure of WO'042 which comprises a central phenyl/pyridine ring fused to an unsaturated six-membered ring containing up to two nitrogen atoms; whereas in WO'051 the central phenyl/pyridine ring is fused to a saturated analog of an identical six-membered ring (i.e. piperidine; containing a single nitrogen atom).

Thus, this application claims another variation of the parent Markush structure claimed in the previous three applications. Both WO'042 and WO'051 have a 6+6 bicyclic core; however in WO'042 both the rings in the 6+6 bicyclic ring system are unsaturated (i.e. have presence of double bonds) whereas in WO'051 one of the rings in the 6+6 bicyclic ring system is saturated (i.e. absence of double bond). Again, having analogous saturated and unsaturated ring systems at an identical position is routinely done in the process of drug development and is obvious to a person skilled in the art. By employing this strategy the applicant has claimed 600 compounds in this application.

Thus, in all the three applications discussed above variations have been made to the ring fused to the central aromatic six-membered ring. Apart from that, the substitution pattern and the substituents claimed across all the three applications remain identical.

It is clear from these three applications that the applicant is trying to exhaust all possibilities within this research area of ASK-1 inhibitors. They have predominantly claimed every possible variation of the core known to have ASK-1 inhibitory activity and compounds that may be derived from such parent Markush structures. Even the modifications made to the scaffolds across these three applications (see figure below) could have been anticipated by a person skilled in the art. Thus, this a classic example of a single applicant claiming closely associated Markush scaffolds across a number of patent documents and keeping the scope of the Markush scaffold so broad that its interpretation leads to an enormous number of compounds being claimed, which results in unnecessary pressure on the patent office reviewing such applications.



(i) Parent Markush scaffold claimed in WO'354

(ii) Parent Markush scaffold claimed in WO'044
Comprises a fused bicyclic core as opposed to the imidazole ring being substituted on the 6-membered ring as seen in WO'354 (5+6 bicyclic ring system).

(iii) Parent Markush scaffold claimed in WO'042
Both the parent Markush scaffolds claimed in WO'044 and WO'042 comprise a fused bicyclic core. The core in WO'042 varies from WO'044 in the ring fused to the 6-membered ring attached to the amide (i.e. 6+6 ring system).

(iv) The parent Markush scaffold claimed in WO'051 also comprises a fused bicyclic core like the previous 2 applications. The core in WO'051 varies from WO'042 in the ring fused to the 6-membered ring attached to the amide (i.e. the ring being saturated/non-aromatic).

Fig. 6: Modification of a single ring at an identical position across four applications

Why were TPOs filed for these applications?

As noted earlier, at the time of filing the TPOs, the class of ASK-1 inhibitors was considered to be of relevance and one such molecule, i.e. selonsertib (GS-4997), was under clinical trials.

The ISR cites common prior art documents across all three applications (i.e. WO'044, WO'042 and WO'051). One of these documents, US 8,378,108 B2 (Corkey et al.), cited in the ISR has also been used in the TPO. This is because the ISR lists this document as an "A" document i.e. a document defining the general state of the art and not of particular relevance whereas as pointed out in the TPO this document was found to be relevant to the novelty and inventive step aspect of these three applications.

The other two documents cited in the ISR of these three applications – US 9,254,284 B2 (Gilead Sciences, Inc.) and US 2014/0329850 A1 (Takeda Pharmaceutical Company Limited) – have also been listed as "A". As the strategy of fusion and replacement with related ring systems has been used by the applicant in these three applications compared to the WO'354 (and such strategies are routinely done and obvious to a person skilled in the art), a prior art search was conducted to check whether the novelty and inventive step aspect for these applications could also be covered.

It is important to note that WO'044 was published as an A2 document, while the other three Enanta applications were published as A1 documents along with the ISR and WOSA. Interestingly, the authorised officer at the ISA for all the Enanta applications is the same and the ISR and WOSA for WO'044 were mailed at around the same time (24.08.2018) as the ISR and WOSA for WO'042 (24.08.2018) and WO'051 (23.8.2018). The ISR and WOSA for WO'044 were published or made available on WIPO Patentscope only on 06.03.2020, whereas the TPO was filed on 24.09.2019, and published on 01.10.2019.

Focus on the TPOs

Due to similar structural features of the Markush scaffolds and compounds claimed for the same target ASK-1 across all three applications, common prior art documents have been cited in the TPOs across these applications.

(i) WO 2011/008709 (WO'709) (applicant: Gilead Sciences, Inc.) is also cited in the ISR; it discloses and claims a Markush scaffold comprising a fused bicyclic core wherein the scope of the Markush scaffold covers an unsaturated/saturated five- or six-membered heteroaryl ring being fused to a six-membered aryl/heteroaryl ring (further substituted with an amide group). WO'709 also claims compounds derived from the parent scaffold and pharmaceutical compositions thereof for treatment of all conditions/diseases mediated by ASK-1.

(ii) WO 2016/049069 (WO'069) (applicant: Gilead Sciences, Inc.) is also cited in the TPO of WO'354; it discloses and claims a Markush scaffold comprising a fused bicyclic core (similar to the Markush scaffold claimed in WO'709). WO'069 also claims compounds derived from the parent scaffold and pharmaceutical compositions thereof specifically for the treatment of liver conditions/ disorders.

Both WO'709 and WO'069 claim Markush scaffolds wherein the core comprises a fused bicyclic ring. Thus, this strategy of having a central bicyclic core in the parent scaffold and compounds having ASK-1 inhibitory activity has already been claimed. Therefore, both these documents cover the novelty and/or inventive step aspect for all three of the applications.

As has been discussed for WO'354, the applicant Enanta Pharmaceuticals, Inc. claims the terminal substituent Ras imidazole, triazole and tetrazole (containing two, three and four nitrogen atoms respectively) in the parent Markush scaffolds of these three applications as well. WO'709 and WO'069 claim imidazole and triazole as the terminal substituent in the Markush scaffolds claimed; only tetrazole is not claimed, which is anyway obvious to a person skilled in the art as exploring the number and position of heteroatoms in a single ring substituted at an identical position is routinely done.

(iii) WO 2009/123986 (WO'986) (applicant: Takeda Pharmaceutical Company Limited) also discloses and claims a parent Markush scaffold comprising a bicyclic core. However, it differs from WO'709 and WO'069 with respect to the ring fused to a six-membered ring substituted with the amide group. In the Gilead applications, this ring may be a five- or six-membered heteroaryl or cycloalkyl ring whereas in WO'986 this ring is specifically claimed to be a five-membered heteroaryl ring. WO'986 also claims compounds derived from the Markush structure for the treatment of various conditions mediated by ASK-1.

Although WO'044 claims a 5+6 bicyclic ring, the five-membered ring claimed for the core is imidazole as opposed to pyrazole claimed at an identical position in WO'986 (differ in placement of nitrogen atoms). WO'042 and WO'051 claim related six-membered rings at an identical position (i.e. at the position where imidazole is substituted in WO'044).

In light of the Markush scaffold claimed in WO'986, the inventive step aspect of the three applications under discussion has been covered.

(iv) Starosyla et al. report the development of a pharmacophore model of ASK-1 inhibitors using the PharmaGist program wherein they had 106,529 organic compounds which included 24 highly active organic compounds. On further optimisation, they found that derivatives of the N-{imidazo1,2-a pyridine-2-yl} benzamidebicyclic ring (essentially nitrogen containing bicyclic ring substituted with the amide group further attached to a benzene ring) were highly active ASK-1 inhibitors. These are similar to compounds claimed in the three applications under discussion and the absence of inventive step (not for all claims) was pointed out in the TPO in light of this document.

It is very clear that both the strategies of fusion and exploring closely related rings for the bicyclic core have already been explored before; thus the subject matter within these three applications lack both novelty and/or inventive step.

National phase

None of these applications have entered the national phase yet.

CASE STUDY 7: Sofosbuvir hydrate

TPO No.:	44
Name of Drug:	Sofosbuvir hydrate
Other Names:	Sofosbuvir (manufacturing code name GS-7977; formerly PSI-7977)
Chemical Class:	Nucleoside analog
Molecular Formula:	C22H29FN3O9P[88]
IUPAC Name:	Propan-2-yl (2S)-2-[[[(2R,3R,4R,5R)-5-(2,4-dioxopyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyloxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate[1]
Name of Target:	HCV NS5B (non-structural protein 5B) RNA-dependent RNA polymerase
Mechanism of Action:	Viral polymerase nucleotide inhibitor
Clinical Trials:	Sofosbuvir approved in December 2013 by the US FDA, and in January 2014 by the European Medicines Agency for the treatment of HCV infection
Application No.:	PCT/EP2018/071156: WO2019025600
Applicant:	Sandoz AG
Application Published on:	07.02.2019
Application Filed on:	03.08.2018
Priority Date:	03.08.2017
Summary:	This application claims the hydrate form of sofosbuvir, characterisation of hydrate forms of sofosbuvir, and pharmaceutical compositions to be used either alone or in combination.
Keywords:	sofosbuvir hydrate, GS-7977, PSI-7977

Background

Sofosbuvir, a viral polymerase nucleotide inhibitor, was a breakthrough new medication for the treatment of chronic hepatitis C. Sofosbuvir has a number of ideal properties, including once daily dosing, no meal restrictions, few adverse effects, minimal drug-drug interactions, and high genetic barrier to resistance. It has relatively good safety and efficacy in patients with advanced liver disease, is a prodrug and after ingestion it is rapidly converted to GS-331007 which is efficiently taken up by hepatocytes, whereby cellular kinases convert GS-331007 to its pharmacologically active uridine analog 5'-triphosphate form (GS-461203). This triphosphate compound mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. The active form GS-461203 targets the NS5B catalytic site and acts as a non-obligate chain terminator. Interestingly, this active form does not inhibit host DNA polymerases, RNA polymerases, or mitochondrial RNA polymerase.[89]

Chemical structure

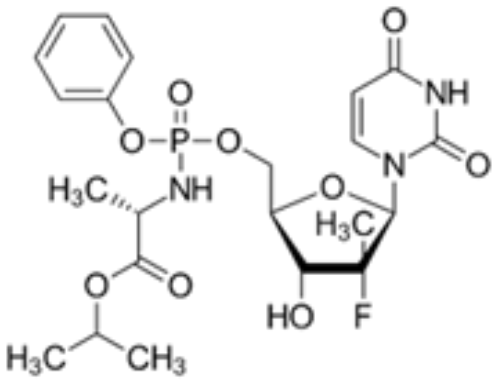


Fig. 1

[88] PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 45375808, Sofosbuvir; [cited 31 March 2021]. Available from:https://pubchem.ncbi.nlm.nih.gov/compound/psi-7977

[89] https://www.hepatitisc.uw.edu/page/treatment/drugs/sofosbuvir-drug

History and timeline of development

Sofosbuvir was approved in December 2013 by the US FDA, and in January 2014 by the European Medicines Agency for the treatment of HCV infection. Sofosbuvir in combination with ribavirin was recommended by the WHO as the first interferon-free HCV treatment. Since then sofosbuvir has been used in combination with other anti-viral medicines as effective treatment for HCV.

Importance of the drug

Sofosbuvir can be administered orally thereby simplifying the treatment and is of value in regions with poor health infrastructure. This drug was developed by Pharmasset Ltd., and the first patent was filed in 2003. Later, it was acquired by Gilead Sciences in 2011.The drug was previously known as GS-7977, which is the more active diastereoisomer form of the parent compound PSI-7851. As a prodrug, sofosbuvir is metabolised to the active antiviral agent 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-monophosphate.[90] A hydrate is a solid adduct containing both the parent compound (e.g., the anhydrate of a drug or excipient) and water. The presence of the water molecules influences the intermolecular interactions (affecting the internal energy and enthalpy) and the crystalline disorder (entropy), and hence influences the free energy, thermodynamic activity, solubility, dissolution rate, stability, and bioavailability.[91]

Patent application WO2019025600 (WO'600)

WO 2019/025600 (WO'600) is an application filed by Sandoz AG wherein a hydrate form of the known compound sofosbuvir has been claimed. The claimed formula contains the hydrate form represented by the structure of sofosbuvir and nH2O where n can be in the range of 0.9 to 1.1, thus making the hydrate form claimed a monohydrate form. However, the monohydrate form has already been claimed in literature, WO 2011/123645 (WO'645), where the hydrate form represented by mH2O claims the number of water molecules to be any integer or non-integer between 0 and 5. The application claims the monohydrate form of sofosbuvir in both crystalline and amorphous forms and the process of preparing it. It is worthwhile to note that hydrates have been known and extensively studied in the pharmaceutical industry owing to the understanding that hydrates impact bioavailability of a drug.

The application claims characterisation of the hydrate form of sofosbuvir by using routinely employed methods such as X-ray diffraction, FTIR and differential scanning calorimetry (claims 2 to 6).

The application claims pharmaceutical compositions containing the monohydrate form of sofosbuvir, either alone or in combination with other known anti-HCV agents including ledipasvir, velpatasavir and voxilaprevir (claims 7 and 10-11). However, WHO has already recommended sofosbuvir to be given in combination with another anti-HCV agent. Also, combinations of ledipasvir and sofosbuvir (Harvoni) and velpatasavir and sofosbuvir (Epclusa) have already been approved and marketed prior to the priority date of this application. Additionally, WO'645 already claims pharmaceutical compositions of the hydrate form of sofosbuvir, alone or in combination with other anti-HCV agents.

The application further claims the above pharmaceutical compositions in oral dosage form such as tablet for the treatment of HCV infection (claims 9, 13, 14 and 16). However, the WHO report already indicates the value of sofosbuvir with respect to ability to administer orally and marketed formulations in the form of tablets are already available. Also, formulations either alone or as combinations have been claimed in prior art (WO'645).

Why was a TPO filed for this application?

The ISR lists five documents of which four are "A" (general documents) and one is a "PX" document – prior to the priority date of the application, though published after the filing date. The ISR does not disclose any document to attack novelty of all claims t to 16 based on documents reported prior to the date of application. However, the parent drug is known for its potent anti-viral activity and hydrates are routinely employed in drug modifications.

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90 Patent situation of key products for treatment of hepatitis c. Sofosbuvir; working paper. Prepared for the World Health Organization (WHO) by Thomson Reuters. Updated version March 2015.

91 Rajendra K. Khankari and David J.W. Grant, Pharmaceutical hydrates, Thermochimica Acta, Volume 248, 1995, Pages 61-79, doi: 10.1016/0040-6031(94)01952-D.

Further, specific sofosbuvir hydrates have been disclosed and claimed in prior art (WO'645). The ISR fails to discuss these aspects in depth.

(i) Document WO 2011/123645 (WO'645) describes Forms 1-6 of sofosbuvir mentioned in application WO'600. Forms 2-6 are converted into Form 1 upon isolation and Form 1 is a non-solvated form. Based on this, WOSA describes this document as dealing with the general state of the art relevant to all claims 1 to 16. But WO'645 also discloses sofosbuvir (Formula 4) and its hydrate, more specifically sofosbuvir mH2O, wherein m varies by an integer or non-integer amount from about 0 to about 5 and these hydrates thereof are crystalline, crystal-like, or amorphous. These forms and their formulations have been claimed to treat hepatitis C infections. However, the ISR does not highlight these aspects of WO'645 or mention WO'645 to attack novelty and/or inventive step.

(ii) Document WO 2015/099989 (WO'989) describes Forms 7-8 of sofosbuvir that are mentioned in application WO'600. However, these forms are anhydrous. Therefore, this document has also been stated as dealing with the general state of the art relevant to all claims 1 to 16.

(iii) Document WO 2016/070569 (WO'569), as per WOSA, describes the monohydrate form H1 of sofoasbuvir. In spite of this disclosure, WO'569 has been mentioned as a document dealing with the general state of the art and not a document dealing with novelty and/or inventive step.

(iv) Document CN104650171 (CN'171) describes a hydrate of sofosbuvir (Sofosbuvir, nH2O) wherein n is 1.5. This has been mentioned as being outside the range of the hydrate form which has been claimed in WO'600. The disclosure of the hydrate form in CN'171 itself destroys novelty and/or inventive step. However, like the earlier document, this has also been mentioned to be a general state of the art disclosing document and not a document attacking novelty and/or inventive step.

(v) WO 2017/158264 (WO'264) has been mentioned as a PX document attacking all the claims 1 to 16. WO'264 discloses a crystalline sofosbuvir form labelled as M3 which is a monohydrate characterised by a PXRD pattern and by a DCS thermogram that are identical with those characterising the compound of WO'600. WO'264 further discloses use of M3 to formulate an oral dosage form for treatment of hepatitis C infection. WOSA indicates WO'264 to be relevant to the novelty of claims 1-7, 9-11, and 13-16 of WO'600.

The ISR documents clearly indicate prior knowledge of the claimed hydrate form of sofosbuvir which has been claimed in WO'600. However, the ISR mentions that none of the prior art documents disclose the sofosbuvir hydrate claimed and characterised by a different X-ray diffractogram and hence are new and also fulfil the criteria of inventive step. The ISR also states that with respect to entering the European regional phase, the document will be relevant as to the novelty of the subject matter of claims 1-7, 9-11, and 13-16 of WO'600 based on comparison with disclosure by WO'264. Efficacy of sofosbuvir alone and in combination has already been established and hydrates have been known for many years. Specifically hydrates of sofosbuvir have also been disclosed in prior art.

Focus on the TPO

Four documents were referred to in the TPO, wherein three were periodical articles and one a patent document. Two of these documents were used for novelty and/or inventive step and two for inventive step. One of these documents has been cited in the ISR and the others arenot addressed in the ISR.

(i) The TPO cites WO 2011/123645 (WO'645), which is the ISR document. As mentioned earlier, it discloses sofosbuvir hydrates in crystalline, crystal-like or amorphous forms or formulations of these forms for the treatment of hepatitis C infection. It has been mentioned as an A document instead of an X or a Y document. The TPO argues that claims 1 to 16 of WO'600 lack both novelty and/or inventive step in light of WO'645.

(ii) The TPO cites a periodical article by Khankari, R. K. and Grant, D. J. W which reviewed pharmaceutical hydrates, more specifically crystalline stoichiometric hydrates. The authors have summarised how the changes in hydrate form can affect various physicochemical properties of a drug molecule and thereby the bioavailability. They also list the various methods used for characterisation of hydrates. As application WO'600 deals with the hydrate of a known drug and its characterisation, in light of the discussions by Khankari, R. K. and Grant, D. J. W, WO'600 was shown to be obvious to a person skilled in the art and thereby lacks inventive step.

(iii) The TPO cites a periodical article by Giron, D. et al. which provides a review of solid-state characterisations of pharmaceutical hydrates. The authors disclose how a monohydrate form of a drug is manufactured via slurrying and by mixture of ethanol/water and how hydration of a molecule changes the physical properties of the molecule. They also state that screening of such hydrate forms is done in the initial stages of drug development and characterisation of such forms is routinely done by a combination of analytical techniques. Based on these insights, it is obvious to a person skilled in the art to synthesise the desired hydrate form of sofosbuvir and characterise it using known analytical techniques. Thus, in light of Giron et al. when read along with WO'645, application WO'600 lacks inventive step.

(iv) The TPO cites a periodical article by Newman, Ann which discloses many hydrate screening methods including the slurry method used in WO'600. Newman also states that screening techniques to find various solid-state forms are routinely done in the process of drug development. When such a screen provides stable hydrates, solvates or other polymorphs, it is obvious to a person skilled in the art to determine the physical properties of such stable forms. Thus, in light of the disclosure in Newman, application WO'600 lacks inventive step.

National phase

As of 07.04.2021, this application has entered the national phase in the EPO. The date of entry was 03.03.2020 and the application is published as 2018748923.

Other patent applications

There are other applications claiming sofosbuvir and its various forms. A few of them are listed below:

1. WO2016016327 (applicant: Hc-Pharma Ag): This application deals with sofosbuvir in crystalline form and the process for its production and use in pharmaceutical compositions.[92]
2. WO2016035006 (applicant: Dr. Reddy's Laboratories Limited): This application relates to novel nucleotide analogs, stereoselective preparation of sofosbuvir, crystalline polymorph, cocrystal of sofosbuvir, processes for their preparation, amorphous solid dispersion of sofosbuvir and processes for the preparation of amorphous sofosbuvir.[93]
3. EP 3107942 (applicant: RATIOPHARM GMBH, TEVA Pharmaceuticals INT GMBH): This application claims solid state forms of sofosbuvir and pharmaceutical compositions thereof.[94]

[92] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2016016327
[93] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2016035006
[94] https://patentscope.wipo.int/search/en/detail.jsf?docId=EP190322456