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Treatment Action Group

Hepatitis C and Tuberculosis Long-Acting Medicines: Analysis of Patenting Trends and Implications for Access

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Activist Reference Tool 2021

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List of Acronyms

API	Active Pharmaceutical Ingredient
BDQ	Bedaquiline
BLAI	Bedaquiline Long-Acting Injectable
CAM	Clarithromycin
CHAI	Clinton Health Access Initiative
CIS	Commonwealth of Independent States
DAA	Direct-Acting Antiviral
DRA	Drug Regulatory Authority
EECA	Eastern Europe and Central Asia
EMA	European Medicines Agency
EPO	European Patent Office
FDA	United States Food and Drug Administration
FDC	Fixed-Dose Combination
GDF	Global Drug Facility
HCV	Hepatitis C Virus
HIC	High-Income Countries
IMPAACT4TB	Increasing Market and Public health outcomes through scaling up Affordable Access models of short-course preventive therapy for TB, a four-year Unitaid-funded project to introduce and scale up new, shorter, rifapentine-based treatment options for people with latent TB infection
J&J	Johnson & Johnson
LAF	Long-acting formulation
LAI	Long-acting injectables
LAP	Long-acting parental
LMIC	Low- and Middle-Income Countries
LTBI	Latent Tuberculosis Infection
Mab	*Mycobacterium abscessus*
MAC-LD	Mycobacterium avium Complex-Lung Disease
MDR-TB	Multidrug-Resistant Tuberculosis (resistant to both rifampicin and isoniazid)
MedsPaL	Medicines Patents and Licenses Database

MIC	Middle-Income Countries
MPP	Medicines Patent Pool
NTM-PD	Nontuberculous Mycobacteria Pulmonary Disease
OTMeds	Observatoire de la Transparence dans les Politiques du Médicaments
PCT	Patent Cooperation Treaty
Pre-XDR-TB	pre-extensively drug-resistant tuberculosis (MDR-TB with additional resistance to the flouoroquinolones, i.e., levofloxacin or moxifloxacin)
PRS	Prior Treatment Experience
R&D	Research and Development
RR-TB	Rifampicin-Resistant Tuberculosis
SDN	Solid Drug Nanoparticle
SVR	Sustained Virologic Response
TAG	Treatment Action Group
TB	Tuberculosis
TNL	Tandem Nano Limited
TRIPS Agreement	Agreement on Trade-Related Aspects of Intellectual Property Rights
UoL	University of Liverpool
US	United States
USPTO	United States Patent and Trademark Office
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis (pre-XDR-TB with additional resistance to other Group A drugs, i.e., bedaquiline or linezolid)

EXECUTIVE SUMMARY

The increasing interest in the development of long-acting medicines for infectious diseases is related to its potential for improving people's acceptability and adherence to medications and reducing clinical intervention, for example for adolescent or pediatric patients; people in rural and remote areas, who may not be able to easily refill prescriptions; and incarcerated individuals, who may benefit from shorter treatment regimens.

In addition to scientific challenges concerning the development of long-acting formulations, there are access issues that need to be addressed to ensure that when those technologies are approved, they can be available for people most in need.

This report aims to investigate if there are potential patent barriers for the development and delivery of long-acting formulations for selected hepatitis C and tuberculosis medicines. The landscape includes four drugs studied under the LONGEVITY Project—glecaprevir and pibrentasvir (for HCV), and rifapentine and isoniazid—and two additional TB drugs outside the scope of the LONGEVITY Project, bedaquiline and delamanid, because they are important in treating multidrug-resistant tuberculosis (MDR-TB) and are under investigation for long-acting formulations by other sponsors.

Building upon and updating existing patent landscapes, a total of 55 patents and/or patent applications were identified, 19 of which were considered updates.

Building upon and updating existing patent landscapes, a total of 55 patents and/or patent applications were identified, 19 of which were considered updates.

Glecaprevir + Pibrentasvir

A total of 26 patents and/or patent applications were identified for both glecaprevir and pibrentasvir, of which 14 are related to the combination

Between 2014 and 2019, at least one patent application per year was filed through the Patent Cooperation Treaty (PCT) system for the combination of G/P.

of at least the two compounds. Between 2014 and 2019, at least one patent application per year was filed through the Patent Cooperation Treaty (PCT) system for the combination of G/P.

While patent applications on the base compounds (API) were filed in 2011–2012, an additional 23 were identified between 2013 and 2019, with **an average of 3.3 patent applications filed per year**.

The most frequent type of secondary patent were on methods of treatment, aiming to protect medical indications for the combination of glecaprevir + pibrentasvir, currently under investigation in clinical trials.

Although no patent application filed by AbbVie on long-acting formulations was found, those related to the **base compound for both glecaprevir and pibrentasvir, whenever filed and granted in a specific country, are expected to expire in 2031, and it is likely to be a barrier for the development and production of and access to long-acting formulations**.

Isoniazid + Rifapentine

Findings indicate **there are no patent barriers for the development of long-acting formulation on isoniazid + rifapentine in relation to Sanofi**.

Bedaquiline

A total of nine patents and/or patent applications on bedaquiline were identified, of which one (WO 2019/012100) is related to a long-acting formulation of bedaquiline in its free form or as a fumarate salt in micro- or nanoparticles. It also aims to protect the use of such pharmaceutical composition in the long-term treatment of *Mycobacterium tuberculosis* (such as the latent/dormant form) and *Mycobacterium leprae* currently being developed by Janssen.

Delamanid

A total of 15 patents and/or patent applications on delamanid were identified, of which one (WO 2019/240104) aims to protect a pharmaceutical composition (oral) in which a process to obtain nanoparticles of the API is described.

A total of nine patents and/or patent applications on bedaquiline were identified, of which one (WO 2019/012100) is related to a long-acting formulation of bedaquiline.

Patent Applications Related to Nanotechnology and Pharmaceutical Composition by the University of Liverpool

A total of 30 patents and/or patent applications were identified related to the University of Liverpool patent search, of which 13 patents/applications were from the license between the Medicines Patent Pool and the University of Liverpool (2015) and the Medicine Patent Pool long-acting formulations landscape (2018). Therefore, **17 new patents/applications were found**

as a result of this study. The 30 patents/applications are detailed in the tables in this section. Although none of them were related to long-acting injectables covering the selected API of this study, they covered the technology platform of the solid drug nanoparticle (SDN), which may be applied for the development of such formulations with those API.

General Recommendations

- In the scope of the LONGEVITY Project, licensing agreements may require negotiations either with originator companies (for the case of glecaprevir and pibrentasvir) or with patent holders of the technonology platform adopted (UoL and Tandem Nano Ltd). Equitable access issues must be addressed from the begining of the development process, which include guaranteeing affordable prices for the population in need in all countries and pursuing more than one producer to ensure a sustainable supply.
- Monitor and follow up at the national level patent filing and status to assess approaches to overcome access barriers.
- In relation to the current MPP license with AbbVie for glecaprevir/pibrentasvir, it is important to review and address concerns previously raised, to provide clear language with regards to the development of long-acting formulations and to **ensure that sublicensees, preferably generic manufacturers, who eventually develop them are able to commercialize in all low- and middle-income countries (LMICs)**. This ensures that any long-acting injectable is made available equitably and at an affordable price.
- Promote the adoption and use of TRIPS flexibilities to challenge patent barriers; activities may include: a) assessing the national law and the possibility of filing patent oppositions for applications related to both glecaprevir and pibrentasvir (base compounds) based on the grounds presented at pre-grant oppositions filed in India as well as other target patent/applications; b) promoting the issuance of compulsory licenses in cases where the patents are granted.
- Explore the so-called "research exemption" or "experimental use," which is possible within the scope of Article 30 of the TRIPS Agreement, in the legislation of countries involved in the LONGEVITY Project, as it may allow the use of patented inventions for research purposes during the patent term. However, once the technology is approved, equitable access issues should be considered from the very early stages of the development process.

Once the technology is approved, equitable access issues should be considered from the very early stages of the development process.

1 BACKGROUND AND RATIONALE

The increasing interest in the development of long-acting medicines for infectious diseases is related to its potential for improving people's acceptability and adherence to medications and reducing clinical intervention, such as for adolescent or pediatric patients; people in rural and remote areas, who may not be able to easily refill prescriptions; and incarcerated individuals, who may benefit from shorter treatment regimens. Although it may be linked to different routes of delivery (for example, oral, injection, transdermal), the term "long-acting formulation" (LAF) is related to those "formulations designed to deliver exposure to therapeutic concentrations of active pharmaceutical ingredients (API) over a protracted period of time."[1]

Long-acting injectable formulations are not an entirely new approach within the field of pharmaceutical compositions and some have been previously approved for contraception and schizophrenia,[2] yet these options may be less familiar to patients and providers, or less available in countries, particularly in the global South. In December 2020, the European Medicines Agency granted market authorization for the first HIV long-acting injectables (LAIs), cabotegravir (ViiV Healthcare) and rilpivirine (Janssen-Cilag International), to be administered monthly or every two months.[3] Both LAIs were developed as basis SDN suspensions,[4] which have been considered mechanisms for such formulations due to their ability to enhance drug delivery.[5]

There are a number of scientific challenges concerning the development of LAFs, but there are also access issues to be considered and addressed to ensure that when those technologies are approved they can be available for those in need. So far, there have been several access barriers to newer medicines for hepatitis C and tuberculosis (TB), including high prices of those under patent monopolies. Although not all access barriers may be related to patent protection, patents are one critical aspect of it,

compromising not only prices but also the ability to scale-up production in different countries to ensure timely availability. The license agreement between Tandem Nano Ltd and the Medicines Patent Pool was signed on 31 August, 2021.[6]

An update on the patent analysis for related hepatitis C and TB medicines can inform applicability and accessibility strategies when used in the development of LAFs.

Project Partners

In 2020, the LONGEVITY Project[7] was approved to develop novel, long-acting preventive formulations for malaria and latent TB infection (LTBI) and "a single-injection cure" for hepatites C.[8] The limited familiarity with and understanding of LAFs among affected communities and the often limited community engagement in Research and Development (R&D) processes shows a need to examine related drugs in the pipeline and potential access issues.

The LONGEVITY Project is implemented by a consortium of partners: the University of Liverpool, John Hopkins University, Clinton Health Access Initiative (CHAI), University of Nebraska, and the Medicines Patent Pool (MPP).[9] An external advisory board contributes expert advice and ensures the latest clinical results and scientific developments are considered. The University of Liverpool coordinates the overall project activities.

The University of Liverpool and John Hopkins University conduct the pre-clinical and clinical development of the malaria and LTBI LAFs; John Hopkins University conducts the clinical development of the formulation for hepatitis C virus (HCV).

There are firewalls to prevent conflict of interest between the partners involved in the R&D and those involved in the manufacturing and commercialization processes. University of Liverpool's start-up firm, Tandem Nano Ltd, is not a consortium member and engages in pre-clinical drug selection and manufacturing stages, including in technology transfer, freedom to operate, and licensing activities. The MPP is involved in contract and licensing negotiations and in selecting commercial partners, including generic manufacturers, through a transparent tendering process. CHAI engages with regulatory authorities and will be involved in cost-of-goods analysis and pricing strategies.

The University of Nebraska conducts the provider and patient/community acceptability surveys about these technologies and manages stakeholder engagement activities. Treatment Action Group (TAG) is not a consortium member but has partnered with the University of Nebraska as a subcontractor to coordinate community engagement in the research, including supporting the acceptability surveys and developing treatment literacy materials about long-acting preventives and therapeutics.

Two pharmaceutical corporations are not consortium members but provide input. AbbVie provides expertise and in-kind drug donations

of glecaprevir and pibrentasvir (which are World Health Organization [WHO] prequalified/stringent regulatory authority approved), which is in development as an LAI. Janssen, which has a history of developing LAFs in other disease areas, has also committed to providing expertise to the consortium.

Objectives

This report aims to investigate if there are potential patent barriers for the development and delivery of LAFs for selected hepatitis C and tuberculosis medicines. The landscape includes four drugs studied under the LONGEVITY Project—glecaprevir and pibrentasvir (for HCV), rifapentine and isoniazid—and two additional TB drugs outside the scope of the LONGEVITY Project, bedaquiline and delamanid, because they are important in treating multidrug-resistant tuberculosis (MDR-TB) and are under investigation for long-acting formulations by other sponsors.

Therefore, the specific objectives are:

- To analyse patenting trends of hepatitis C medicines (glecaprevir + pibrentasvir) and tuberculosis medicines (rifapentine + isoniazid, bedaquiline and delamanid);
- To develop a preliminary and non-exhaustive patent landscape on the technology used to make the drugs into long-acting formulations under the LONGEVITY Project and its subsidiary Tandem Nano Ltd.

2 METHODOLOGY

The detailed methodology is described in Appendix 1. To analyze patenting trends of selected medicines, the study aimed to update the existing patent landscapes on glecaprevir + pibrentasvir, rifapentine + isoniazid, and bedaquiline and delamanid.

The first step was to identify patents and/or patent applications (hereafter patent[s]/application[s]) from secondary sources such as reports on the patent landscape and databases. The second step involved searches in publicly available primary sources, such as the US FDA Orange Book, Health Canada Patent Register, Canadian Intellectual Property Office, and Google Patents Advanced Search, using different combinations of keywords. This search focused on those patents/applications filed by the companies who first obtained market approval for each medicine. The search was carried out in September 2020. For the purposes of this report, we adopted the PCT international publication number (WO) to refer to each application identified.

Defining the patent status (carried out in October 2020 with some complementary updates from February-July 2021 for some cases) of a select list of 36 countries required gathering information from, whenever possible, the websites of National and Regional Patent Offices, and in databases such as the Medicines Patents and Licenses Database (MedsPaL), World Intellectual Property Organization (WIPO) Patent Scope, and European Patent Office – Espacenet (EPO Espacenet). The tables with status and national patent numbers are detailed in Appendix 2. Countries selected are high-burden HCV and TB countries, part of the IMPAACT4TB[10] project,[11] and are part of our activist networks. This includes several high-income countries that could benefit from the long-acting technologies.

The reference document for the analysis of the content of the claims was the international application published under the WIPO PCT, with

the International Publication Number (WO), applying the classification proposed by ICTSD/UNCTAD/WHO (2007) and UNDP (2016).[12]

A similar approach was adopted to identify patent(s)/application(s) related to LAFs by the University of Liverpool, where an initial list was first identified in a publicly available document. We then carried out a search in Google Patents Advanced Search and EPO Espacenet. Preliminary analysis aimed to identify whether a specific API was covered by the patent/application and what type of protection was covered for the pharmaceutical composition. No patent status analysis was carried out in selected countries. The content of the PCT application and the publication number were adopted as reference for the analysis.

3 CASE ANALYSIS

1. Glecaprevir + Pibrentasvir

1.1 Background

Glecaprevir is a HCV NS3/4A protease inhibitor; pibrentasvir is a HCV NS5A inhibitor. Both are direct-acting antiviral medications, which can effectively cure over 95% of people with HCV by achieving a sustained virological response in 8, 12, or 16 weeks, depending on genotype and stage of liver disease. The current available version, under the brand names Mavyret or Maviret, is a solid dosage-form (tablet) as a fixed-dose combination (FDC) containing 100 mg of glecaprevir and 40 mg of pibrentasvir.

Mavyret received US FDA market approval on August 3, 2017, with AbbVie Inc. as the applicant.[13] In 2019, glecaprevir + pibrentasvir FDC was included in the WHO Essential Medicines List (21st version).[14]

Glecaprevir + pibrentasvir FDC is considered a pan-genotype medicine for hepatitis C, covering genotypes 1, 2, 3, 4, 5, and 6 within some specific indications[15] as described in Table 1.

In 2017, the indications approved were as follows:

- Treatment of patients with chronic HCV genotype (GT) 1, 2, 3, 4, 5, or 6 infection without cirrhosis and with compensated cirrhosis (Child-Pugh A);
- Treatment of adult patients with HCV genotype 1 infection who have been previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

Recommended dosage for adults was three tablets once a day with food (total 300 mg of glecaprevir and 120 mg of pibrentasvir per day).

The duration of the treatment proposed in Table 1 is based on the following population:

- HCV mono-infected;
- HCV/HIV-1 co-infected patients with compensated liver disease (with or without cirrhosis) and with or without loss of kidney functions, including patients receiving dialysis.

TABLE 1.
Indication and Treatment Duration for Glecaprevir + Pibrentasvir FDC, US 2017

HCV genotype	Patients previously treated with a regimen containing	Treatment duration	
		No cirrhosis	Compensated cirrhosis (Child-Pugh A)
Treatment-naive patients			
1, 2, 3, 4, 5, or 6	-	8 weeks	12 weeks
Treatment-experienced patients			
1	An NS5A inhibitor without prior treatment with an NS3/4A protease inhibitor (ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin)	16 weeks	16 weeks
1	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor (simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin)	12 weeks	12 weeks
1, 2, 3, 4, 5, or 6	PRS = Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor	8 weeks	12 weeks
3	PRS = Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor	16 weeks	16 weeks

Source: US FDA Highlights of Prescribing Information (2017).

Since its 2017 market approval, glecaprevavir + pibrentasvir FDC has been incorporating new indications and recommendations of use.

In 2018, the FDC was also recommended[16] for liver and kidney transplant recipients with different durations of treatment, as follows:

- 12 weeks;
- 16 weeks for genotype 1-infected patients who are NS5A inhibitors-experienced but without prior treatment with an NS3/4A protease inhibitor, or for genotype 3-infected patients who are PRS treatment-experienced.

In 2019, notably, indications were expanded from the adult population to include pediatric patients for all gentoypes 12 years and older or weighing at least 45 kg (or 99 lbs), covering the durations of treatments described in Table 1. The use of the FDC for liver and kidney transplant recipients was also extended to this age/weight group.

As a pangenotypic treatment with high sustained virologic response (SVR) rates and a shorter treatment duration, the G/P combination has the potential to treat older children and adolescents and populations that could benefit from fewer refills, such as remote or rural communities and people with short sentences who are waiting for release from detainment or incarceration. LAFs that shorten and simplify treatment from daily pills to one administration could reduce stigma and provide discretion for the person.

1.2 Patent Landscape

In 2017, Unitaid published two reports[17] with the patent landscapes of glecaprevir and pibrentasvir, identifying those related to each compound as well as to the combination. The search for those patents was conducted in December 2016.

For glecaprevir, the three patents/applications identified covered the API, method of treating HCV infection for genotypes 2, 3, 4, or 6 (when genotype is not established) and crystalline forms of the API (see Table 2).

For pibrentasvir, two patents/applications identified covered the API, one claimed a method of treatment of HCV where genotype is not established and two claimed crystalline forms of the API (see Table 3).

The search identified eight patents/applications that included the combination of glecaprevir and pibrentasvir, five of them claimed largely through the "method of treatment." This type of patent aims to protect an interferon-free method for treating HCV infection involving the combination of glecaprevir and pibrentasvir, either with or without ribavirin, for a duration of 12 weeks. One patent/application was related to a pharmaceutical composition involving different therapeutic agents against HCV, including the combination of two or more compounds, such as glecaprevir and pibrentasvir. Two patents/applications covered a solid pharmaceutical composition with 100 mg of glecaprevir and 40 mg of pibrentasvir.

MedsPaL shows three additional patents/applications related to the combination, covering both pharmaceutical compositions and method of treatment.

The present research identified ten additional patents/applications: two related to glecaprevir, two related to pibrentasvir, and six related to the combination glecaprevir + pibrentasvir.

TABLE 2.
Patents and/or Patent Applications for Glecaprevir, as of September 2020

Patent	International publication number (publication date) Title*	Applicant	Brief analysis
Patent 1	WO 2012/040167 (29/03/2012) Macrocyclic proline derived HCV serine protease inhibitors	Enanta Pharma Inc.	Covers the active pharmaceutical ingredient. Where the patent is granted, it is likely to block generic production, import, market, and use.**
Patent 2	WO 2015/061742 (30/04/2015) Methods for treating HCV	AbbVie	Method of treating with glecaprevir HCV genotypes 2, 3, 4, or 6 when genotype is not established. It covers methods of treatment of glecaprevir in combination and duration of treatment.
Patent 3	WO 2015/188045 (10/12/2015) Crystal Forms	AbbVie	Crystalline forms of glecaprevir.**
Patent 4	No PCT filed (US patents only) US9809534 B1 (17/11/2017) Difluoroalkylcyclopropyl amino acids and esters, and syntheses thereof ***	AbbVie	Key-intermediates for the synthesis of glecaprevir and their synthesis process.
Patent 5	No PCT filed (US only) US9809576 B1 (07/11/2017) Synthetic route to anti-viral agents ***	AbbVie	Synthesis process for glecaprevir.

Source: Unitaid report (2017); MedsPaL; MSF patent opposition database and Pat-informed database.
*As described in the PCT application.
**Analysis obtained from Unitaid reports (2017) for glecaprevir.
***Identified in Pat-Informed database (https://www.wipo.int/patinformed/).
Rows colored in light red are updated patents/applications.

TABLE 3.
Patents and/or Patent Applications for Pibrentasvir, as of September 2020.

Patent	International publication number (publication date) Title*	Applicant	Brief analysis
Patent 1	WO 2012/051361 (19/04/2012) Antiviral compounds	AbbVie	Covers the active pharmaceutical ingredient. Where the patent is granted, it is likely to block generic production, import, market, and use.**
Patent 2	WO 2012/116257 (30/08/2012) Antiviral compounds	AbbVie	Covers the active pharmaceutical ingredient.** (identical patent to the previous one)
Patent 3	WO 2014/047039 (27/03/2014) Methods for treating hepatitis C	AbbVie	Claims a method of treatment for HCV that comprises administration of pibrentasvir or a salt thereof, where genotype is not established.**
Patent 4	WO 2015/171993 (12/11/2015) Crystal forms	AbbVie	Claims crystalline forms of pibrentasvir.**
Patent 5	WO 2016/053869 (07/04/2016) Solid forms of antiviral compounds	AbbVie	Crystalline forms of pibrentasvir.**
Patent 6	WO 2018/093717 (24/05/2018) Compositions and methods for treating HCV infection	AbbVie	Pharmaceutical composition (tablet) involving combinations of HCV inhibitors, such as: pibrentasvir + a specific inhibitor of HCV polymerase (compound 1); Compound 1 + different options of pibrentasvir prodrugs; Compound 1+pibentrasvir+glecaprevir; Compound 1+glecaprevir+different options of pibentrasvir prodrugs. Methods of treatment. Doses.
Patent 7	WO 2020/047182 (05/03/2020) Process for manufacturing pibrentasvir active drug substance	AbbVie	Key-intermediates to synthetize pibrentasvir, process to synthetize pibrentasvir, compositions involving pibrentasvir, pibrentasvir (API) linked to its impurities.

Source: Unitaid report (2017); MedsPaL; MSF patent opposition database and patent search described in the Methodology.
*As described in the PCT application.
**Analysis obtained from Unitaid reports (2017) for pibrentasvir.
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

TABLE 4.
Patents and/or Patent Applications Involving the Combination of Glecaprevir and Pibrentasvir, as of September 2020, and Related Clinical Trials

Patent	International publication number (publication date) Title*	Applicant	Brief analysis	Clinical trials related to the indication described
Patent 1	WO 2014/152514 (25/09/2014) Combination of two antivirals for treating hepatitis C	AbbVie	Method of treatment for HCV infection, which comprises administration of at least two DAAs, including glecaprevir and pibrentasvir, wherein neither interferon nor ribavirin is administered during the treatment. Duration of no more than 12 weeks.**	
Patent 2	WO 2014/152635 (25/09/2014) Combination of direct-acting agents and ribavirin for treating HCV patients	AbbVie	Method for treatment for HCV infection, which comprises administration of ribavirin and at least two DAAs, including glecaprevir and pibrentasvir, without administration of interferon. Duration of no more than 12 weeks.**	
Patent 3	WO 2015/153792 (08/10/2015) Methods for treating HCV	AbbVie	Method of treatment for HCV infection, which comprises administration of at least two DAAs, including glecaprevir and pibrentasvir, wherein neither interferon nor ribavirin is administered during the treatment. Duration of no more than 12 weeks.**	
Patent 4	WO 2015/153793 (08/10/2015) Methods for treating HCV	AbbVie	Method for treating HCV infection, which comprises administration of at least two DAAs selected from glecaprevir, pibrentasvir, and sofosbuvir, without administration of either interferon or ribavirin. Duration of no more than 12 weeks.**	
Patent 5	WO 2016/134058 (25/08/2016) Combinations useful to treat Hapatitis C virus	AbbVie	Pharmaceutical composition comprising two or more therapeutic agents that are useful for treating HCV, including a nucleoside/nucleotide-based NS5B inhibitor (A-1 to A-6) and pibrentasvir or ombitasvir). The composition may further contain glecaprevir.**	
Patent 6	WO 2016/210273 (29/12/2016) Solid pharmaceutical compositions for treating HCV	AbbVie	Solid pharmaceutical composition involving 100 mg of glecaprevir and 40 mg of pibrentasvir.	Early dosing studies: SURVEYOR-1, -2 NCT02243280 https://clinicaltrials.gov/ct2/show/NCT02243280 Study completed: 2/2016.

Patent 7	PCT not found US2017/15431906 US2017/0151238 (granted Number) Methods for treating HCV	AbbVie	Method for treating HCV infection (genotypes 1–6, with or without cirrhosis) with glecaprevir and pibrentasvir. It includes specific doses and duration of treatment.	
Patent 8	WO 2017/015211 (26/01/2017) Solid pharmaceutical compositions for treating HCV	AbbVie	Solid pharmaceutical composition involving 100 mg of glecaprevir and 40 mg of pibrentasvir. Similar/identical to WO2016210273.	Early dosing studies: SURVEYOR-1, -2 NCT02243280 https://clinicaltrials.gov/ct2/show/NCT02243280 Study completed: 2/2016.
Patent 9	WO 2017/007934 (12/01/2017) Methods for treating HCV	AbbVie	Method of treatment for HCV involving one of the following combinations: glecaprevir+pibrentasvir; glecaprevir+pibrentasvir+sofosbuvir; pibrentasvir+sofosbuvir. The method of treatment does not include ribavirin and interferon and can last 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks. It applies to patients with HCV genotypes 1–6, without cirrhosis, with compensated cirrhosis, treatment-naive, or interferon non-responder.	**Relevant clinical trials:** ENDURANCE-1 NCT02604017 https://clinicaltrials.gov/ct2/show/NCT02604017; study completed: 1/2017. ENDURANCE-2 NCT02640482 https://clinicaltrials.gov/ct2/show/NCT02640482; study completed: 2/2017. ENDURANCE-3 NCT02640157 https://clinicaltrials.gov/ct2/show/NCT02640157; study completed: 2/2017. ENDURANCE-4 NCT02636595 https://clinicaltrials.gov/ct2/show/NCT02636595; study completed: 1/2017. *SURVEYOR-II (Part 4) coincides with ENDURANCE-2 and ENDURANCE-4 NCT02243293 https://clinicaltrials.gov/ct2/show/NCT02243293; study completed: 2/23/2017. ENDURANCE-5, 6 NCT02966795 https://clinicaltrials.gov/ct2/show/NCT02966795; study completed: 8/29/2018.

				EXPEDITION-1 NCT02642432 https://clinicaltrials.gov/ct2/show/NCT02642432; study completed: 2/10/2017. EXPEDITION-2 NCT02738138 https://clinicaltrials.gov/ct2/show/NCT02738138; study completed: 6/7/2017. EXPEDITION-4 NCT02651194 https://clinicaltrials.gov/ct2/show/NCT02651194; study completed: 1/2017. EXPEDITION-5 NCT03069365 https://clinicaltrials.gov/ct2/show/NCT03069365; study completed: 6/5/2017. EXPEDITION-8 NCT03089944 https://clinicaltrials.gov/ct2/show/NCT03089944; study completed: 11/8/2019.
Patent 10	WO 2018/057919 (A1) (29/03/2018) Dose adjustment	AbbVie	Method for treating HCV in patients with an independent comorbid condition in which dose of medicines are adjusted before administering glecaprevir and pibrentasvir (once a day). Such medicines are substrates of Organic Anion Transporting Polypetide, P-glycoprotein, and Breast Cancer Resistance Protein. Establishes doses for G+P (300 mg+120 mg) as well as period of treatment and HCV genotypes or patient profile. Establishes for certain medicines indicated for co-morbidity.	

Patent 11	WO 2019/074507 (A1) (18/04/2019) Methods for treating HCV	AbbVie	Method for re-treating HCV patients that have previously failed glecaprevir and pribentasvir combination treatment. This treatment involves: glecaprevir+pibrentasvir+sofosbuvir+ribavirin. Period of treatment can be 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks. Indications include for HCV genotypes 1–6, patients without cirrhosis, with compensated cirrhosis, treatment-naive, interferon non-responder, or patients with resistance-related substitutions. Doses for the combination are 300 mg of glecaprevir (once a day), 120 mg of pibrentasvir (once a day), 400 mg of sofosbuvir (once a day), and ribavirin (1000–1200 mg) based on weight (twice a day).	MAGELLAN-1 Part 1, interim results: https://pubmed.ncbi.nlm.nih.gov/28128852/ MAGELLAN-2 Part 2 NCT02446717 https://clinicaltrials.gov/ct2/show/NCT02446717; study completed: 1/2017. MAGELLAN – 3 NCT02939989 https://clinicaltrials.gov/ct2/show/NCT02939989
Patent 12	WO 2019/027694 (07/02/2019) Methods for treating HCV	AbbVie	Method for treating or preventing HCV (genotypes 1–6) infection in a transplant recipient receiving a solid organ (kidney or liver) from an HCV-infected donor. Treatment based on glecaprevir (300 mg) and pibrentasvir (120 mg) for no more than 16 weeks and does not include ribavirin and interferon. Indications include either HCV-free prior to receiving the transplant or HCV patients treatment-experienced (not related to transplant).	EXPEDITION-4 NCT02651194 https://clinicaltrials.gov/ct2/show/NCT02651194; study completed: 1/2017; results posted: 10/16/2017 EXPEDITION-5 NCT03069365 https://clinicaltrials.gov/ct2/show/NCT03069365; study completed: 6/5/2017; results posted:5/4/2019 SURVEYOR-3 NCT02243293 https://clinicaltrials.gov/ct2/show/NCT02243293; study completed: 2/23/2017; results posted: 10/2/2017
Patent 13	WO 2019/046569 (07/03/2019) Methods for treating HCV	AbbVie	Method for treating or preventing HCV (genotypes 1–6) infection in a transplant recipient receiving a solid organ (kidney or liver) from an HCV-infected donor. Treatment based on glecaprevir (300 mg) and pibrentasvir (120 mg) for no more than 16 weeks and does not include ribavirin and interferon. Indications include patients HCV-free prior to receiving the transplant or without cirrhosis.	EXPEDITION-4 NCT02651194 https://clinicaltrials.gov/ct2/show/NCT02651194; study completed: 1/2017. EXPEDITION-5 NCT03069365 https://clinicaltrials.gov/ct2/show/NCT03069365; study completed: 6/5/2017.

Patent 14	WO 2020/106835 (A1) (28/05/2020) Methods for treating acute HCV	AbbVie	Method for treating acute HCV involving glecaprevir+pibrentasvir for 6 weeks, without interferon and ribavirin. Indications include patients co-infected with HCV-HIV, without cirrhosis, with compensated cirrhosis, treatment-naive, interferon non-responder, kidney or liver transplanted, or with a degree of renal impairment, for genotypes 1–6.	EXPEDITION-4 NCT02651194 https://clinicaltrials.gov/ct2/show/NCT02651194; study completed: 1/2017. EXPEDITION-5 NCT03069365 https://clinicaltrials.gov/ct2/show/NCT03069365; study completed: 6/5/2017.

Source: Unitaid report (2017); MedsPaL; MSF patent opposition database and patent search described in the Methodology.
*As described in the PCT application.
**Analysis obtained from Unitaid reports (2017) for glecaprevir/pibrentasvir.
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

The two updated patents on glecaprevir (Patents 4 and 5, Table 2) are filed only in the US and are related to processes and intermediates to the synthesis of the API.

In relation to the first updated patent/application for pibrentasvir (Patent 6, Table 3), WO 2018/093717 covers not only pharmaceutical compositions (tablet) involving at least two HCV inhibitors but also methods for treating HCV with such combinations (Appendix 2, Table 2.1). The following combinations are claimed in this patent as pharmaceutical compositions:

- Compound 1 (described as a HCV polymerase inhibitor, US Application No 15/254,342) (Appendix 2, Figure A2.1) and pibrentasvir (claim 1);
- Compound 1 and prodrugs of pibrentasvir (compounds 2b–2k and examples 3–1 to 3–10) (claims 3–8). In the description report, dozens of prodrugs molecules can be selected from the basic structures disclosed. Examples of some of the prodrugs claimed are illustrated in Appendix 2, Figure A2.2;
- Compound 1 + pibrentasvir + glecaprevir (claim 33);
- Compound 1 + prodrugs of pibrentasvir + glecaprevir (claim 33).

The second patent/application related to pibrentasvir (WO 2020/047182, Patent 7, Table 3) discloses a process to obtain "pibrentasvir in substantially pure form" (97% pibrentasvir and 3% impurities) more suitable for the manufacturing process of the final product in a commercial scale. However, the process to achieve this level of purity is not only claimed in different ways, but product claims are also identified that aim to protect pibrentasvir as a "composition" and as a "drug product":

> "A **composition** comprising **pibrentasvir**; and an impurity; wherein the composition comprises at least **97 weight percent** of pibrentasvir and not more than **3 weight percent of the impurity**; wherein the composition is **prepared by a process** comprising..." (claim 18)

> "A **drug product** comprising a **drug substance**; wherein the drug substance comprises at least **97 weight percent of pibrentasvir** and not more than **3 weight percent of an impurity**; wherein the drug substance is **prepared by a process** comprising..." (claim 23)

The six updated patents/applications related to the combination of glecaprevir + pibrentasvir (Patents 9–14, Table 4) are related to methods of treatment. All of them aim to protect an interferon-free approach and five of them are also ribavirin-free. The detailed analysis of those six patent/applications is available in Appendix 2, Table A2.2.

WO 2017/007934 (Patent 9, Table 4) involves the method of treatment for HCV infection including sofosbuvir as a third direct-acting antiviral (DAA) in the combination or in combination with pibrentasvir only. As detailed in Table 4, there are several clinical trials related to indications covered by the patent.

WO 2018/057919 (Patent 10, Table 4) is focused on adjusting the doses of certain medicines indicated for an independent co-morbidity. It also aims to protect a list of medicines not recommended or contraindicated when administering the combination of glecaprevir + pibrentasvir.

WO 2019/074507 (Patent 11, Table 4) is proposing a regimen involving glecaprevir + pibrentasvir + sofosbuvir as well as ribavirin for patients who failed a previous treatment with glecaprevir + pibrentasvir. The content of this patent application is related to three clinical trials: MAGELLAN-1, MAGELLAN-2, and MAGELLAN-3.

WO 2019/027694 and WO 2019/046569 (Patents 12 and 13, Table 4) are related to either treating or preventing HCV in a transplant recipient patient (liver or kidney) from an HCV-infected donor. These indications were investigated in some clinical trials, such as EXPEDITION 4 and 5, and for Patent 12, also in the study called SURVEYOR-3 (Table 4). They are also associated with the newer 2018[18] FDA recommendation of the combination in liver and kidney transplant recipients.

WO 2020/106835 (Patent 14, Table 4) focuses on acute HCV by administering the combination over 6 weeks. The medical indication is being studied in the following clinical trials: Expedition 4 and 5.

The patent status in selected countries,[19] as of October 2020, with complementary updates in February-July 2021 for some cases, are described in Tables 5, 6, and 7. The tables with status and national patent numbers are detailed in Appendix 5.

TABLE 5.
Patent Status in Selected Countries for Glecaprevir

WO (International publication number) Title	Granted	Pending	Not filed	Not found	Withdrawn
Patent 1 WO 2012/040167 (A1) Macrocyclic proline derived HCV serine protease inhibitors	Australia (A); Belarus (B and D); Canada (A); EU (EPO) (B); Kazakhstan (B); Kyrgyzstan (B); Mexico (D); Pakistan (D); Peru (A); Russia (B); South Africa (A); Tajikistan (B); Turkey (B); Ukraine (C and D); US (USPTO) (A)	Brazil (A); India (A); Indonesia (A); Vietnam (A)	Burkina Faso (B); Cambodia (D); Côte d'Ivoire (D); DRC (D); Ethiopia (C and D); Ghana B); Kenya (B); Nigeria (B); Malawi (B); Morocco (C and D); Mozambique (B); Rwanda (B); Senegal (B); Tanzania (B); Uganda (B); Uzbekistan (D); Zimbabwe (B)		
Patent 2 WO 2015/061742 (A2) Methods for treating HCV			Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Cambodia (D); Côte d'Ivoire (D); DRC (B); Ethiopia (B); Ghana (B); India (A) Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Morocco (C and D); Mozambique (B); Nigeria (D); Pakistan (D); Peru (A); Russia (B); Rwanda(B); Senegal (B); Tajikistan (B); Tanzania (C); Turkey (D); Uganda (B); Ukraine (C and E); South Africa (A); Zimbabwe (B)		Canada (A); EU (EPO) (B); US (USPTO) (A); Mexico (A)
Patent 3 WO 2015/188045 (A1) Crystal Forms	Australia (A); Mexico (C); US (USPTO) (A)	Brazil (A); Canada (A); EU (EPO) (E); Turkey (D)	Belarus (B); Burkina Faso (C); Côte d'Ivoire (D); DRC (D); Ethiopia (D); Ghana (B); India (A); Indonesia (D); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Morocco (B); Nigeria (D); Rwanda (B); Peru (A); Senegal (D); South Africa (A); Tanzania (B); Tajikistan (B and D); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; Pakistan; Russia (C and E); Ukraine; Uzbekistan	
Patent 4 US9809534 (B1) Difluoroalkylcy-clopropyl amino acids and esters, and syntheses thereof	US (USPTO) (A)*				
Patent 5 US9809576 (B1) Synthetic route to antiviral agents	US (USPTO) (A)*				

Sources: (A): National Patent Office; (B): Regional Patent Office; (C): WIPO Patent Scope; (D): MedsPaL; and (E): EPO Espacenet.
*No PCT filed (US patents only). The status was not searched in other countries.
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

TABLE 6.
Patent Status in Selected Countries for Pibrentasvir

WO (International publication number) Title	Granted	Pending	Not Filed	Not Found	Withdrawn
Patent 1 WO 2012/051361 (A1) Antiviral compounds	Australia (A); Belarus (B); Canada (A); EU (EPO) (B)*; Indonesia (A); Kazakhstan (B); Kyrgyzstan (B); Mexico (C); Peru (A); Russia (B); South Africa (A)*; Tajikistan (B); Ukraine (D); US (USPTO) (A); Vietnam (A)	Brazil (A); EU (EPO) (B)*; India (A); Pakistan (D);; Turkey (D)	Cambodia (D); Burkina Faso (D); Côte d'Ivoire (D); DRC (D); Ethiopia (D); Morocco (D); Nigeria (D); Senegal (D); Uzbekistan (D); Rwanda (B); Ghana (B); Kenya (B); Malawi (B); Mozambique (B); Tanzania (B); Zimbabwe (B)		
Patent 2 WO 2012/116257 (A1) Antiviral compounds	EU (EPO) (B); Mexico (C); US (USPTO) (A)		Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Côte d'Ivoire (D); Ghana (B); Indonesia (A); India (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (D); Peru (A); Russia (B); Senegal (B); South Africa (A); Tanzania (B); Tajikistan (B); Uganda (B); Rwanda (B); Zimbabwe (B); Uzbekistan (D); Vietnam (A)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Turkey; Ukraine	Canada (A); US (USPTO) (A)
Patent 3 WO 2014/047039 (A1) Methods for treating hepatitis C	Australia (A); EU (EPO) (A)**; Mexico (C); Russia (A); South Africa (A); Turkey (D)***	Brazil (A); Canada (A); EU (EPO) (A)**; Turkey (D)***	Belarus (B); Burkina Faso (B and D); Côte d'Ivoire (D); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (D); Peru (A); Senegal (B and D); Tanzania (B); Tajikistan (B); Uganda (B); Zimbabwe (B); Rwanda (B); Vietnam (A)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Ukraine (C and E); Uzbekistan	US (USPTO) (A)
Patent 4 WO 2015/171993 (A1) Crystal forms	US (USPTO) (A)	Australia (E); Canada (A); EU (EPO) (B); Mexico (C); Turkey (D)	Belarus (B); Brazil (A); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Nigeria (D); Mozambique (B); Peru (A); Tanzania (B); Uganda (B); Zimbabwe (B); Rwanda (B); Russia (B); Senegal (D); South Africa (A); Tajikistan (B); Vietnam (A)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Ukraine (C and E); Uzbekistan	Australia (A)****
Patent 5 WO 2016/053869 (A1) Solid forms of antiviral compounds			Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (D); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); Uzbekistan (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Mexico; Morocco; Pakistan; Turkey, Cambodia; Ukraine	US (USPTO) (A)

Patent 6 WO 2018/093717 (A1) Compositions and methods for treating HCV infection			Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Côte d'Ivoire (B); EU (EPO); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (D); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); Uzbekistan (B); Ukraine (C); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Mexico; Morocco; Pakistan; Turkey	US (USPTO) (A)
Patent 7 WO 2020/047182 (A1)***** Process for manufacturing pibrentasvir active drug substance		Australia (A); Brazil (A); Canada (A); EU (EPO); US (USPTO) (A)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Nigeria (D); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); Ukraine (C); Uzbekistan (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Turkey	

Sources: (A): National Patent Office; (B): Regional Patent Office; (C): WIPO Patent Scope; (D): MedsPaL; and (E): EPO Espacenet.
*At EPO we found one patent application pending and one patent granted.
**At EPO we found one patent granted and one application pending related to WO2014/047039 (A1).
***At MedsPaL related to Turkey we found one patent granted and one application that is pending related to WO 2014/047039 (A1) both stemming form relevant EP cases.
****The status of WO 2015/171993 (A1) appears at Australian Patent Office as "Lapsed."
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.
*****Considering the international filing date through the PCT system was 29 August 2019, the entry in the national phase is expected to be 29 August 2020. Therefore, the national application number might not yet be available in some of the selected countries.

TABLE 7.
Patent Status in Selected Countries for the Combination Glecaprevir + Pibrentasvir

WO (International publication number) Title	Granted	Pending	Not Filed	Not Found	With-drawn	Re-voked	Re-jected
Patent 1 WO 2014/152514 (A1) Combination of two antivirals for treating hepatitis C	Australia (A); Belarus (B)**; Canada (A); EU (EPO) (B); Kazakhstan (B)**; Kyrgyzstan (B)**; Mexico (A and C); Russia (B); South Africa (D); Tajikistan (B)**	Belarus (B)**; Brazil (A); Kazakhstan (B)**; Kyrgyzstan (B)**; Russia (B); Tajikistan (B)**	Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kenya (B); Malawi (B); Mozambique (B); Nigeria (D); Rwanda (B); Senegal (B); Tanzania (B); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Turkey; Ukraine (C); Uzbekistan	US (USPTO) (A)		
Patent 2 WO 2014/152635 (A1) Combination of direct-acting agents and ribavirin for treating HCV patients	Australia (A)****; Belarus (B)***; Canada (A); Kazakhstan (B)***; Kyrgyzstan (B)***; Russia (B); South Africa (A); Tajikistan (B)***	Australia (A)****; Belarus (B)***; Brazil (A); Mexico (A); Kazakhstan (B)***; Kyrgyzstan (B)***; Russia (B); Tajikistan (B)***	Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kenya (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tanzania (B); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Morocco; Nigeria; Pakistan; Ukraine; Uzbekistan	US (USPTO) (A)	EU (EPO) (B); Turkey (D)	
Patent 3 WO 2015/153792 (A1) Methods for treating HCV	Australia (A)	Brazil (A); Canada (A); EU (EPO) (B); Mexico (C); US (USPTO) (A)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (B); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tanzania (B); Tajikistan (B); Uganda (B); Uzbekistan (D); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Indonesia; Morocco; Pakistan; Turkey; Ukraine	Australia (B)		
Patent 4 WO 2015/153793 (A1) Methods for treating HCV	Australia (A)	Brazil (A); Canada (A); EU (EPO) (B); Mexico (A); South Africa (A); US (USPTO) (A)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (B); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tanzania (B); Tajikistan (B); Uganda (B); Uzbekistan (D); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Indonesia; Morocco; Pakistan; Turkey; Ukraine			US (USPTO) (A)

Patent 5 WO 2016/134058 (A1) Combinations useful to treat Hepatitis C virus		US (USPTO) (A)	Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Côte d'Ivoire (B); Canada (A); EU (EPO) (B); Ghana (B); India (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Nigeria (B); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tanzania (B); Tajikistan (B); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Indonesia; Morocco; Pakistan; Turkey; Ukraine; Uzbekistan			
Patent 6 WO 2016/210273 (A1) Solid pharmaceutical compositions for treating HCV	South Africa (A)	Australia (A); Belarus (B); Brazil (A); Canada (A); EU (EPO) (B); India (A); Indonesia (A); Kazakhstan (B); Kyrgyzstan (B); Mexico (A); Tajikistan (B) Russia (B); Turkey (D); Ukraine (D); US (USPTO) (A); Vietnam (A)	Burkina Faso (B); Cambodia (D); Côte d'Ivoire (B); DRC (D); Ethiopia (D); Ghana (B); Kenya (B); Malawi (B); Morocco (D); Mozambique (B); Nigeria (B); Pakistan (D); Rwanda (B); Tanzania (B); Uganda (B); Uzbekistan (D); Zimbabwe (B)		US (USPTO) (A)		
Patent 7 US2017/ 15431906 (WO not found) Methods for treating HCV		Australia (A); Brazil (E); Canada (A); EU (EPO) (B); Mexico (C); US (USPTO) (A); Turkey (D)	Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kenya (B); Malawi (B); Mozambique (B); Nigeria (B); Peru (A); Rwanda (B); Tanzania (B); Uganda (B); South Africa (A); Zimbabwe (B)	Belarus; Cambodia; DRC; Ethiopia; Morocco; Kazakhstan; Kyrgyzstan; Pakistan; Russia; Tajikistan; Ukraine; Uzbekistan; Vietnam			
Patent 8 WO 2017/015211 (A1) Solid pharmaceutical compositions for treating HCV	South Africa (A)	Australia (A); Belarus (D); Brazil (E); Canada (A); Peru (A); EU (EPO); India (A); Indonesia (A); Kazakhstan (B); Kyrgyzstan (B); Mexico (A); Russia (B); Tajikistan (B); Turkey (D); Ukraine (D); US (USPTO) (A) Vietnam (A)	Burkina Faso (B); Cambodia (D); Côte d'Ivoire (B); DRC (D); Ethiopia (D); Ghana (B); Kenya (B); Malawi (B); Morocco (D); Mozambique (B); Nigeria (D); Pakistan (D); Rwanda (B); Senegal (B); Tanzania (B); Uganda (B); Uzbekistan (D); Zimbabwe (B)				

Patent 9 WO 2017/007934 (A1) Methods for treating HCV		Australia (A); Brazil (E); Canada (A); EU (EPO) (B); Mexico (A); South Africa (A); US (USPTO) (A)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (B); Russia (B); Rwanda (B); Senegal (B); Tanzania (B); Tajikistan (B); Uganda (B); Ukraine (C); Uzbekistan (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Turkey			
Patent 10 WO 2018/057919 (A1) Dose adjustment		Australia (A); Brazil (A); Canada (A); EU (EPO) (B); Mexico (A)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Nigeria (B); Rwanda (B); Russia (B); Senegal (B); South Africa (A); Tanzania (B); Tajikistan (B); Uganda (B); Ukraine (C); Uzbekistan (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Morocco; Pakistan; Turkey			US (USPTO) (A)
Patent 11 WO 2019/074507 (A1) Methods for treating HCV		Australia (A); Brazil (A); Canada (A); EU (EPO) (B); US (USPTO)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); Ghana (B); India (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Rwanda (B); Russia (B); Senegal (B); South Africa (A); Tanzania (B); Tajikistan (B); Uganda (B); Ukraine (C); Uzbekistan (B); Vietnam (A); Zimbabwe (B)	Cambodia; DRC; Ethiopia; Indonesia (C and E); Nigeria; Uzbekistan (B); Morocco; Pakistan; Turkey			
Patent 12 WO 2019/027694 (A1) Methods for treating HCV		Australia (A); Belarus (B); Brazil (A/C); Canada (A); EU (EPO) (B); Kazakhstan (B); Kyrgyzstan (B); Mexico (A); Russa (B); Tajikistan (B); US (USPTO) (A)	Burkina Faso (B); Côte d'Ivoire (B); DRC (D); Ghana (B); India (A); Kenya (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); South Africa (A); Tanzania (B); Uganda (B); Ukraine (C); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Indonesia; Nigeria; Morocco; Pakistan; Turkey; Uzbekistan			
Patent 13 WO 2019/046569 (A1) Methods for treating HCV		South Africa (A); US (USPTO) (A)	Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); EU (EPO) (B); Ghana (B); India (A); Kenya (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tanzania (B); Tajikistan (B); Uganda (B); Ukraine; (C); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Indonesia; Morocco; Nigeria; Pakistan; Turkey; Uzbekistan			

Patent 14 WO 2020/106835 (A1)***** Methods for treating acute HCV		Australia (A); Canada (A); EU (EPO) (B); US (USPTO) (A)	Australia (A)*; Belarus (B)*; Brazil (A)*; Burkina Faso (B)*; Canada (A)*; Côte d'Ivoire (B)*; DRC (B)*; Ghana (B)*; India (A)*; Indonesia (C, D and E)*; Kazakhstan (B)*; Kenya (B)*; Kyrgyzstan (B)*; Malawi (B)*; Mozambique (B)*; Nigeria (B)*; Peru (A)*; Rwanda (B)*; Russia (B)*; Senegal (B)*; South Africa (A)*; Tanzania (B)*; Tajikistan (B)*; Uganda (B)*; Uzbekistan (B)*; Ukraine (C); *Vietnam (A)*; Zimbabwe (B)*	Cambodia; Ethiopia; Morocco*; Pakistan; Turkey*			

Sources: (A): National Patent Office; (B): Regional Patent Office; (C): WIPO Patent Scope; (D): MedsPaL; and (E): EPO Espacenet.
*Countries that appear as "designated States" in the international application at PCT system.
**For Belarus; Kazakhstan; Kyrgyzstan; and Tajikistan we found one patent granted and one application pending related to WO2014152514 (A1).
***For Belarus; Kazakhstan; Kyrgyzstan; and Tajikistan we found one patent granted and one application pending related to WO 2014/152635 (A1).
****At Australian Patent Office we found two patents granted and one pending related to WO 2014/152635.
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.
*****Considering the international filing date through the PCT system was 20 November 2019, the limit date for entry in the national phase is expected to be 29 November 2020. Therefore, the application number might not yet be available in some of the selected.

1.3 Trends in the Pharmaceutical Patenting

One of the evergreening strategies[20] to extend the monopoly of existing medicines is based on the filing of patents with "secondary" types of claims. This means that they are filed after a primary patent, which is the one related to the active pharmaceutical ingredient[21] and also to the synthetic process of such API.[22]

Secondary patents will aim to protect pharmaceutical compositions (formulation), methods of treatment, uses (including second medical use), combinations, doses, polymorphs, prodrugs, salts, enantiomers, route of administrations, among others.[23]

Figure 1 estimates the expected patent term of the identified patent/applications related to glecaprevir, pibrentasvir, and their combination if they are granted in countries.

The findings indicate that the company, after filing patent applications covering the API for either glecaprevir or pibrentasvir as isolated compounds, filed for the crystalline forms of those API. The updated findings for glecaprevir have shown two patents related to process and intermediates to manufacture the API in the United States. For pibrentasvir, findings have shown patents/applications covering its prodrugs, key-intermediates of the API, and the API in its "pure form."

Some API may have different physical forms (polymorphic forms), including crystalline or amorphous forms, that might have an important role in the solubility and bioavalability of the compound. Although polymorphism is an intrinsic feature of a molecule, companies apply for patents on

FIGURE 1.
Timeline of Potential Patent Protection Related to Glecaprevir, Pibrentasvir and Their Combination

Source: The authors. Estimates based on 20 years patent term counted from the international filing date. Scenario based on patents filed or granted in selected countries.

polymorphic forms (crystalline forms) of existing API as an evergreening approach.[24]

A prodrug is an inactive derivative of an API "that must undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then exert its desired pharmacological effect."[25] In other words, a prodrug is a molecule that is metabolyzed in the human body to become the API in itself.

Prodrug strategy has been used during the development process as an approach to improve solubility of some drugs and has also been reported to be useful in the development of long-acting formulations.[26] According to the status analysis, the patent on the prodrug of pibrentasvir was only filed and granted in the United States and then withdrawn.

The base compound (API) of pibrentasvir has already been subject to patent protection through WO 2012/051361 (Patent 1, Table 6) and WO 2012/116257 (Patent 2, Table 6). However, WO 2020/047182 (Patent 7, Table 6) aims to protect a process of preparing pibrentasvir "in substantially pure form" and a pharmaceutical composition or a "drug product" involving 97% of pibrentasvir and 3% impurities.

In other words, whenever a compound is synthesized from a chemical reaction, there is concern of how much of such compound yields from this reaction. Together with the aimed compound there are also other sub-products, such as key-intermediates, other reagents, and other compounds resulting from previous reactions, including enantiomers. All of these sub-products could be considered as "impurities" and some of them are disclosed in WO 2020/047182.

For this reason, it is a common practice in organic chemistry to submit the result of a chemical reaction to obtain a specific compound through a purification process in order to eliminate as much as possible such "impurities." Other approaches may also consider purification techniques through the synthesis processes to achieve the target compound with less impurities.

Although this is a relevant step in the process of producing the active principle of a medicine, the filing of patent for a process to obtain a "pure form" of an existing API is an evergreening strategy and, if granted, is estimated to expire eight years after the expiration of the related API patent.[27]

Other types of patents/applications identified for both pibrentasvir and the combination of glecaprevir and pibrentasvir were related to pharmaceutical compositions, including with specific doses. Patents on pharmaceutical compositions cover dosage forms (tablets, capsules, injectables) and the formulation of such dosage forms involving an API and excipients (non-active ingredients).[28]

The most prevalent type of secondary patent within those identified for glecaprevir and pibrentasvir is the method of treatment (a total of 13, as shown in Tables 2, 3, and 4). In the scope of such patents/applications, the company aims to protect the combination of glecaprevir and pibrentasvir with or without other compounds such as other DAAs, different indications, the duration of treatment, and doses as well as contraindications.

Method of treatment type of claims link a certain product to treat, prevent, cure, relieve, and diagnosis a certain disease.[29] According to Article 27 of the World Trade Organization (WTO) TRIPS Agreement, Member States can exclude from patentability "(a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals." Whenever the country's legislation excludes this option from patentability, this is usually grounds to oppose this type of patent/application. Method of treatment can also be considered as lacking the patentability requirement of industrial application, as the effect of a method of treatment is in the body and cannot be subject to an industrial process.[30]

In the US context, the criteria for method of treatment patents includes novelty, non-obvious, utility, and providing written descriptions. Method of treatment patents, which meet patentabilty criteria in US patent law, often already disclose or claim the active ingredient(s) and the use for different indications. These patents can be feasible to obtain but are often difficult to challenge once granted, therefore, strengthening patentabilty requirements and inter partes or post-grant review processes at the USPTO are warranted to curb excessive patenting.

This approach allows the company to pursue protection on medical indications being investigated in clinical trials. The early identification of those types of patents/applications allows the monitoring of future indications and recommendation of the medicine and may indicate how promising it is within the therapeutic options for HCV infection.

1.4 Access Implications

A total of 26 patents and/or patent applications were identified for both glecaprevir and pibrentasvir, of which 14 are related to the combination of at least the two compounds, mostly through method of treatment type of claims. Between 2014 and 2019, at least one application per year was filed through the PCT system for the combination of G/P.

While patent applications on the base compounds (API) were filed in 2011–2012, an additional 23 were identified between 2013 and 2019, with an average of 3.3 patent applications filed per year (Figure 1).

Wherever the patents on the base compounds are granted, it is expected to expire in 2031 (based on 20 years patent term). However, in case there are multiple additional patent applications in countries, as part of the evergreening strategy, it may represent further challenges for access to alternative generic versions of those medicines. If granted, those multiple patents may act as a disincentive for generics to get into the market. While pending decision in relation to the patentability, for some countries this may also act as a disincentive for competitors to bring generics into the market as multiple patent applications seems to bring "legal uncertainty" with regards to the patentability of the medicine and some legislation allows patent applicants to claim retrospective compensations to the pending period in case the patents are granted.[31]

In relation to international approaches to address patent barriers, in November 2018, the MPP signed a royalty-free license agreement with AbbVie for glecaprevir/pibrentasvir,[32] covering 96 countries and territories.

According to an analysis published by MSF Access Campaign in August 2019,[33] the positive aspects of this license are related to transparency (as the license was made publicly available on the website); it is royalty-free and "sublicensees do not have to pay royalties out of their net sales"; sublicensees could sell the product in case a country outside the territory scope of the license issues a compulsory license; sublicensees can file patent challenges; MPP can request AbbVie to "provide a waiver on exclusivity of data concerning new chemical entities or other exclusivity

in territory countries in order to enable the registration of the generic medicines produced under the license."

In terms of geographic scope, although the license covers some countries with high prevalence of HCV[34] where the generic version can be supplied, it excludes China and India, which have, respectively, 10 and 6 million people living with HCV. The coverage of the license is 47.5% of the global HCV population. The license limits India to a manufacturer country; they are not allowed to supply domestically.[35]

The license only refers to the FDC of G/P as licensed compounds and with no mention on whether sublicensees could develop pharmaceutical compositions with single compounds or in combination with other compounds. The license also does not include pediatric formulation and the potentials for LAFs.[36]

Within the license, sublicensees are allowed to commercialize the generic version outside the covered countries as long as there are no patents being infringed upon. However, it is unclear how this is applied where patent applications are still pending decision in relation to their patentability.[37]

Other approaches to address patent barriers at the national level have been to file patent oppositions that are relevant and block generic competition. Patent/applications related to the base compound (API) of both glecaprevir[38] and pibrentasvir[39] have been opposed in India by civil society organizations in 2018 and 2019.

The PCT International Preliminary Report on Patentability for six of the seven patents/applications related to the combination of glecaprevir and pibrentasvir, updated in the current landscape, indicate either lack of inventive step and/or novelty according to the cited documents used as prior art,[40] which provides an initial ground for patent oppositions where there are applications filed.

1.5 GSK Patents/Applications on Long-Acting Formulation for HCV Medicines

The MPP/Unitaid (2018)[41] report on intellectual property rights for long-acting technologies identified the involvement and patent filing from GSK in this field for both HIV and HCV technologies.

In relation to HCV, the report mentions the compound GSK2878175 (now since abandoned), subjected to Phase II study, in which three patents/applications on LAI were identified: WO 2016/075582, WO 2016/075583, and WO 2016/075584.

Although WO 2016/075583 was identified in the pibrentasvir patent search, it is not focused on this API in itself. It comprises claims on "methods of treatment" (1–27 and 49–55) and on "pharmaceutical composition" (28–48). The compounds focused by this patent/application are the so-called compound of Formula I (GSK2878175) in combination with either compounds of Formula IIA or Formula IIB (known as anti-miR122 compounds or anti-miR-122 oligonucleotides). It also aims to protect a

method of treatment with the above-mentioned compounds in combination with one or more additional Long-Acting Parenteral (LAP) pharmaceutical compositions of several DAA, among which there are ABT-493 (glecaprevir) and ABT-530 (pibrentasvir). There is a pre-grant opposition filed in India related to this application.

WO2016/075584 aims to protect a LAP pharmaceutical composition comprising a compound of Formula IIA or IIB. It also aims to protect a method of treatment with those compounds in combination with one or more additional LAP pharmaceutical compositions of several DAA, among which there are ABT-493 (glecaprevir) and ABT-530 (pibrentasvir).

Main Conclusions

In relation to potential barriers to the development of and access to long-acting formulations

- No patent application filed by AbbVie on long-acting pharmaceutical composition was found. However, patents (whenever filed and granted in a specific country) related to the base compound for both glecaprevir and pibrentasvir are expected to expire at least in 2031 and it is likely to be a barrier for the development of, production of, and access to long-acting formulations.
- GSK has at least three patents/applications involving the long-acting pharmaceutical composition of HCV medicines. They target a specific compound (GSK2878175) developed by the company in which either glecaprevir and pibrentasvir are one of multiple options to be in combination in this specific pharmaceutical composition. Where compound GSK2878175 is included in the development of long-acting formulations, those patents can be considered relevant.
- Considering the prodrug strategy can be adopted for the development of LA solution-based injections, it is important to monitor the patent landscape regarding patents covering prodrugs of the API. However, the one patent covering prodrugs of pibrentasvir (WO 2018/093717) does not seem to be a barrier as it was only identified in the US, and was later withdrawn.
- Most patents/applications related to method of treatments are linked to specific dosage and therapeutic regimens involving existing oral pharmaceutical form, therefore they are unlikely to block the availability of long-acting pharmaceutical composition.

In relation to what was found in the pipeline

- Updating the patent landscape allowed the authors to identify newer medical indications for the combination of glecaprevir + pibrentasvir (i.e., short treatment of acute HCV infection, in combination with sofosbuvir for re-treatment cases) as well as the adoption of approaches such as prodrugs of pibrentasvir.

Recommendations

- To monitor and follow up at the national level patent filing and status in countries to assess approaches to overcome access barriers.
- In relation to the current MPP license with AbbVie for glecaprevir/pibrentasvir, it is important to review and address concerns previously raised,[42] to provide clear language with regards to the development of long-acting formulations, and to ensure that sublicensees who eventually develop them are able to commercialize in all low- and middle-income countries. To ensure that any long-acting injectable is made available at an affordable price.
- To promote the adoption and use of TRIPS flexibilities in order to challenge patent barriers; activities may include: a) assessing the national law and the possibility of filing patent oppositions for applications related to both glecaprevir and pibrentasvir (base compounds) patents based on the grounds presented at pre-grant oppositions filed in India as well as other target patent/applications; b) promoting the issuance of compulsory licenses in cases where the patents are granted.
- The so-called "research exemption" or "experimental use," possible within the scope of Article 30 of the TRIPS Agreement, should be explored in the legislation by countries involved in the LONGEVITY Project, as it may allow the use of patented inventions for research purposes during the patent term. However, access issues, once the technology is approved, should be considered from the beginning of the development process.

2. Isoniazid + Rifapentine (3HP)

2.1 Background

In 2020, TAG published a report *Isoniazid/Rifapentine (3HP) Access Roadmap and Patent Landscape*[43] which covered two patent applications (WO 2015/011161 and WO 2015/011162) filed by Sanofi as described in Table 8.

The only patent application filed by Sanofi, in addition to the two described and discussed in TAG's report, is the WO 2014/037121, which is prior to them: "Use of rifapentine in the treatment of tuberculosis in patients." The patent application was filed in 2012, before the two other patents/applications were filed. Most of the claims are related to the use of rifapentine to treat active tuberculosis disease or tuberculosis infection in people with HIV/AIDS on antiretroviral (ARV) treatment (claims 1–8; 11).

Such regimen is based on the following efavirenz-based combination:

- efavirenz at a daily dosage of 600 mg
- 300 mg of emtricitabine
- 200 mg tenofovir disoproxil fumarate

The regimen for rifapentine aimed to be protected is as follows:

- administered once a week during the treatment period, in particular at doses varying from 300 to 900 mg
- administered at a dosage of 900 mg once a week during the treatment period of 12 weeks

It also recommends the use of rifapentine and isoniazid to treat tuberculosis infection among people with HIV/AIDS being treat with an efavirenz-based combination.

Claims 9 and 10 are related to a pharmaceutical composition involving rifapentine and isoniazid to treat tuberculosis infection or latent tuberculosis in patients with HIV/AIDS being treated with ARV combination.

Finally, claim 12 aims to protect a pharmaceutical kit comprising:

> "(i) a first pharmaceutical composition comprising rifapentine, possibly in combination with an appropriate companion anti-tuberculosis drug, for example isoniazid;
>
> (ii) a second galenic formulation comprising a combination of efavirenz, emtricitabine and tenofovir; both pharmaceutical compositions (i) and (ii) being intended to be independently administered, each administration with regard to the other one being simultaneous, separated or spread over the time."

TABLE 8.
Patent and/or Patent Applications by Sanofi SA Related to Isoniazid+Rifapentine, as of September 2020

Patent	International publication number (publication date) Title *	Brief analysis
Patent 1	WO 2015/011161 (A1) (29/01/2015) Antituberculosis stable pharmaceutical composition in the form of a coated tablet comprising granules of isoniazid and granules of rifapentine and its process of preparation	Adult composition Process
Patent 2	WO 2015/011162 (A1) (29/01/2015) Antituberculosis stable pharmaceutical composition in the form of dispersible tablet comprising granules of rifapentine and its process of preparation	Pediatric composition Process
Patent 3	WO 2014/037121 (A1) (13/03/2014) Use of rifapentine in the treatment of tuberculosis in patients infected with the Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) and treated with antiretroviral combination	Use of rifapentine for active tuberculosis disease or tuberculosis infection in patients with HIV/AIDS and on antiretroviral treatment. Doses of rifapentine varying from 300 to 900 mg; administration once a week over 12 weeks. ARV treatment described is an efavirenz-based combination (i.e., efavirenz, emtricitabine, and tenofovir disoproxil fumarate). Pharmaceutical composition involving rifapentine and isoniazid for patients with HIV/AIDS on ARV treatment (efavirenz-based combination). Pharmaceutical kit involving (a) pharmaceutical composition of rifapentine+isoniazid and (b) galenic formulation of efavirenz, emtricitabine, and tenofovir.

Source: TAG (2020) and patent search as described in the methodology.
*As described in the PCT application.
Row colored in light red is updated patent/application based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

In August 2020, TAG and the French partner OTMeds (Observatoire de la transparence dans les politiques du médicaments) sent a letter to the company requesting that it reverse its efforts to patent two obvious combinations of rifapentine and isoniazid.[44] Sanofi's response indicated they have begun the process of withdrawing those two patent/applications in countries and have committed "not to reinstate any of the patent/applications, and not to initiate any action against any party who would like to manufacture the specific formulations of the combinations once covered by Sanofi's two patent families, before the abandonments become effective under the relevant national patent regulations."

Table 9 provides an overview of the status of those patents/applications in selected countries. Considering the update patent was only found filed at the European Patent Office (EPO) but in none of the selected countries, it seems this is not a relevant patent that will affect the development of LAF or access strategies.

TABLE 9.
Patent Status in Selected Countries for Isoniazid + Rifapentine

WO (International publication number) Title	Granted	Pending	Not filed	Not found	With-drawn	Re-voked	Re-jected
Patent 1 WO 2015/011161 Antituberculosis stable pharmaceutical composition in the form of a coated tablet comprising granules of isoniazid and granules of rifapentine and its process of preparation	South Africa (A)	Nigeria (D)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kenya (B); Malawi (B); Mozambique (B); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Ukraine (D); Zimbabwe (B)	Cambodia; Ethiopia; Kazakhstan; Kyrgyzstan; Morocco; Pakistan; Uzbekistan	Brazil (A); Canada (A); EU (EPO) (B); India (A); Indonesia (A); Mexico (A); Russia (B); Turkey (B); US (USPTO) (A)	Austra-lia (A)	Peru (A); Vietnam (A)
Patent 2 WO 2015/011162 Antituberculosis stable pharmaceutical composition in the form of dispersible tablet comprising granules of rifapentine and its process of preparation	US (USPTO) (A)	Nigeria (D)	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Malawi (B); Mozambique (B); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Zimbabwe (B)	Ethiopia; Morocco; Pakistan; Uzbekistan; Ukraine	Brazil (A); Canada (A); EU (EPO) (B); India (A); Indonesia (A); Mexico (A); Russia (B); Turkey (B); South Africa (A)	Austra-lia (A)	Peru (A); Vietnam (A)
Patent 3 WO 2014/037121 Use of rifapentine in the treatment of tuberculosis in patients infected with the HIV/ Acquired Immune Deficiency Syndrome (AIDS) and treated with antiretroviral combination			Australia (A); Belarus (B); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); Ghana (B); India (A); Kazakhstan (B); Kenya (B); Malawi (B); Mozambique (B); Peru (A); Russia (A); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); US (USPTO) (A); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Indonesia (A); Morocco; Pakistan; Turkey; Ukraine; Uzbekistan	EU (EPO) (B)		

Sources: (A): National Patent Office; (B): Regional Patent Office; (C): WIPO Patent Scope; (D): MedsPaL; and (E): EPO Espacenet. Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

Main Conclusion

Findings indicate there are not patent barriers for the development of long-acting formulation on isoniazid + rifapentine in relation to Sanofi.

3. Bedaquiline

3.1 Background

In December 2012, bedaquiline was granted accelerated approval for pulmonary MDR-TB by the FDA on grounds it addresses an unmet medical need.[45] Shortly thereafter, in 2013, the WHO published an interim policy guidance recommending that bedaquiline be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB.[46]

In 2015, bedaquiline was added to the 19th WHO Essential Medicines List,[47] being part of the complementary list, reserved to "second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB control." In 2019, bedaquiline was also included in the 7th WHO Model List of Essential Medicines for Children for children six years old or older.[48]

In 2019, the WHO released a consolidated Guideline for DR-TB, listing bedaquiline as a Group A drug, making it a core component of longer regimens for rifampicin- or multidrug-resistant TB (RR-/MDR-TB) with or without additional drug-resistance.[49]

In 2020, WHO released an updated, consolidated Guideline for DR-TB[50] in which bedaquiline is indicated as a core component of nearly all regimens recommended for the treatment of drug-resistant TB, including shorter[51] and longer[52] regimens for RR-/MDR-TB and the shorter regimen recommended under conditions of operational research for MDR-TB with additional fluoroquinolone resistance (pre-XDR-TB).[53]

In May 2020, the US FDA approved the pediatric formulation of bedaquiline (tablet 20 mg, dispersible in water) indicated for pulmonary MDRTB in children five years old and older and weighing at least 15 kg, as part of combination therapy.[54] In November, Janssen applied for the inclusion of this dosage-form in the WHO EML for children.[55]

3.2 Patent Landscape

Unitaid's report (2014)[56] on the patent landscape of bedaquiline, with search as of June 2011, brings five relevant patents and/or patent applications covering the following general content:

- Base compound of bedaquiline (WO 2004/011436);
- A process to synthetize bedaquiline (WO 2006/125769);
- The fumarate salt of the enantiomer of bedaquiline (WO 2008/068231);
- Methods of use of bedaquiline to treat drug-resistant mycobacteria (WO 2005/117875), in particular MDR-TB, and latent TB (WO 2006/067048).

Two additional patents and/or patent applications were identified in MedsPaL: one related to a pharmaceutical composition (WO 2016/120258)

and one on a combination regimen (WO 2017/066053). By updating the existing landscapes, two patents and/or patent applications filed by Janssen were identified, as described in Table 10.

TABLE 10.
Patent and/or Patent Applications Related to Bedaquiline, as of September 2020

Patent	International publication number (publication date) Title*	Applicant	Brief analysis
Patent 1	WO 2004/011436 (05/02/2004) Quinoline derivatives and their use as mycobacterial inhibitors	Janssen Pharmaceutica NV	Substituted quinolone derivative compounds, including the free base, enantiomers and isomers of bedaquiline.**
Patent 2	WO 2005/117875 (15/12/2005) Use of substituted quinolone derivatives for the treatment of drug-resistant mycobacterial diseases	Janssen Pharmaceutica NV and others	Use of substituted quinoline derivative compounds for the treatment of drug-resistant mycobacterial diseases.**Also aims to protect pharmaceutical composition involving combination of compounds.
Patent 3	WO 2006/067048 (29/06/2006) Quinoline derivatives for the treatment of latent tuberculosis	Janssen Pharmaceutica NV and others	Use of quinoline derivative compounds, including bedaquiline, for the treatment of latent tuberculosis.**
Patent 4	WO 2006/125769 (30/11/2006) Process for preparing (alpha S, beta R)-6-bromo-alpha- [2-(dimethyllamino) ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quinolineethanol	Janssen Pharmaceutica NV and others	Process for preparing the enantiomer form of bedaquiline. It covers a process for the isolation of the enantiomer of bedaquiline from a mixture of stereoisomeric forms by optical resolution.**
Patent 5	WO 2008/068231 (12/06/2008) Fumarate salt of (alpha S, beta R)-6-bromo-alpha- [2-(dimethyllamino) ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quinolineethanol	Janssen Pharmaceutica NV and others	Fumarate salt of bedaquiline and the enantiomer of bedaquiline. It also covers pharmaceutical compositions; the processes to produce fumarate of bedaquiline and the pharmaceutical composition; use of bedaquiline fumarate for the treatment and prevention of mycobacterial infection.
Patent 6	WO 2016/120258 (04/08/2016) Dispersible compositions	Janssen Pharmaceutica NV	Dispersible composition (tablet) of bedaquiline fumarate useful for pediatric and geriatric population. It also includes the process to produce the composition.
Patent 7	WO 2017/066053 (20/04/2017) Combination antibacterial composition and short-course antibacterial regimen	The Global Alliance for TB Drug Development, INC.	Pharmaceutical composition involving the combination of linezolid, bedaquiline, and pretomanid, and optionally, pyrazinamide. It also covers methods of treating tuberculosis with such a combination. Within these two types of claims, there are specific doses for each compound as well as the duration of treatment (1, 2, and 3 months).
Patent 8	WO 2019/012100 (17/01/2019) Long-acting formulations	Janssen Pharmaceutica NV [BE]	Pharmaceutical composition for administration by intramuscular or subcutaneous injection with bedaquiline or its salts in the form of a suspension of micro- or nanoparticules. The use of such composition to treat mycobacterial infection, long-term treatment of *Mycobacterium tuberculosis* (such as latent/dormant form), or *Mycobacterium leprae*. The use of the composition can involve administration: intermittently at a time interval of one week to two years; of at an interval of at least one month to one year; different ranges (one to three month, three to six months, etc.); once every two weeks, once every month, once every three months. Also aims to protect the process to prepare such composition.

Patent 9	WO 2020/144197 (16/07/2020) Combination in the treatment of nontuberculous mycobacterial diseases	Janssen Pharmaceutica NV	Combination involving bedaquiline, a macrolide (clarithromycin or azithromycin), and ethambutol. Methods of treatment and use of such combinations, including establishing the doses of each medicine.

Source: Unitaid report (2014); MedsPaL and MSF patent opposition database and patent search as described in the Methodology.
*As described in the PCT application.
**Analysis from Unitaid report (2014).
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

In relation to the two updated patents/applications, WO 2019/012100[57] (Patent 8, Table 10) aims to protect an LAF of bedaquiline in its free form or as a fumarate salt in micro- or nanoparticles as well as the use of such pharmaceutical composition for long-term treatment of *Mycobacterium tuberculosis* (such as the latent/dormant form) and *Mycobacterium leprae* (Appendix 3, Tables A3.1 and A3.2).

As described by the applicants, LAF can reduce the so-called "pill burden" of some treatments—"the number and/or volume of dosage forms that need to be administered" (p. 1)—by increasing the interval in which a medicine should be administered. The "pill burden" is of great concern, especially for longer treatment regimens, because it can compromise patient adherence and may contribute to the emergence of resistance (in the case of infectious diseases).

Several use claims provide different intervals for the administration of the medicine such as intermittently from one week to two years; or at least one month to one year; or ranging from one week to one month, one month to three months, three months to six months, six months to twelve months, 12 months to 24 months; or once every two weeks, or every month, or every three months (Appendix 3, Table A3.1).

An LAF of bedaquiline is already in pre-clinical development, being tested in animal models.[58] A recent study, funded by Janssen, presents an initial evaluation of the formulation in paucibacillary mouse model of latent tuberculosis infection[59] and is illustrated in Example 3 (p. 46) of Patent 8. According to the article, bedaquiline long-acting injectable (BLAI) was administered in intervals of 28 days (either one, two, or three times) and compared with different bedaquiline administered with daily oral doses. According to the authors:

> *"In mice that received a total bedaquiline dose of 320 mg/kg either through two injections of BLAI-160 or through daily oral dosing of daily bedaquiline at 5.33 mg/kg (B5.33) (5/7), the decline in lung CFU counts was similar at about 3 log10 CFU/lung (P 0.05) (Fig. S1E). For mice that received a total bedaquiline dose of 480 mg/kg via three injections of BLAI-160 (1/28), the lung CFU counts were modestly higher than those in mice that received the equivalent total dose through daily oral dosing with B8 (5/7) (Fig. S1F), and the difference was not statistically significant." (p. 5)*
>
> *(…)*

> *"One of the most striking findings from this study was the apparent duration of bactericidal activity associated with a single dose of the long-acting bedaquiline formulation. One injection of BLAI-160 at day 0 continued to exert bactericidal activity up to the 12-week time point; these data are supported by the PK data indicating that the plasma bedaquiline levels remained above the MIC for M. tuberculosis for at least 12 weeks postadministration." (p. 6)*

In relation to the use of bedaquiline in *Mycobacterium leprae*, there is currently a Phase II clinical study,[60] sponsored by Janssen Research and Development, exploring the efficacy of bedaquiline in 100 mg[61] tablets for multibacillary (MB) leprosy, but not with the LAF aimed in Patent 8. In the description, there is no data provided on biological studies testing the LAF of bedaquiline in *Mycobacterium leprae*.

WO 2020/144197[62] (Patent 9, Table 10) aims to protect a combination involving (a) bedaquiline, (b) a macrolide (e.g., clarithromycin or azithromycin), and (c) ethambutol indicated to treat nontuberculous mycobacteria pulmonary disease (NTM-PD). Such type of pulmonary disease is caused by mycobacterium species called *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus* (Mab), and *Mycobacterium kansasii*. The patent also covers the doses of each API as well as the treatment regimen (Appendix 3, Table A3.3).

In November 2020, Janssen Pharmaceutical posted a phase III study aiming to investigate the efficacy of the combination of bedaquiline, clarithromycin, and ethambutol in patients with *Mycobacterium avium* Complex-lung Disease (MAC-LD).[63] The therapeutic regimen is as follows:

- **Bedaquiline (BDQ):** 400 milligrams (mg) (4*100 mg tablets) once daily (qd) from Week 1–2 (loading phase), BDQ 200 mg (2*100 mg tablets) bi-weekly (biw) from Week 3 to 48 (maintenance phase);
- **Clarithromycin (CAM):** 400 mg twice daily (2*200 mg tablets) along with;
- **Ethambutol (EB):** 500–750 mg qd or maximum daily dose of 1.0 gram for up to Week 48.

3.3 Trends in the Pharmaceutical Patenting

Trends in bedaquiline patenting indicate approaches (a) to protect the API, a process to isolate its isomer forms and the production of its fumarate salt form; (b) protect pharmaceutical compositions available in the market or in development, including long-acting formulations and combinations of bedaquiline with other compounds; and, (c) indications of bedaquiline, approved and under investigation.

WO 2004/011436 (Patent 1, Table 10) aims to protect base compound (API).

The molecule of bedaquiline has two quiral centers and can produce four enantiomers (isomers). In other words, the molecule of bedaquiline can

present four options of special configuration, one of which (the 1R, 2S stereoisomer) has been shown to be the most active against tuberculosis.[64] Under a chemical reaction, it is expected that the four isomers will be produced. Therefore, it is a practice in organic chemistry to separate those forms or to develop reactions with the aim to produce more of one form than the others. WO 2006/125769 (Patent 4, Table 10) aims to protect such type of process.

WO 2008/068231 (Patent 5, Table 10) aims to protect the fumarate salt form of bedaquiline. This is the current commercially available form of bedaquiline. Salts of active compounds are usually adopted in the development of drug candidates to achieve an "optimal form" to address specific objectives such as improvement of solubility and increase of chemical stability so that it can be applied for a pharmaceutical dosage-form and therapeutic use.[65] Salt selection is part of the drug development process.

Approaches to isolate enantiomers forms or to obtain salt forms of API are an evergreening strategy to extend the protection of essential medicines such as bedaquiline.[66]

Pharmaceutical dosage forms commercially available or under investigation were also targeted through pharmaceutical compositions type of claims. WO 2016/120258 (Patent 6, Table 10) aims to protect a tablet (dispersible) of bedaquiline fumarate, which includes the currently available pediatric dosage-form of 20 mg.

WO 2017/066053 (Patent 7, Table 10) aims to protect a composition with the combination of bedaquiline, linezolid, and pretomanid (known as BPaL), which is currently recommended by the WHO under conditions of operational research for the treatment of MDR-TB with additional flouoroquinolone resistance (pre-XDR-TB).[67]

WO 2019/012100 (Patent 8, Table 10), as previously described, aims to protect the LAF currently being developed by Janssen.

The third approach to patenting is related to specific indications of bedaquiline. WO 2005/117875 (Patent 2, Table 10) aims to protect the use of bedaquiline for the treatment of drug-resistant tuberculosis, which is so far the only approved indication.

WO 2006/067048 (Patent 3, Table 10) and WO 2020/144197 (Patent 9, Table 10) aim to protect, respectively, the use of bedaquiline for the treatment of latent tuberculosis and the method for treating nontuberculous mycobacterial diseases with a combination of bedaquiline, a macrolide (clarithromycin or azithromycin), and ethambutol. Studies of bedaquiline for both indications are ongoing.[68]

3.4 Patent Status for Selected Countries

Table 11 provides an overview of patent status in selected countries as of October 2020, with complementary updates in some cases for February-July 2021. The tables with status and national patent numbers are detailed in Appendix 5.

TABLE 11.

Patent Status in Selected Countries for Bedaquiline

WO (International publication number) Title	Granted	Pending	Not filed	Not found	With-drawn	Re-voked
Patent 1 WO 2004/011436A1 (A1) Quinoline derivatives and their use as mycobacterial inhibitors	Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); EU (EPO) (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Pakistan (D); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Turkey (D); Uganda (B); Ukraine (B); US (USPTO) (A); Vietnam (A); Zimbabwe (B)		Cambodia (D); Ethiopia (D); Morocco (D); Nigeria (D); Peru (A); Uzbekistan (D)			
Patent 2 WO 2005/117875A1 (A1) Use of substituted quinolone derivatives for the treatment of drug-resistant mycobacterial diseases	Australia (A); Belarus (B); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); EU (EPO) (B); Ghana (A); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Turkey (D); Uganda (B); Ukraine (B); Vietnam (A); Zimbabwe (B)	Pakistan (D)	Cambodia (D); DRC (D); Ethiopia (D); Morocco (D); Nigeria (B and D); Uzbekistan (D)		US (USPTO) (A)	Brazil (A)**
Patent 3 WO 2006/067048A1 (A1) Quinoline derivatives for the treatment of latent tuberculosis	Australia (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); EU (EPO) (B); Ghana (B); Kenya (D); Malawi (D); Mozambique (D); Pakistan (D); Russia (B); Rwanda (B); Senegal (D); South Africa (A); Tanzania (B); Turkey (D); Uganda (D); Ukraine (D); Vietnam (A); Zimbabwe (B)	Brazil (A)	Belarus (B); Cambodia (D); DRC (D); Ethiopia (D); Indonesia (A); Kazakhstan (B); Kyrgyzstan (B); Mexico (A); Morocco (D); Nigeria (D); Peru (A); Tajikistan (B)	Uzbekistan	US (USPTO) (A)	India (A)
Patent 4 WO 2006/125769A1 (A1) Process for preparing (alpha S, beta R)-6-bromo-alpha- [2-(dimethyllamino) ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quinolineeth-anol	Australia (A); Belarus (B); Canada (A); EU (EPO) (B); India (A); Indonesia (A); Kazakhstan (B); Kyrgyzstan (B); Mexico (A); Russia (A); South Africa (A); Tajikistan (B); Turkey (D); Ukraine (D); US (USPTO) (A); Vietnam (A)	Brazil (A)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kenya (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Uzbekistan		
Patent 5 WO 2008/068231A1 (A1) Fumarate salt of (alpha S, beta R)-6-bromo-alpha- [2-(dimethyllamino) ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quino-lineethanol	Australia (A); Belarus (B); Burkina Faso (D); Canada (A); Côte d'Ivoire (D); EU (EPO) (A); Ghana (D); Indonesia (A); Kazakhstan (B); Kenya (D); Kyrgyzstan (B); Malawi (D); Mexico (A); Mozambique (D); Rwanda (D); Senegal (D); Russia (B); South Africa (A); Tajikistan (B); Tanzania (B); Turkey (D); Uganda (B); Ukraine (B); US (USPTO) (A); Vietnam (A); Zimbabwe (D)	Brazil (A); India (A); Pakistan (D)	Peru (A)	Cambodia; DRC; Ethiopia; Morocco; Nigeria; Uzbekistan		

Patent 6 WO 2016/120258 (A1) Dispersible compositions	Burkina Faso (B); Côte d'Ivoire (B); Senegal (B)	Australia (A); Belarus (B); Brazil (A); Canada (A); EU (EPO) (B); Ghana (B); India (A)*; Indonesia (D); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Morocco (D); Mozambique (B); Peru (A); Russia (B); Rwanda (B); South Africa (A); Tajikistan (B); Tanzania (B); Turkey (D); Uganda (B); Ukraine (D); US (USPTO) (A); Zinbabwe (B)	Cambodia (D); DRC (D); Ethiopia (D); Nigeria (D); Pakistan (D); Uzbekistan (D). Vietnam (A)		India (A)***	
Patent 7 WO 2017/066053 (20/04/2017) Combination antibacterial composition and short-course antibacterial regimen		Australia (A); Belarus (C and D); Brazil (C); Canada (A); EU (EPO) (B); India (A); Kazakhstan (B); Kyrgyzstan (B); Morocco (D); Russia (B); Tajikistan (B); Turkey (B); US (USPTO) (A)	Indonesia (A); Mexico (A); Peru (A); South Africa (A); Vietnam (A)	Burkina Faso; Cambodia; Côte d'Ivoire; DRC; Ethiopia; Ghana; Kenya; Malawi; Mozambique, Nigeria; Pakistan; Rwanda; Senegal; Tanzania; Uganda; Uzbekistan; Zimbabwe; Ukraine		

Patent 8 WO 2019/012100 (17/01/2019) Long-acting formulations	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Nigeria (B)	Australia (A); Belarus (B); Brazil (A); Canada (A); EU (EPO) (B); Ghana (B); India (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Peru (A); Russia (B); Rwanda (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); Ukraine (D and A); US (USPTO) (A); Zimbabwe (B)	Vietnam (A)	Cambodia; Ethiopia; Indonesia; Morocco; Pakistan; Senegal; Turkey; Uzbekistan		
Patent 9 WO 2020/144197 (16/07/2020) Combination in the treatment of nontuberculous mycobacterial diseases		US (USPTO) (A)	Australia (A)*; Belarus (B)*; Brazil (A)*; Burkina Faso (B)*; Canada (A)*; Côte d'Ivoire (B)*; DRC (B)*; EU (EPO) (B)*; Ghana (B)*; India (A)*; Kazakhstan (B)*; Kenia (B)*; Kyrgyzstan (B)*; Malawi (B)*; Mozambique (B)*; Nigeria (B)*; Peru (A)*; Rwanda (B)*; Russia (B)*; Senegal (B)*; South Africa (A)*; Tanzania (B)*; Tajikistan (B)*; Uganda (B)*; Ukraine (A); Uzbekistan (B)*; Vietnam (A)*; Zimbabwe (B)*	Cambodia; Ethiopia; Indonesia; Morocco; Pakistan; Turkey		

Sources: (A): National Patent Office; (B): Regional Patent Office; (C): WIPO Patent Scope; (D): MedsPaL; and (E): EPO Espacenet.
*Countries that appear as "designated States" in the international application filed through the PCT system. According to the PCT, the 12 months time limit to entry into National/Regional Phase is July 16, 2021. Therefore, it was not possible to check if the patent application was filed.
**Under appeal.
***At the Indian Patent Office we found two patent applications, one pending and one withdrawn, related to WO 2016/120258.
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

3.5 Access Implications

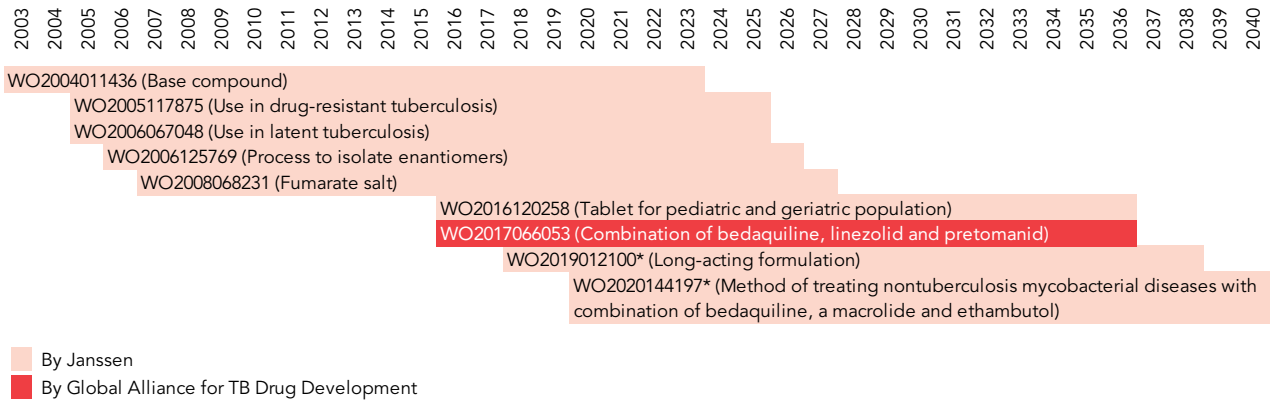
The analysis of patent status (Table 11) indicates that patents/applications identified are either granted or pending in most selected countries.

Figure 2 provides a timeline with a scenario in which all patents related to bedaquiline in a certain country would be granted with a 20 year patent term. However, as patent filing and status varies across countries, this is presented to illustrate the risk of evergreening approach in patenting to extend the monopoly of the company on a specific medicine. If we consider the 12 countries that are part of the IMPAACT4TB project,[69] there are patent applications filed in most countries.

Although the patent covering the base compound (API) (WO 2004/011436) is expected to expire in 2023, the one related to the fumarate salt (WO 2008/068231) is expected to expire in 2027, potentially extending the exclusivity situation over the API by four years, as this is the form commercially available.[70]

In relation to latent TB infection (LTBI), the company also filed a specific patent application for methods of using bedaquiline for that indication (WO 2006/067048), expected to expire in 2025. The one LAF of bedaquiline (WO 2019/012100) is also related to this indication and is expected to expire in 2038. Therefore, if a long-acting form goes through clinical phase studies, gets the market approval (registration), and becomes the preferred option to treat LTBI, then this patent is likely to extend the exclusivity on this indication by 13 years, or on the base compound by 15 years.

FIGURE 2.
Timeline of Potential Patent Protection Related to Bedaquiline



*Update patents

Source: The authors. Estimates based on 20 years patent term counted from the international filing date. Scenario based on patents filed or granted in selected countries.

Bedaquiline (tablet 100 mg) was launched with tiered-prices for high-income countries ($159.574/tablet), upper middle-income countries ($15.957/tablet), and least-developed/resource-limited countries ($4.787/tablet), which would reflect an estimated cost per person for a six-month course of treatment at $30,000, $3,000 and $900 respectively.[71]

Civil society organizations have been raising concerns on the bedaquiline prices to scale-up access in high DR-TB burden countries. Médecins Sans Frontières campaigned for years for the price reduction of bedaquiline to $1 a day.[72] In July 2020, Johnson & Johnson (J&J) offered bedaquiline (tablet 100 mg) to the Global Drug Facility (GDF) at $1.5 a day, under a number of conditions, to 139 countries. Although this would allow the cost per person per month to be $45, high DR-TB burden countries not procuring through the GDF are unable to benefit from this price.[73]

In 2012, J&J established a license agreement with Pharmstandard (based in the Russian Federation) to commercialize bedaquiline in the Russian Federation, some countries of the Commonwealth of Independent States (CIS), Eastern Europe, and Asia. In 2018, the agreement expanded to production and supply.[74] However, under this deal, the Russian Federation would pay $8 per day for bedaquilne.[75]

Several patent oppositions[76] have been filed by civil society organizations from different countries (Table 12) as an approach to prevent the monopoly extension through secondary patents, especially considering the expectation of generic alternatives to be launched after 2023, and that some generic companies are already preparing submissions to get WHO pre-qualification approval.[77]

For further information on access challenges for bedaquiline, see *An Activist's Guide to Treatment for Drug-Resistant TB*.[78]

TABLE 12.
Patent Oppositions Filed on Bedaquiline Patent Applications and/or Patents, as of May 2021

Patent	Type of opposition (Country/Organization)	Year
Patent 2 WO 2005/117875A1 Use of substituted quinolone derivatives for the treatment of drug-resistant mycobacterial diseases	Third Party Observations* (Thailand/AIDS Access Foundation And Thai Network For People With HIV/AIDS)	2020
Patent 3 WO 2006/067048A1 Quinoline derivatives for the treatment of latent tuberculosis	Third Party Observations* (Thailand/AIDS Access Foundation)	2020

Patent 5 WO 2008/068231 Fumarate salt of (alpha S, beta R)-6-bromo-alpha- [2-(dimethyllamino)ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quino-lineethanol	Pre-grant (India/Network of Maharashtra People Living with HIV - NMP+)	2013
	Pre-grant (India/Nandita Venkatesan and Phumeza Tisile - TB survivors)	2019
	Pre-grant (Brazil/Working Group on Intellectual Property - GTPI)	2020
	Third Party Observations* (Thailand/AIDS Access Foundation and Thai Network For People With HIV/AIDS)	2020
Patent 6 WO 2016/120258 Dispersible compositions	Pre-grant (Ukraine/100 Percent Life)	2020
	Third Party Observations* (Thailand/AIDS Access Foundation)	2020
Patent 7 WO 2017/066053 Combination antibacterial composition and short-course antibacterial regimen	Pre-grant (India/Eldred Tellis And Ganesh Acharya)	2020
	Pre-grant (India/Delhi Network of Positive People - DNP+)	2020
Patent 8 WO 2019/012100 Long-acting formulations	Pre-grant (India/Ganesh Acharya and Delhi Network of Positive People - DNP+)	2021

Source: MSF Patent Opposition database.
*In Thailand, third party observation is an option for civil society organizations to present arguments to challenge the patentability of a patent application at the Patent Office after the allowed period to file a pre-grant opposition (90 days after the publication of the patent application). However, the Patent Office is not formally obliged to consider a third party observation in the patent examination.

Main Conclusions

In relation to potential barriers to the development of and access to long-acting formulations of bedaquiline:

- Where granted, the patent covering the base compound (API) is expected to expire in 2023, and the one related to the fumarate salt (WO 2008/068231) is expected to expire in 2027. Therefore, it is likely to be the main barrier for the development of and access to long-acting formulations.
- One patent was identified related to a long-acting formulation (pharmaceutical composition) for administration by intramuscular or subcutaneous injection of bedaquiline, and it is related to the indication of latent TB infection.

Recommendations

- To monitor and follow up at the national level patent filing and status in countries to assess approaches to overcome access barriers.
- To promote the adoption and use of TRIPS flexibilities in order to challenge patent barriers; activities may include: a) assessing the national law and the possibility of filing patent oppositions; b) promoting the issuance of compulsory licenses in cases where the patents are granted.
- The so-called "research exemption" or "experimental use," possible within the scope of Article 30 of the TRIPS Agreement, may allow the use of patented inventions for research purposes during the patent term. However, access issues, once the technology is approved, should be considered from the beginning of the development process.

4. Delamanid

4.1 Background

In April 2014, delamanid was granted a conditional marketing authorization (registration) by the European Medicines Agency (EMA) based on the fulfillment of the following requirements: (a) "benefit-risk balance of the product is positive"; (b) "it is likely that the applicant will be able to provide comprehensive data"; (c) "unmet medical needs will be fulfilled"; and (d) "the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data."[79]

In 2014, the WHO issued an interim policy guidance[80] recommending the inclusion of delamanid in WHO-recommended regimens for adult patients with pulmonary MDR-TB.[81] In 2015, delamanid was added to the 19th *WHO Model List of Essential Medicines* as part of the complementary list[82] of antituberculosis medicines, which should be reserved as second-line drugs for the treatment of MDR-TB to "be used in specialized centres adhering to WHO standards for TB control" (p. 11).[83] According to the most recent *WHO Model List of Essential Medicines* (21st edition and the 7th edition for children, 2019), delamanid continues to be part of the complementary list for individuals from six years old and above.[84]

In 2016, the WHO published another interim policy guidance stating that delamanid "may be added to the WHO-recommended longer regimen in children and adolescents (aged 6–17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not eligible for the shorter MDR-TB regimen, under specific conditions" (p. 26).[85]

In the WHO consolidated guidelines on drug-resistant tuberculosis treatment (2019),[86] delamanid is recommended for inclusion in longer regimens for the treatment of RR-/MDR-TB. Delamanid is categorized as a Group C agent,[87] which are recommended when an effective regimen of 4–5 medicines cannot otherwise be composed using drugs from Groups A and B. Delamanid can be included in longer regimens for children aged three years or more. This recommendation is maintained in the WHO consolidated guidelines on tuberculosis (2020).[88]

In September 2020, EMA approved the extension of the indication of delamanid to include, besides adults, adolescents and children with a body weight of at least 30 kg (66.14lb).[89]

4.2 Patent Landscape

The patent landscape on delamanid, published in 2014,[90] identified nine patents and/or patent applications filed by Otsuka (Table 13). Two of those patents/applications were related to the API, three to pharmaceutical compositions (of which one is related to a combination of delamanid with other tuberculosis agents), two on process for synthetizing key-intermediates, and two on key-intermediates for the synthesis of the API.

By updating the patent landscape (Patents 10 to 15, Table 13), six additional patents/applications were identified (Table 13): five on routes and key-intermediates to synthetize the API (more detail in Appendix 4, Table A4.1) and one on pharmaceutical composition (more detail in Appendix 4, Table A4.2).

WO 2006/035960 (Patent 13, Table 13) discloses a process to produce high-yield and high-purity of 2-chloro-4-nitroimidazole, which can be used as a key-intermediate to the synthesis of delamanid.

WO 2008/140090 (Patent 10, Table 13) discloses key-intermediates for the synthesis of delamanid (epoxy compounds), the process for synthesis of such key-intermediates, and the process for the synthesis of possible compounds (Markush Formula), of which delamanid is one.

WO 2010/021409 (Patent 14, Table 13) discloses a process to produce key-intermediates (2-halo-4-nitroimidazole) of delamanid as well as a process to produce a very similar compound to delamanid (claim 13).

WO 2016/158737 (Patent 11, Table 13) discloses a method of synthesis of a key-intermediate[91] of delamanid and a method of synthesis of delamanid, considering three possible routes and intermediates.

WO 2019/146113 (Patent 12, Table 13) discloses key-intermediates[92] to synthetize delamanid and methods to synthetize such key-intermediates.

WO 2019/240104 (Patent 15, Table 13) discloses a pharmaceutical composition in which a process to obtain the API in submicron particles[93] is described, to be used in the production of oral solid preparation (tablet or capsule). Claim 13 aims to protect delamanid particles with an average size of 350 nm or less (more detail in Appendix 4, Table A4.2).

TABLE 13.
Patent and/or Patent Applications Related to Delamanid by Otsuka Pharmaceutical Co., Ltd., as of September 2020

Patent	International publication number (publication date) Title	Brief analysis*
Patent 1	WO 2004/033463 (22/04/2004) 2,3-dihydro-6-nitroimidazo [2,1-b]oxazoles	2,3-dihydro-6- nitroimidazo [2, 1-b] oxazoles. It involves compounds, including delamanid and its racemates and single isomers.**Where the patent is granted, it is likely to block generic production, import, market, and use. (base compound)
Patent 2	WO 2005/042542 (12/05/2005) 2,3-dihydro-6- nitroimidazo [2, 1-b] oxazole compounds for the treatment of tuberculosis	Covers various compounds, including delamanid.**(compound)
Patent 3	WO 2007/013477 (01/02/2007) Pharmaceutical composition comprising 2,3-dihydro-6- nitroimidazo [2, 1-b] oxazole derivatives	Covers a pharmaceutical composition comprising delamanid, its optically active isomers and pharmaceutically acceptable salts, with a cellulose compound.**(composition, entantiomer)

Patent 4	WO 2007/043542 (19/04/2007) Antituberculous composition comprising oxazole compounds	Delamanid in combination with other antituberculous drugs, including rifamycin, isoniazid, ethambutol, streptomycin, pyrazinamide, enviomycin, and kanamycin.**(composition; combination)
Patent 5	WO 2007/052738 (10/05/2007) Medicinal composition showing improved drug absorbability	Pharmaceutical composition comprising delamanid and a fatty acid and organic acid glycerol ester and/or a fatty acid and organic acid polyglycerol ester, which presents improved drug absorbability.**(composition)
Patent 6	WO 2011/093529 (04/08/2011) Synthetic intermediate of oxazole compound and method for producing the same	New synthetic intermediate compounds useful for producing an oxazole compound, including delamanid, at a high-yield and high optical purity.**(key-intermediate)
Patent 7	WO 2004/035547 (29/04/2004) 1-Substituted 4-nitroimidazole compound and process for producing the same	Nitroimidazole compounds and methods of their preparation as early intermediates.**(key-intermediates; process)
Patent 8	WO 2005/077913 (25/08/2005) Method for producing 4-nitroimidazole compound	Method for preparing nitroimidazole compounds as early intermediates. This patent relates closely to WO 2004/035547.**(process)
Patent 9	WO 2005/092832 (06/10/2005) Method of producing aminophenol compounds	Process for producing aminophenol compounds, which could act as intermediates in relation to nitroimidazole compounds.**(process)
Patent 10	WO 2008/140090 (20/11/2008) Epoxy compound and method for manufacturing the same	Key-intermediate for the synthesis of delamanid. Discloses key-intermediates for the synthesis of delamanid (epoxy compounds), the process for synthesis of such key-intermediates, and process for the synthesis of possible compounds (Markush Formula), of which delamanid is one.
Patent 11	WO 2016/158737 (06/10/2016) Method for producing 1-(4-hydroxyphenyl)-4-(4-trifluoromethoxyphenoxy) piperidine or salt thereof	Process to synthethize delamanid. Discloses a method of synthesis of a key-intermediate[94] of delamanid and a method of synthesis of delamanid, considering three possible routes and intermediates.
Patent 12	WO 2019/146113 (01/08/2019) Process for production of 2-chloro-4-nitroimidazole derivatives	Process to synthethize key-intermediates[95] to synthetize delamanid and methods to synthetize such key-intermediates.
Patent 13	WO 2006/35960 (06/04/2006) Process for production of 2-chloro-4-nitroimidazole	Key-intermediate for the synthesis of delamanid. Discloses a process to produce high-yield and high-purity of 2-chloro-4-nitroimidazole, which can be used as a key-intermediate to the synthesis of delamanid.
Patent 14* **	WO 2010/021409 (25/02/2010) Methods for the production of 2-halo-4-nitroimidazole and intermediates thereof	Key-intermediate for the synthesis of delamanid. Discloses a process to produce key-intermediates (2-halo-4-nitroimidazole) of delamanid as well as a process to produce a very similar compound to delamanid. (claim 13)
Patent 15	WO 2019/240104 (19/12/2019) Delamanid-containing composition	Discloses a pharmaceutical composition in which a process to obtain the API in submicron particles is intended to be used in the production of oral solid preparation (tablet or capsule). Claim 13 aims to protect delamanid particles with an average size of 350 nm or less. (composition)

Source: Unitaid report (2014); MedsPaL and MSF patent opposition database and patent search as described in the Methodology.
*As the PCT documents were in Japanese, we used the equivalent US patent for the analysis.
**Analysis obtained from Unitaid report (2014).
***Application filed by Application filed by Otsuka Pharmaceutical Co., Ltd., Dynamit Nobel Gmbh Explosivstoff - Und Systemtechnik and Asahi Kasei Chemicals Corporation.
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

4.3 Preliminary Analysis and Comparison of the Synthetic Routes and Key-Intermediates of Delamanid Patents/ Applications[96]

In order to investigate the connections between routes and key-intermediates for the synthesis of delamanid, the following patent/applications were analyzed:

- WO 2004/033463 (Patent 1 – Unitaid report)
- WO 2005/042542 (Patent 2 – Unitaid report)
- WO 2011/093529 (Patent 6 – Unitaid report)
- WO 2004/035547 (Patent 7 – Unitaid report)
- WO 2005/077913 (Patent 8 – Unitaid report)
- WO 2005/092832 (Patent 9 – Unitaid report)
- WO 2008/140090 (Update Patent 10)
- WO 2016/158737 (Update Patent 11)
- WO 2019/146113 (Update Patent 12)
- WO 2006/035960 (Update Patent 13)
- WO 2010/021409 (Update Patent 14)

Preliminary analysis indicates that in **Patent 1** the process comprises the reaction between a 4-nitroimidazol compound with an epoxy compound to give a compound of Formula 4a or 4b, and that after a ring closure the compound of Formula 1a or 1b is obtained.

In **Patent 2**, the process comprises the reaction between a 4-nitroimidazol compound with an epoxy compound to give a compound of Formula 4a/4c.

In **Patent 6**, the process is essentially the same as in **Patents 1 and 2**, but in this case, the production of the compounds of Formula 11 is also disclosed, including the production of its intermediaries of formulas 9 and 10. This process is closely related to **Update Patent 10**, wherein Formula 2 of that document would be Formula 12 in this one.

Patent 7 covers the synthesis of 1-Substituted 4-nitroimidazole compounds. These compounds are used as an intermediate for the synthesis of delamanid in **Patents 1, 2, and 6**.

As with **Patent 7**, **Patent 8** covers the synthesis of 4-nitroimidazole compounds. These compounds are used as an intermediate for the synthesis of delamanid in **Patents 1, 2, and 6**.

Patent 9 covers the synthesis of aminophenol compounds, which could act as intermediates to produce nitroimidazole compounds of **Patents 7 and 8.**

Update Patent 10 consists of four claims; the first two are compound claims (Markush) and the last two are process claims. In a general analysis of **Update Patent 10**, we could say that some of the processes and the intermediates disclosed in this patent are the same as those disclosed in some of the patents identified in the Unitaid report with potentially slight differences that would require further in-depth analysis.

Update Patent 11 consists of 11 claims and a method to produce the 1-(4-hydroxyphenyl)-4-(4-trifluoromethoxyphenoxy) piperidine. There are several common processes within this patent and patents from the Unitaid report. In particular, the intermediates disclosed in **Patents 1, 2, 6, 7, 8, and 9** are used in the steps named as b2 and b3 in this patent.

Update Patent 12 consists of 16 claims; claims 1–14 are process claims to obtain key nitroimidazole intermediates (uses of different activating agents, etc.). Claims 15–16 are compound claims where the applicant is trying to protect specific key-intermediates that are also covered by some of the process claims 1–14. In particular, compound of Formula Ia (with some of the possible R1a substituents) resembles the intermediates used in **Update Patents 10 and 11**.

Update Patents 13 and 14 were identified in **Update Patent 12** as part of the description in terms of options to obtain key nitroimidazoles intermediates.

Preliminary analysis suggests that those patents/applications seem to be related to a common synthetic route.

4.4 Trends in the Pharmaceutical Patenting

A total of 15 patents and/or patent applications on delamanid were identified, of which (a) 11 either focus on the API or its synthetic routes (processes) and key-intermediate, (b) three focus on pharmaceutical compositions and, (c) one focuses on a combination.

It seems Ostuka is following the trend of pursuing nanotechnology as an approach to the development of pharmaceutical compositions for delamanid (WO 2019/240104, Patent 15).

There have been efforts to explore new drug delivery systems for tuberculosis agents that aim to improve patient adherence and to reduce both pill burden and treatment duration. Among those systems, there are liposomes, polymeric micro/nanoparticles, and solid lipid nanoparticles that can be administered through oral, subcutaneous, intravenous, or inhaled routes. Nanotechnology has been explored in the tuberculosis field for the development of nanodispersions (nanosuspensions, nanoemulsions, and niosomes), polymeric and nonpolymeric nanoparticles, and polymeric micelles and other self-assembled structures.[97]

As discussed by Nasiriddin et al. (2017),[98] nanoparticles are considered promising because they can be "taken up more efficiently by cells than larger molecules" (p. 4). They list some advantages of having this type of drug delivery system applied for tuberculosis treatment:

"(1) High constancy/longer time period (2) High carrier ability; that is, multiple drugs can be encapsulated in the matrix (3) Less side effects compared to conventional drugs (4) Increased bioavailability (slow, sustained, and controlled drug release) (5) Viability of various routes of administration like oral delivery and inhalation (6) Minimal side effects and improved compliance" (p. 4)

4.5 Patent Status in Selected Countries

Table 14 provides an overview of patent status in selected countries as of October 2020, with complementary updates for some cases for February-July 2021. The tables with status and national patent numbers is detailed in Appendix 5.

TABLE 14.
Patent Status in Selected Countries for Delamanid

WO (International publication number) Title	Granted	Pending	Not filed	Not found	With-drawn	Re-voked	Re-jected
Patent 1 WO 2004/033463 (A1) 2,3-dihydro-6-ni-troimidazo [2,1-b]oxazoles	Australia (A); Brazil (A); Canada (A); EU (EPO)****; (B); India (A)*****; Indonesia (A); Mexico (C); Russia (B); South Africa (A); Turkey (D)*; Ukraine (D); US (USPTO) (A); Vietnam (A)	EU (EPO) (B)****	Belarus (B); Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Uzbekistan	Turkey (D)*		India (A)*****
Patent 2 WO 2005/042542 (A1) 2,3-dihydro-6-nitroimidazo [2, 1-b] oxazole compounds for the treatment of tuberculosis	Belarus (C); EU (EPO) (A); Indonesia (A); Mexico (A); Russia (A); Vietnam (A)		Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Uzbekistan	Australia (A)**; Brazil (A)**; Canada (A); India (A); South Africa (A); Turkey (D); Ukraine (D)**; US (USPTO) (A)**		
Patent 3 WO 2007/013477 (A1) Pharmaceutical composition comprising 2,3-dihydro-6-nitroimidazo [2, 1-b] oxazole derivatives	Australia (A); Belarus (C); Canada (A); EU (EPO) (B); India (A); Indonesia (A); Mexico (A); Russia (A); South Africa (A); Turkey (D); Ukraine (D); US (USPTO) (A); Vietnam (A)	Brazil (A); Pakistan (D)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Uzbekistan			

Patent 4 WO 2007/043542 (A1) Antituberculous composition comprising oxazole compounds	Belarus (B); India (A); Mexico (A); South Africa (A)	Brazil (A); EU (EPO) (B); Pakistan (B)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Uzbekistan	Australia (A)**; Canada (A)**; Indonesia (A)**; Russia (A); Ukraine (D); US (USPTO) (A)**		
Patent 5 WO 2007/052738 (A1) Medicinal composition showing improved drug absorbability	India (A)	Pakistan (D)	Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); EU (EPO) (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Ukraine; Uzbekistan	US (A)**; Turkey (D)		
Patent 6 WO 2011/093529 (A1) Synthetic intermediate of oxazole compound and method for producing the same	EU (EPO) (B); Indonesia (A)***; Mexico (A); South Africa (A); Turkey (D); US (USPTO) (A)	Belarus (B); Kazakhstan (B); Kyrgyzstan (B); Russia (B); Tajikistan (B)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kenya (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Uzbekistan	Australia (A)**; Brazil (A)**; Canada (A); Ukraine (B)		
Patent 7 WO 2004/035547 (A1) 1-Substituted 4-nitroimidazole compound and process for producing the same	Belarus (C); Canada (A)**; India (A); Indonesia (A); Mexico (A); Russia (B); Ukraine (C);Vietnam (A)		Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Turkey; Uzbekistan	Australia (A)**; Brazil (A)**; EU (EPO) (B)**; South Africa (A)**; US (USPTO) (A)**		
Patent 8 WO 2005/077913 (A1) Method for producing 4-nitroimidazole compound	Belarus (C); EU (EPO) (B); India (A); Indonesia (A); Mexico (A); Russia (B); Ukraine (C); Vietnam (A)		Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Turkey; Uzbekistan	Australia (A)**; Brazil (A)**; Canada (A); South Africa (A)**; US (USPTO) (A)**		

Patent 9 WO 2005/092832 (A1) Method for producing aminophenol compounds.	Belarus (C); Canada (A)**; EU (EPO) (B)**; India (A); Indonesia (A)**; Mexico (A); Russia (C); South Africa (A); Ukraine (C); US (USPTO) (A)**; Vietnam (A)		Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Turkey; Uzbekistan	Australia (A)**; Brazil (A)**		
Patent 10 WO 2008/140090 (A1) Epoxy compound and method for manufacturing the same	Australia (A)**; Belarus (C); Canada (A)**; EU (EPO) (B); India (A); Indonesia (A)**; Mexico (A); Russia (B); Ukraine (C); US (USPTO) (A); Vietnam (A)	South Africa (A)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tajikistan (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Turkey; Uzbekistan	Brazil (A)**		
Patent 11 WO 2016/158737 (A1) Method for producing 1-(4-hydroxy-phenyl)-4-(4-tri-fluorome-thoxyphenoxy) piperidine or salt thereof	EU (EPO) (B); US (USPTO) (A)	India (A); Belarus (B); Kazakhstan (B); Kyrgyzstan (B); Russia (B); Tajikistan (B)	Australia (A); Brazil (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); Ghana (B); Indonesia (A); Kenya (B); Malawi (B); Mexico (A); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); South Africa (A); Tanzania (B); Uganda (B); Ukraine (A); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Senegal; Turkey; Uzbekistan			
Patent 12 WO 2019/146113 (A1) Process for production of 2-chloro-4-nitroimidazole derivatives		Belarus (B); EU (EPO) (B); India (A); Kazakhstan (B); Russia (B); Tajikistan (B); US (USPTO) (A)	Australia (A); Brazil (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); Ghana (B); Indonesia (A); Kenya (B); Malawi (B); Mexico (A); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); South Africa (A); Tanzania (B); Uganda (B); Ukraine (A); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Nigeria; Pakistan; Turkey; Uzbekistan			
Patent 13 WO 2006/35960 (A1) Process for productio of 2-chloro-4-nitroimidazole	EU (EPO) (B); India (A); South Africa (A)	Mexico (A); Russia (B)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Kenya (B); Malawi (B); Mozambique (B); Peru (A); Rwanda (B); Senegal (B); Tanzania (B); Uganda (B); Zimbabwe (B)	Cambodia; Ethiopia; Indonesia; Morocco; Nigeria; Pakistan; Turkey; Uzbekistan	Australia (A)**; Belarus (B); Brazil (A); Canada (A); US (USPTO) (A)**; Ukraine (A)		Vietnam (A)

Patent 14 WO 2010/021409 (A1) Methods for the production of 2-halo-4-nitro-imidazole and intermediates thereof	India (A); US (USPTO) (A)		Australia (A); Belarus (B); Brazil (A); Burkina Faso (B); Canada (A); Côte d'Ivoire (B); DRC (B); Ghana (B); India (A); Indonesia (A); Kazakhstan (B); Kenya (B); Kyrgyzstan (B); Malawi (B); Mexico (A); Mozambique (B); Nigeria (B); Peru (A); Russia (B); Rwanda (B); Senegal (B); South Africa (A); Tajikistan (B); Tanzania (B); Uganda (B); US (USPTO) (A); Ukraine (A); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Pakistan; Turkey; Uzbekistan	EU (EPO) (B)*		
Patent 15 WO 2019/240104 (A1) Delamanid-containing composition		Australia (A); Belarus (B); Canada (A); EU (EPO) (B); Kazakhstan (B); Kyrgyzstan (B); India (A); Russia (B); South Africa (A); Tajikistan (B); Ukraine (A); US (USPTO) (A)	Burkina Faso (B); Côte d'Ivoire (B); DRC (B); Ghana (B); Indonesia (A); Kenya (B); Malawi (B); Mexico (A); Mozambique (B); Nigeria (B); Peru (A); Rwanda (B); Senegal (B); Tanzania (B); Uganda (B); Vietnam (A); Zimbabwe (B)	Cambodia; Ethiopia; Morocco; Pakistan; Turkey; Uzbekistan			

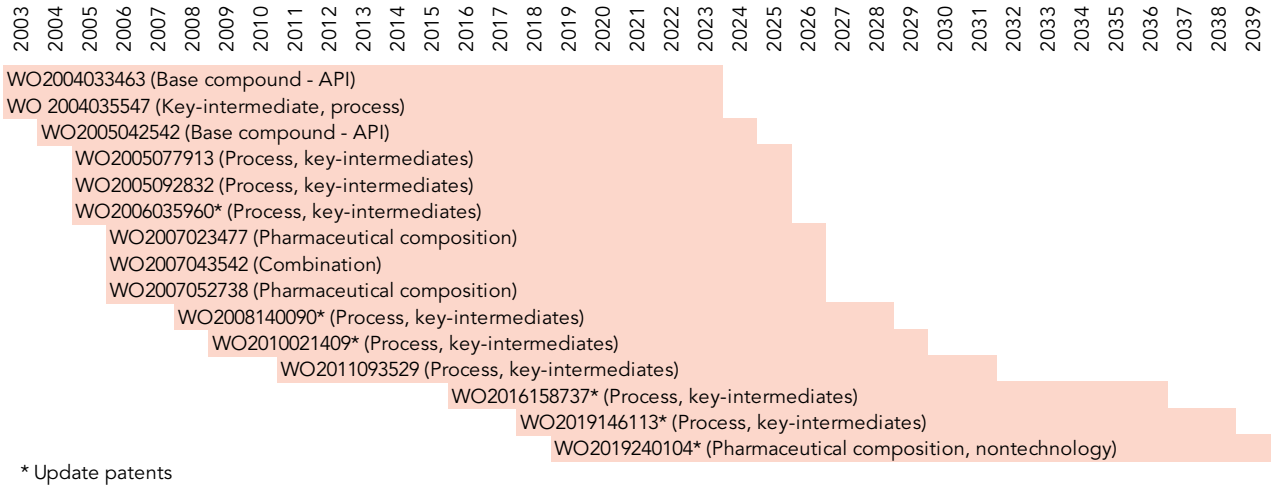
Sources: (A): National Patent Office; (B): Regional Patent Office; (C): WIPO Patent Scope; (D): MedsPaL; and (E): EPO Espacenet.
*In Turkey, one patent granted and one application withdrawn were found related to WO 2004/033463.
**Appears as lapsed at database.
***Appears as canceled at database. At EPO we found one patent granted and one application pending related to WO 2004/033463 (A1).
****At the Indian Patent Office we found one patent granted and one patent application rejected related to WO 2004/033463 (A1).
Rows colored in light red are updated patents/applications based on patent searches described in the Methodology, focusing on those presented by the company who obtained the first market approval of the medicine.

4.6 Access Implications

The main patent on the base compound is expected to expire in 2023. Otsuka adopted the approach to file several patent applications around delamanid synthesis, aiming to protect the process and key-intermediates. The risk of this approach to generic competition is that, where those secondary patents are filed and granted, they can potentially be an additional barrier to the process of production of the API, even if the base compound patent has already expired. In India, an analysis of granted patents indicated that generic manufacturers will be able to produce the API once the patent on the base compound expires by circumventing the other ones.[99]

Figure 3 provides an estimate of expiry dates for delamanid patents in case they are filed and granted in countries (based on a 20 years patent term). For example, the patent related to the pharmaceutical composition involving nanoparticles of delamanid is expected to expire in

FIGURE 3.
Timeline of Potential Patent Protection Related to Delamanid



Source: The authors. Estimates based on 20 years of patent term counted from the international filing date. Scenario based on existing patents filed or granted in countries.

2039. If eventually this pharmaceutical composition gets market approval (registration) and becomes the preferred option for the treatment of TB infection and/or disease, it would add 16 years of exclusivity in relation to the first patent related to the API, expected to expire in 2023. Although this is currently a hypothetical scenario, it indicates one approach taken by the company in terms of patenting.

The high price of delamanid (US$157–283 per month; $5.0–9.5 per day; $942–1,698 per six-month treatment course in LMICs) greatly affects the cost of an 18–20 month treatment regimen and is considered to be a financial burden to national TB programs. The classification of the medicine by the WHO as Group C has also had an effect on demand for the medicine and can be an additional explanation for the lack of competitors in the market so far. It is estimated that only 3,750 people had access to delamanid between 2015 and 2019. Emerging data from clinical trials, operational research initiatives, and TB programs may further expand the WHO's recommendations and demand for delamanid in 2022 and 2023. An ongoing Phase III trial of delamanid (administered orally) is investigating its potential as TB preventive therapy among household contacts of persons with MDR-TB (NCT03568383).

Access challenges from the supply side include high prices charged by the originator company (Otsuka) as a consequence of the exclusivity situation of the company in the market. Patent protection over the API also explains this exclusivity situation, along with a number of additional patents/applications with the potential to extend the term of this situation beyond 2023.

In 2017, based on an agreement with Ostuka, Mylan was allowed to distribute delamanid in India, South Africa, and several other countries

where Otsuka has no commercial presence. Mylan could also produce the medicine based on API supplied by Ostuka and, by the end of 2021, will be able to use its own API. Others restrictions to Mylan are linked to the terms on technology transfer, as the company is prevented from supplying to certain countries even if there is not patent protection for delamanid there.[100]

For delamanid supply in Eastern European and Central Asian countries (EECA), Otsuka signed an agreement with R-Pharm in 2017.[101]

For further information on access challenges for delamanid, see *An Activist's Guide to Treatment for Drug-Resistant TB*.[102]

Main Conclusions

In relation to potential barriers to the development of and access to long-acting formulations of delamanid:

- Where granted, the patent on the API is expected to expire in 2023 and is likely to be an important barrier.
- There are a number of patents/applications related to synthetic routes and key-intermediates that might have an effect on the synthesis of the API. They seem to be related to a similar synthetic route.
- WO 2019/240104 is related to an oral pharmaceutical composition involving delamanid in submicron particles; the average particle size of the delamanid particles is 350 nm or less. Although this is unlikely to block the development of long-acting injectables, it should be assessed if the protection of submicron particles of delamanid claimed in this patent application overlaps with the development of nanoparticles for use in long-acting injectables.

Recommendations

- To monitor and follow up at the national level patent filing and status in countries to assess approaches to overcoming access barriers.
- To promote the adoption and use of TRIPS flexibilities in order to challenge patent barriers; activities may include: a) assessing the national law and the possibility of filing patent oppositions; b) promoting the issuance of compulsory licenses in cases where the patents are granted.
- The so-called "research exemption" or "experimental use," possible within the scope of Article 30 of the TRIPS Agreement, may allow the use of patented inventions for research purposes during the patent term. However, access issues, once the technology is approved, should be considered from the beginning of the development process.

5. Preliminary and Non-Exhaustive List of Patents and/or Patent Applications Related to Nanotechnology and Pharmaceutical Composition by the University of Liverpool

Approaches for long-acting formulation may consider different routes of administration, such as oral or parenteral. Formulation of LAIs have been focused on (a) injection of solutions or (b) particle suspensions. Emerging technologies for the development of LAIs, evolving to commercial application, include among others (a) nanoparticles suspensions, (b) injectable monoliths, (c) *in situ*-forming depots/implants, and (d) microneedle delivery.[103]

Developers and corporations with expertise in formulation will have different nanotechnology platforms that will be covered by intellectual property rights. Those companies may license a patent related to a certain technology to allow the formulation of a specific API.[104] Some examples of devices and platforms for the development of LAFs are as follows:[105]

- Solid drug nanoparticle long-acting injectables for HIV, malaria and other areas (by University of Liverpool and Johns Hopkins University);
- Intarcia Medici implant (by Intarcia Therapeutics);
- Auritec implant (by Auritec and Oak Crest Institute of Science);
- Microneedle patch (by the Queen's University of Belfast);
- Lyndra long-acting oral/gastric residence system (by Lyndra Inc—a spinout from Massachusetts Institute of Technology);
- NanoCrystal® technology (by Alkermes);
- BEPO® technology (by MedinCell).

The University of Liverpool (UoL) created a start-up called Tandem Nano Ltd (TNL),[106] which owns the technology platform of solid drug nanoparticle (SDN) with application in different fields, including long-acting medicines. Nanoparticles may be achieved by stabilizing the API with a polymer and/or surfactant excipients.[107] SDN not only has application for long-acting medicines, but it has also been described as useful to overcoming bio-availability problems of low-soluble API, applicable for sustainable release and to address food effects after oral dosing.[108]

Existing patent applications (total 13, Table 15) from the UoL in this field have been identified in two publications by the MPP: the *Collaboration Agreement & Patent and Know-How License* (2015) and *Intellectual Property Report on Long-acting Technologies* (2018).

An additional 17 patents and/or patent applications were identified from patent search following a preliminary effort of classification as follows:

- focused on pharmaceutical composition involving a specific API or therapeutic class (Table 16);
- focused on the development of nanoparticles (Table 17);
- focused on materials for pharmaceutical compositions (Table 18);
- focused on nanodispersions or nanoemulsions (Table 19).

None of the identified patents/applications covered the API included in this review and were of relevance to the LONGEVITY Project. Only one patent/application (WO 2011/128623, Table 15) mentioned other API used for viral hepatitis (adefovir, boceprevir, entecavir, ribavirin, and taribavirin).

The four licensed patents described in the recently signed "Patent and Know-How Licensce" between Medicines Patent Pool and Tandem Nano Ltd (September, 2021)[109] are covered by the current search as follows: WO 2011/128623 and WO 2017/216564 (Table 15); WO 2008/006713 (Table 16) and WO 2013/030535.

Main Conclusions

- Patents on the selected API, and potentially on the processes to produce those API, as described in the previous case studies, might be the main barrier for access to those long-acting technologies in case they get market approval before the expiry date of those patents.
- Patents/applications filed by Janssen on long-acting bedaquiline and Ostuka on nanoparticles of delamanid may be a potential barrier if the technology platform applied for both cases is related to SDN. If approaches to developing long-acting injectables are different than those disclosed in these patents/applications, they might not be considered blocking patents.
- Although there are no patents filed by the University of Liverpool on long-acting injectables covering the selected API of the present study, knowledge and patents covering the technology platform of SDN by other patents/applications may be applied for the development of the formulation involving those API. Therefore, in the scope of LONGEVITY Project, licensing agreements may require negotiations either with originator companies (in the case of glecaprevir and pibrentasvir) and with patent holders of the technonology platform adopted (UoL and Tandem Nano Ltd). In order to ensure that resulting technolgies are available at affordable prices, access issues must be addressed from the begining of the development process.
- The license agreement should be fully open to any willing licensees, including global coverage license, where full text is publicly available. There should be no exclusive arrangements for significant enough markets with any company; if such arrangements are done for very small markets, there should be mechanisms ensuring competitive price levels, e.g., maximum/ceiling price. Tandem should ensure registration of the product in all middle-income countries (MICs), and ensure that there are resources to conduct local clinical trials if those are required under

national law. If data exclusivity is applicable to products registered by Tandem, it should have an obligation in the voluntary license to provide a letter to the Drug Regulatory Authority (DRA) regarding waiver of data exclusivity rights for the purposes of generic product registration; the same approach should be taken in relation to unlicensed generic versions.

TABLE 15.
Patents and/or Patent Applications Found in the Literature (MPP Report/License) From University of Liverpool on Solid Drug Nanoparticles for Pharmaceutical Compositions

WO (date) PCT (date)	Title (WO)	Applicant	Comments
WO 2004/011537* (05/02/2004) PCT/ GB2003/003226 (29/07/2003)	POROUS BEADS AND METHOD OF PRODUCTION THEREOF	Unilever NV Unilever PLC Hundistan Lever Limited	No mention of specific API or some aspect related to pharmaceutical composition. Claim 1 seems to be related to nanotechnology (nanoparticles): 1. A hydrophilic porous polymeric bead comprising a three dimensional open-cell lattice of a water-soluble polymeric material, the lattice having a porous structure providing in the bead an intrusion volume of at least about 3 ml/g.
WO 2005/075547* (18/08/2005) PCT/EP2004/014777 (23/12/2004)	POROUS BODIES AND METHOD OF PRODUCTION THEREOF	Unilever NV Unilever PLC Hundistan Lever Limited	No mention of specific API; mention of solutions and dispersions. Claims 1 and 23 seems to be related to nanotechnology (nanoparticles): 1. Water dispersible or water soluble porous bodies comprising a three dimensional open-cell lattice containing (a) 10–95% by weight of a water soluble polymeric material and (b) 5–90% by weight of a surfactant, said porous bodies having an intrusion volume as measured by mercury porosimetry of at least about 3 ml/g with the proviso that said porous bodies are not spherical beads having an average bead diameter of 0.2 to 5 mm. 23. Solutions or dispersions comprising water soluble polymeric materials, surfactant, and a hydrophobic material formed by exposing the porous bodies of claim 8 having the hydrophobic material contained therein to an aqueous medium.
WO 2005/073296* (11/08/2005) PCT/ GB2005/000315 (28/01/2005)	POROUS MATERIALS AND METHOD OF PRODUCTION THEREOF	Unilever NV Unilever PLC Hundistan Lever Limited	No mention of specific API; mention of solutions and dispersions. Claims 1 and 17 seem to be related to nanotechnology (nanoparticles): 1. A porous body which is soluble or dispersible in aqueous media comprising a three dimensional open-cell lattice containing: (a) 10–95% by weight of a polymeric material which is soluble in water, and, (b) less than 5% by weight of a surfactant, said porous bodies having an intrusion volume as measured by mercury porosimetry (as hereinafter described) of at least about 3 ml/g, and, with the provison that said porous bodies are not spherical beads having an average bead diameter of 0.2 to 5 mm. 17. Solutions or dispersions comprising a polymeric material, surfactant, and a hydrophilic material obtainable by exposing the porous bodies of claim 5 water having insoluble materials incorporated into the polymeric lattice to an aqueous medium.

WO 2006/079409* (03/08/2006) PCT/EP2005/013933 (20/12/2005)	IMPROVEMENTS RELATING TO RAPIDLY DISSOLVING COMPOSITIONS	Unilever PLC Unilever NV	No mention of specific API (only that it is related to water-insoluble API); mention of emulsion. Claim 1 seems to be related to a process in the field of nanotechnology (nanoparticles): 1. A method comprising the steps of: (i) providing an emulsion of: a) an aqueous solvent, b) a carrier material dispersible or soluble in (a) said carrier material being solid at ambient temperature, c) a volatile second liquid phase which is not miscible with (a) , and d) a material which is dispersible or soluble in (c) but not in (a), and, (ii) Drying the emulsion above ambient temperature to simultaneously remove (a) and (c) and thereby obtain the material (b) in solid form with (d) dispersed therein.
WO 2010/020518* (25/02/2010) PCT/EP2009/059546 (24/07/2009)	IMPROVEMENTS RELATING TO NANODISPERSE COMPOSITIONS	Unilever PLC Unilever NV	No mention of specific API (only that it is related to water-insoluble API); mention of water-soluble composition comprising a water-insoluble active. Claim 1 seems to be related to a process in the field of nanotechnology (nanoparticles): 1. A process for the production of a water-soluble composition comprising a water-insoluble active which comprises the steps of: a) providing a liquid mixture comprising: i) a dissolved water-insoluble active, ii) a dissolved water-soluble carrier, iii) a solvent for each of the active and the carrier, and b) spray-granulating the mixture to remove the, or each, solvent and obtain a substantially water- and solvent-free nanodispersion of the water-insoluble active in the carrier said water-insoluble active being in nanoparticles having a size range of 999–20 nm.
WO 2011/128623* (20/10/2011) PCT/ GB2011/000549 (08/04/2011)	IMPROVEMENTS RELATING TO ANTIVIRAL COMPOSITIONS	Iota Nanosolutions Limited	Mention of a composition involving an API in nanodisperse form. Mention of the following ARV: amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir, abacavir (ABC), amdoxovir, apricitabine (ATC), didanosine (ddl), elvucitabine, emtricitabine (FTC), entecavir (INN), lamivudine (3TC), racivir, stampidine, stavudine (d4T), zalcitabine (ddC) and zidovudine (AZT), adefovir (also known as bis-PO PMPA) and tenofovir, delavirdine, efavirenz, etravirine, lersivirine, loviride, nevirapine and rilpivirine; elvitegravir, globoidnan A, GSK-572, MK-2048 and raltegravir; enfuviritide, ibalizumab, maraviroc and vicriviroc; bevirimat and vivecon; aciclovir, docosanol, edoxudine, famciclovir, foscarnet, idoxuridine, penciclovir, trifluridine, tromantidine, valaciclovir and vidarabine (all of which treat infection caused by one or more herpes viruses); adefovir, boceprevir, entecavir, ribavirin and taribavirin (all of which treat infection caused by one or more hepatitis viruses); amantadine, arbidol, oseltamivir, peramivir, rimantidine and zanamivir (all of which treat infection caused by one or more influenza viruses).
WO 2012/045994* (12/04/2012) PCT/ GB2011/001441 (04/10/2011)	PROCESSES FOR PREPARING IMPROVED COMPOSITIONS	Iota Nanosolutions Limited	No mention of specific API; method to produce a composition involving an API in nanodisperse form.
WO 2013/034925* (14/03/2013) PCT/ GB2012/052208 (07/09/2012)	COMPOSITIONS OF EFAVIRENZ	The University of Liverpool	A solid efavirenz composition, comprising nanoparticles of efavirenz dispersed within a mixture of at least one hydrophilic polymer and at least one surfactan. (claim 1) Also involves a mention of a process for preparing such composition (claim 14) and its use for the treatment and prevention of retroviral infections (e.g., HIV). (claim 24)

WO 2013/034926* (14/03/2013) PCT/GB2012/05220 (07/09/2012)	COMPOSITIONS OF LOPINAVIR	The University of Liverpool	A solid lopinavir composition, comprising nanoparticles of lopinavir dispersed within a mixture of at least one hydrophilic polymer and at least one surfactant. (claim 1) Also involves a mention of a process for preparing such composition (claim 14) and its use for the treatment and prevention of retroviral infections (e.g., HIV). (claim 23)
WO 2013/034927* (14/03/2013) PCT/GB2012/05221 (07/09/2012)	COMPOSITIONS OF LOPINAVIR AND RITONAVIR	The University of Liverpool	A solid composition, comprising nanoparticles of lopinavir and ritonavir dispersed within a mixture of at least one hydrophilic polymer and at least one surfactant. (claim 1) Also involve a mention a process for preparing such composition (claim 14) and its use for the treatment and prevention of retroviral infections (e.g., HIV). (claim 23)
WO 2017/216564 (21/12/2017)** PCT/ GB2017/051746 (15/06/2017)	CHEMICAL COMPOSITION	The University of Liverpool The Johns Hopkins University	A solid composition comprising nanoparticles of atovaquone dispersed within one or more carrier materials, wherein the atovaquone is present in an amount of at least 10 wt%. (claim 1) Specific mention of long-acting injectables: an intramuscularly-injectable formulation or a subcutaneously-injectable formulation when administered to a patient releases atovaquone into the bloodstream of the patient over a period of at least about two weeks from the date of administration. (claim 20)
WO 2018/178722 (04/10/2018)** PCT/GB2018/05088 (29/03/2018)	PRODRUG COMPOSITIONS	The University of Liverpool The Johns Hopkins University	Prodrug compounds (described) in nanoparticles of less than 1000 nm diameter. (claims 1 and 11) Mention of long-acting injectables: an intramuscularly-injectable formulation, or a subcutaneously-injectable formulation, when administered to a patient releases the prodrug compound as defined in any one of claims 35 to 49 into the bloodstream of the patient over a period of at least about two weeks from the date of administration. (claim 28) Use to prevent or treat HIV infection. (claim 52)
WO 2018/178721 (04/10/2018)** PCT/ GB2018/050887 (29/03/2018)	METHOD FOR PRODUCING A LIQUID COMPOSITION	The University of Liverpool The Johns Hopkins University	Specific focus on tenofovir prodrugs (tenofovir disoproxil, tenofovir alafenamide, their salts or combinations thereof). Mention of an intramuscularly-injectable and/or subcutaneously-injectable forms; a pharmaceutical or veterinary composition in a form suitable to be administered orally (capsule or syrup).

Sources: Authors, based on consultation at WIPO Patent Scope.
*Licensed patents in the scope of the Collaboration Agreement & Patent and Know-how license between the University of Liverpool and the Medicines Patent Poll (2015).
**MPP/Unitaid patent landscape on long-acting technologies (2018).

TABLE 16.

Update Patents and/or Patent Applications From University of Liverpool Related to Nanotechnology and Pharmaceutical Compositions (With Specific Active Pharmaceutical Ingredients or Therapeutic Classes)

WO (date) PCT (date)	Title (WO)	Applicant	Comments
WO 2008/006713* (17/01/2008) PCT/ EP2007/056561 (29/06/2007)	IMPROVEMENTS RELATING TO ANTI-PARASITIC COMPOSITIONS	Unilever PLC Unilever NV	The present invention relates to nanodisperse antiparasitics and provides a composition comprising at least one water-insoluble antiparasitic drug and a water-soluble carrier material, wherein the water-insoluble antiparasitic drug (preferably an Artemisinin-type drug or a quinine-type drug) is dispersed through the carrier material in nanodisperse form having a peak diameter of the nanodisperse form below 1000 nm. (abstract) Active ingredients: peroxide, lactone, peroxy-lactone, quinine, quinoline and/or quinidine, artemisinin, artemether, arteether, dihydroartemisinin, and mixtures thereof. (claims 10–13)
WO 2016/009227 (21/01/2016) PCT/ GB2015/052089 (17/07/2015)	PARTICLES CONTAINING BRANCHED POLYMERS	The University of Liverpool	Particles comprising a branched polymer and either a block copolymer or a linear dendritic hybrid represent a category of useful materials. They may be used in for example drug delivery applications. (abstract) Active ingredients: HIV antiretroviral, anticancer drug, or ibuprofen
WO 2018/029477 (15/02/2018) PCT/ GB2017/052356 (09/08/2017)	OPHTHALMIC COMPOSITIONS	The University of Liverpool	An (ophthalmic) composition comprises: a base oil, an additive, and a drug. The additive has segments which are conjugated, e.g., covalently linked, together. A first segment facilitates solubility in the base oil, whereas a second segment facilitates drug solubility and/or modifies drug release or other behavior. (abstract) Active ingredients: ibuprofen, anti-inflammatory drug, an anti-proliferative, an anti-oxidant drug, an anti-neoplastic drug, an anti-growth factor
WO 2019/166834 (06/09/2019) PCT/ GB2019/050594 (04/03/2019)	SOLID COMPOSITIONS OF ACTIVES, PROCESSES FOR PREPARING SAME AND USES OF SUCH SOLID COMPOSITIONS	The University of Liverpool	Solid composition (and a process for preparing it) comprising nanoparticles comprising at least one water-insoluble active and at least one oil, dispersed within a water-soluble mixture of at least one hydrophilic polymer and at least one surfactant. (abstract) Intramuscularly-injectable and/or subcutaneously-injectable form; a pharmaceutical composition suitable to be administered orally. (claims 26 and 27) Active ingredients: an anti-parasitic, a biocide, an opioid, a non-steroidal anti-inflammatory (NSAID), a sartan, a statin, or a steroid; antiretroviral drug (HIV) is separately selected from one or more of the following: protease inhibitors (Pis), nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, entry inhibitors, maturation inhibitors, and pharmaceutically acceptable salts and prodrugs thereof (claims 5 and 6)
WO 2020/128525 (25/06/2020) PCT/ GB2019/053678 (20/12/2019)	NRTI therapies	The University of Liverpool The Johns Hopkins University	Polymer-of-prodrug (POP) materials enable new nucleoside reverse transcriptase inhibitor (NRTI) therapy strategies. The materials are prodrugs of NRTIs in the form of polymers. Suitable materials include products which are polymeric NRTI delivery systems. The invention facilitates long-acting (LA) regimens. Constructs of the materials may be in the form of injectable compositions or implants. (abstract) Active ingredients: FTC, 3TC, EFdA, and TFV (claim 3)

Source: Authors, based on patent search as described in the Methodology and consultation at WIPO Patent Scope.
*Patent identified in the patent search and also included in the list of licensed patents of the "Patent and Know-How license" between Tandem Nano Ltd. and the Medicines Patent Pool (2021).

TABLE 17.
Update Patents and/or Patent Applications From University of Liverpool Related to Nanotechnology With Medical Application (With Focus on Nanoparticles)

WO (date) PCT (date)	Title (WO)	Applicant	Comments
WO 2004/047870 (10/06/2004) PCT/GB2003/005157 (28/11/2003)	NANOPARTICLE CONJUGATES AND METHOD OF PRODUCTION THEREOF	The University of Livepool	A method for the preparation of nanoparticle conjugates. No mention of a specific API.
WO 2005/029076 (31/03/2005) PCT/GB2004/003986 (20/09/2004)	NANOPARTICLE CONJUGATES AND METHOD OF PRODUCTION THEREOF	The University of Livepool	A nanoparticle conjugate comprising a nanoparticle conjugated to a plurality of peptides of a substantially similar amino acid sequence.
WO 2012/143733 (26/10/2012) PCT/GB2012/050884 (20/04/2012)	NANOPARTICLES	The University of Livepool	A porous composite material comprising a hydrophobic carrier carrying a magnetic material and a hydrophobic material or organic compound (pharmaceutically active ingredient). A product for use in cancer therapy.
WO 2017/058113 (06/04/2017) PCT/SG2016/050480 (28/09/2016)	COATING FOR METAL NANOPARTICLES	Agency for Science, Technology and Research (Singapore) The University of Liverpool	A ligand compound having the structure A-B-C. (claim 1) The coated metal nanoparticle wherein the additional group is selected from the group consisting of a dye, a radionuclide, a pharmaceutical agent, a biotherapeutic agent, a chemotherapeutic agent, a radiotherapeutic agent, and combinations thereof. (claim 18)

Source: Authors, based on patent search as described in the Methodology and consultation at WIPO Patent Scope.

TABLE 18.
Update Patents and/or Patent Applications From University of Liverpool Related to Nanotechnology and Pharmaceutical Compositions (With Focus on Materials for Pharmaceutical Compositions)

WO (date) PCT (date)	Title (WO)	Applicant	Comments
WO 2014/199174 (18/12/2014) PCT/GB2014/051822 (13/06/2014)	POLYDENDRONS	The University of Livepool	Protection focused on: A method of preparing a non-gelled branched vinyl polymer scaffold carrying dendrons, comprising the living or controlled polymerization of a monofunctional vinyl monomer and a difunctional vinyl monomer, using a dendron initiator and at least one further initiator. (Claim 1) A product wherein the further moiety is selected from one or more of the following: a small molecule, a drug, an active pharmaceutical ingredient. (claim 16) A product for use as an orally, topically, or parenterally administered medicament. (claim 30)

WO 2014/199175 (18/12/2014) PCT/GB2014/051823 (13/06/2014)	POLYDENDRONS	The University of Livepool	Protection focused on: A method of preparing a branched vinyl polymer scaffold carrying comprising the living or controlled polymerization of a monofunctional vinyl monomer and a difunctional vinyl using a dendron. (claim 1) A nanoparticle comprising a product to a pharmaceutical composition comprising a product and a pharmaceutically acceptable.
WO 2017/118842 (13/07/2017) PCT/GB2016/054084 (29/12/2016)	BRANCHED POLYESTER CARRYING DENDRONS	The University of Livepool	Branched polyesters carrying dendrons are a useful class of nanomaterials which exhibit good handling properties and stability, can degrade to a high extent, and are effective encapsulation materials. They can be used to make nanoprecipitated particles which may for example be used in therapy. (abstract) Protection focused on: A product that is a branched polyester carrying dendrons; a pharmaceutical composition; a product, loaded with a therapeutically active material, for use in therapy; a method of medical treatment comprising administration of a product, loaded with a therapeutically active material, to a subject.
WO 2018/029462 (15/02/2018) PCT/GB2017/052334 (08/08/2017)	BRANCHED POLYMERS	The University of Livepool	Protection focused on: A branched amphiphilic polymer, suitable for stabilizing an emulsion, comprising: a) a plurality of polymer chains comprising hydrophobic chain ends; b) a plurality of polymer chains comprising functional chain ends capable of associating to a biological substrate; and c) a plurality of branching units. (claim 1) A pharmaceutical composition, wherein the composition is an oil-in-water emulsion and the droplet size of the oil-in-water emulsion formulation as measured by the z-average diameter and determined by dynamic light scattering is between 1-100 μιη. (claim 17)

Source: Authors, based on patent search as described in the Methodology and consultation at WIPO Patent Scope.

TABLE 19.

Update Patents and/or Patent Applications From University of Liverpool Related to Nanotechnology and Pharmaceutical Compositions (With Focus on Nanodispersion or Nanoemulsions)

WO (date) PCT (date)	Title (WO)	Applicant	Comments
WO 2008/006712 (17/01/2008) PCT/EP2007/056560 (29/06/2007)	PREPARATION OF NANODISPERSIONS	Unilever PLC* Unilever NV	A process for making contra-soluble nanodispersions of at most sparingly-soluble materials in a soluble carrier material comprising several steps.
WO 2013/030535 (07/03/2013) PCT/GB2012/052028 (20/08/2012)	METHOD OF PREPARING CARRIER LIQUIDS	Iota Nanosolutions Limited**	Protection focused on: A process for making contra-soluble nanodispersions of at most sparingly-soluble materials in a soluble carrier material comprising several steps.
WO 2016/124925 (11/08/2016) PCT/GB2016/050252 (03/02/2016)	NANOEMULSIONS	The University of Livepool	Protection focused on: An oil-in-water emulsion, comprising an emulsifier which is a non-gelled branched polymer, wherein the ends of at least some of the chains of said polymer terminate in an alkyl chain of 5 carbon atoms or more, and wherein the oil-in-water emulsion takes the form of particles having a z-average diameter of no greater than about 1000 nm. A pharmaceutical composition, optionally for oral administration, comprising an oil- in-water emulsion as claimed in any preceding claim. A method of medical treatment comprising the administration of an effective amount of an oil-in-water emulsion or pharmaceutical composition.
WO 2018/029476 (15/02/2018) PCT/GB2017/052355 (09/08/2017)	OPHTHALMIC COMPOSITIONS	The University of Livepool	A (ophthalmic) composition comprises: a base oil; an additive comprising a copolymer comprising hydrophobic and hydrophilic units; and a drug.

Source: Authors, based on patent search as described in the Methodology and consultation at WIPO Patent Scope.
*Patent identified in the patent search and assuming University of Liverpool is the assignee, as identified in preivous cases.
**University of Liverpool as assignee.

APPENDIX 1. DETAILED METHODOLOGY AND GENERAL RESULTS

1. Patent Search

The current research aims to update patents related to hepatitis C (glecaprevir, pibrentasvir, and the fixed-dose combination [FDC]) and tuberculosis medicines (Isoniazid/Rifapentine—3HP, bedaquiline, and delamanid) to identify if companies are filing applications related to LAFs.

Therefore, the patent search involved the following three steps.

Step 1: Identifying the Existing Patents in Secondary Sources

Secondary sources are those sources in which a patent search was already carried out, adopting specific methodology with keywords and databases, and up to a defined date (month/year).

This step was crucial to avoid duplication of work done on patent searches.

The secondary sources were the following: Unitaid reports on patent landscaping, the Medicines Patents and Licenses Database (MedsPaL), MSF Patent Opposition Database, and TAG reports.

There were reports published by Unitaid for most of the following cases and dates of search:

- **Glecaprevir:** report[110] published in March 2017 with patent searches carried out in December 2016 (total of eight patents identified, including some related to the FDC with pibrentasvir);
- **Pibrentasvir:** report[111] published in March 2017 with patent searches carried out in December 2016 (total of 10 patents filed by AbbVie,

including some related to the FDC with glecaprevir, and two patents filed by two other companies);

- **Bedaquiline:** report[112] published January 2013 with patents identified up to June 2011 (total of five patents identified);
- **Delamanid:** report[113] published January 2014 with patents identified up to February 2013 (total of nine patents identified).

The report[114] published by TAG on the 3HP identified two patents.

The search at MedsPaL brought *additional* patents to those already identified in Unitaid's report:

- Glecaprevir/pibrentasvir: three patents;
- Bedaquiline: two patents.

Searches in MSF patent opposition database did not add new patents in relation to those already found in the previous sources.

Step 2: Updating the Patent Landscape

This step involved search for patents in primary sources, based on keywords (defined case-by-case) whenever required in specific databases. The searches were carried out in September-October 2020.

- **FDA Orange Book:**[115] name of the active pharmaceutical ingredient, "Patent and Exclusivity information" to access the list of US patents. In order to identify the international publication number (WO), the US patent numbers were then used in the European Patent Office Espacenet – advanced search.[116]

  Information was only available for glecaprevir and pibrentasvir FDC (three patents) and bedaquiline.

- **Health Canada Patent Register:**[117] name of the active pharmaceutical ingredient to obtain the list of Canadian patent numbers. In order to identify the international publication number (WO), the Canadian patent numbers were then used in the European Patent Office Espacenet – advanced search.

  Information was only available for glecaprevir and pibrentasvir FDC (the three same patents as identified in FDA Orange Book).

- **Canadian Intellectual Property Office:** a complementary search was carried out on the Canadian Patent Office (CPO) database[118] using the keyword "bedaquiline" (the result was one new patent found for this drug). In the case of glecaprevir and pibrentasvir FDC, two patents were found. In the case of rifanpentine, 10 patents were found.

  The criteria to exclude nine of the patents from the report results from the fact that the company Sanofi was not the applicant. Of those nine patents that were excluded: **1)** two (2) are expired (Le Petit SA); **2)** one (1) does not cover rifapentine, it only covers a composition of

ripampicin and isoniazid (Panacea Biotec LTD); **3)** one (1) patent for which the object is a number of new compounds, rifapentine is only mentioned, among other older medicines, as one possible agent in combination with the aimed compounds (Otsuka Pharmaceuticals Co., Ltd.); **4)** two (2) patents are focused on anti-TB compounds, although rifapentine is only mentioned as one possible agent to be used in combination, among other agents (one of Pfizer and one of Glaxomithkline Dev. Ltd.).

- **Google Patents Advanced Search:**[119] filters were used considering different combinations of keywords, the main ones are as follows:
    - Filter "search terms"—the name of the active pharmaceutical ingredient;
    - Filter "Assignee"—the name of the pharmaceutical company commercializing the product;
    - Filter "Patent Office"—WO (international publication number).

Findings in Google Patents added[120] new patents to those already identified in previous sources as follows:

- Pibrentasvir: three patents (two from AbbVie and one from GSK);
- Glecaprevir/pibentrasvir: one patent;
- 3HP: one patent;
- Bedaquiline: one patent;
- Delamanid: four patents.

In order to select the patents above from searches at Google Patents, some cases had to go through analysis of the claims, such as:

- Glecaprevir: 18 patents were excluded because they are focused on HCV polymerase inhibitors;
- Bedaquiline: four patents were excluded because they covered molecules for TB and key-intermediates with no mention to bedaquiline in the claims.

Based on the content analysis of identified patents, two additional patents were included for delamanid.

Two additional patents related to glecaprevir, only filed in the US, were identified at the WIPO Pat-informed database (https://www.wipo.int/patinformed/).

The final result involved 55 patents and/or patent applications, of which 19 were considered as new filings in comparison to what was available in secondary sources.

Step 3: Download of WO Documents and Mapping Country's Application/Patent Number

Once the list of patents and/or patent applications per medicine was defined, based on the international publication number (WO), the 55[121] international applications under the WIPO PCT (WO documents) were downloaded from the EPO Espacenet. The list of patent and/or application numbers from different countries for each of the 55 patents were also exported to an Excel spreadsheet to facilitate the following step related to patent status.

Additional list of countries patent and/or application numbers were also collected from WIPO Patent Scope database,[122] based on the international publication number (WO).

The list of countries in which a patent/application number is available in either EPO Espacenet or WIPO Patent Scope is not exhaustive and therefore does not mean a certain patent application is not filed in countries not listed there. A patent search at the national level was carried out to confirm whether an application was filed or not. However, for the purposes of this analysis, this information was relevant to support the search of patent status in most of the countries.

2. Preliminary Claim Analysis

The preliminary content analyses of the updated patents were based on the classification of the claims according to ICTSD/UNCTAD/WHO (2007) and UNDP (2016) guidelines,[123] such as: compositions (formulations), Markush Formula, selection, doses, polymorphs, salts, ethers and esters, combinations, enantiomers, prodrugs, metabolites, uses (second medical uses), and method of treatment.

The reference document for the analysis of the content of the claims was the international application published under the WIPO Patent Cooperation Treaty (PCT), with the international publication number (WO) whenever they were available in English.

3. Patent Status

The 36 countries searched in relation to status at the national level were selected according to the following criteria:

- **TB country scope:** Peru and 12 countries in the IMPAACT4TB[124] project (Ethiopia, Malawi, Tanzania, Ghana, Mozambique, Zimbabwe, Kenya, South Africa, Cambodia, India, Indonesia, and Brazil);
- **HICs**: Australia, Canada, US (USPTO), and EU (EPO);
- **HCV country scope (up to 31 countries):** Côte d'Ivoire, Ghana, Kenya, Morocco, Nigeria, Pakistan, Senegal, South Africa, Tanzania, Uganda, Vietnam, Belarus, Brazil, India, Indonesia, Kazakhstan,

Kyrgyzstan, Mexico, Russia, Tajikistan, Turkey, Ukraine, Uzbekistan; Burkina Faso, Cambodia, DRC, Ethiopia, Mozambique, Rwanda; US (USPTO), and EU (EPO).

In order to update the patent status, a combination of approaches was adopted.

The first step was to try to identify the information on national or regional databases, which for several cases were not feasible. For those countries where information was available (Table 3), different approaches were applied in terms of data to be inserted to get the status, for example, the international publication number (WO), PCT numbers, patent applications titles, or national numbers (obtained for some of the cases from EPO Espacenet or WIPO Patent Scope).

Whenever it was not feasible to collect the information at the national level (including due to language barriers or fee requirements), information with regards to status was checked at the WIPO Patent Scope database.

The last source of information was the status available at the MedsPaL.

The patent status was classified as follows:

- "**Granted**" means that a patent was granted for a minimum period of 20 years starting from the filing date of the national application in a given country or the date of filing of the Patent Cooperation Treaty application.
- **"Pending"** means that the patent application was filed and that the patent office is reviewing the application and has not taken a decision on the application or published the decision.
- "**Not Found**" means that no patent application could be found for a given patent with the relevant patent office. This means that generic producers would have the freedom to operate in these territories.
- "**Withdrawn**" means that the applicant withdrew the application. Applications might be withdrawn for several reasons, including anticipation that the application would be rejected.
- "**Rejected**" means that the application was not approved by the patent office. A rejection can result from the decision of the patent officers after their examination or from a pre-grant opposition submitted by a third party.
- "**Revoked**" means that the patent office decided to accept the arguments of the opposition for an already granted patent, and/or that some administrative requirements were not fulfilled, or the courts have concluded that the patent is void.
- **"Lapsed"** means that a patent that was previously granted by the Patent Office has "lapsed" due to non-payment of the maintenance fee.

Whenever a patent was not found in the referred sources or in any source at all, we opted to classify it as "not found." This means it was not available in the country's database on the day of the search and we recommend to double-check at the national level whenever any action is considered for implementation in a specific application/patent and country.

Patent status was conduct in October 2020, with complementary updates from February-July 2021 for some cases.

In addition, considering some of the updated patent applications that were recently filed, some patents may not have been found because they are still going through PCT process and getting into national phases. According to the PCT system, it takes up to 18 months from the first application in the country of origin (priority date) to the publication of the international application and up to 12 months from the publication of the international application to PCT national phase entry.[125] In some cases, it was possible to obtain information regarding designated States in the PCT international application.

TABLE A1.1.
National and Regional Intellectual Property Offices Consulted.

Patent Office	Name	Scope	Source
National Intellectual Property Offices	National Institute of Industrial Property (INPI)	Brazil	https://gru.inpi.gov.br/pePI/jsp/patentes/PatenteSearchAvancado.jsp
	Canadian Intellectual Property Office	Canada	https://www.ic.gc.ca/opic-cipo/cpd/eng/search/basic.html
	Australian Patent Office	Australia	http://pericles.ipaustralia.gov.au/ols/auspat/
	United States Patent and Trademark Office	United States of America	https://portal.uspto.gov/pair/PublicPair
	National Office of Intellectual Property of Vietnam	Vietnam	http://iplib.noip.gov.vn/WebUI/WSearchPAT.php
	Intellectual Property database	Indonesia	https://pdki-indonesia.dgip.go.id/
	Indian Patent Advanced Search System	India	https://ipindiaservices.gov.in/publicsearch
	INDECOPI (Instituto Nacional de Defensa de la Competencia y de la Propiedad Intelectual)	Peru	https://servicio.indecopi.gob.pe/portalSAE/Personas/tituloOIN.jsp
	South Africa's official portal for IP services	South Africa	https://iponline.cipc.co.za/Patents/Search/FreePTSearch.aspx
	Ukrainian Intellectual Property Institute	Ukraine	https://ukrpatent.org/en
	Instituto Mexicano de la Propiedad Industrial	Mexico	https://patmedsp.impi.gob.mx/Paginas/Inicio.aspx https://vidoc.impi.gob.mx/Busqueda-Expedientes

Regional Intellectual Property Offices	Eurasian Patent Organization (EAPO)	Belarus, Kazakhistan, Kyrgyzstan, Russia, Tajikistan*	https://www.eapo.org/ru/publications/publicat/publicat.php
	Organisation Africaine de la Propriété Intellectuelle (OAPI)	Burkina Faso, DRC, Côte d'Ivoire, Senegal*	http://www.oapi.int/index.php/en/component/k2/item/556-recherche-en-ligne
	African Regional Intellectual Property Organization (Aripo)	Ghana, Kenya, Malawi, Mozambique, Rwanda, Tanzania, Uganda, Zimbabwe	http://eservice.aripo.org/pmi/PMIMain.do
	European Patent Office (EPO)	https://www.epo.org/about-us/foundation/member-states.html	https://register.epo.org/regviewer

*This table only mentions countries selected by the TAG team even though regional offices cover further countries. Russia also had complementary patent applications filed at the national level.

4. Preliminary Patent Search on Long-Acting Formulation by the University of Liverpool

An initial list of patents and/or patent applications was obtained from the report *Intellectual Property report on long-acting technologies*[126] and the *Collaboration Agreement and Patent and Know-how license.*[127]

Then, a search in Google Patents Advanced Search and EPO Espacenet[128] was carried out in January 2021, and considered a combination of keywords such as pharmaceutical composition and the name of the University.

Preliminary analysis aimed to identify whether specific API was covered by the patent/application and what type of protection was desirable in terms of pharmaceutical composition. No patent status analysis was carried out in selected countries. The content of the PCT application and the publication number were adopted as reference for the analysis.

APPENDIX 2. DETAILED ANALYSIS OF UPDATED PATENTS/APPLICATIONS RELATED TO PIBRENTASVIR AND THE COMBINATION OF GLECAPREVIR AND PIBRENTASVIR

FIGURE A2.1.
Molecular Structure of Compound 1 in WO 2018/093717

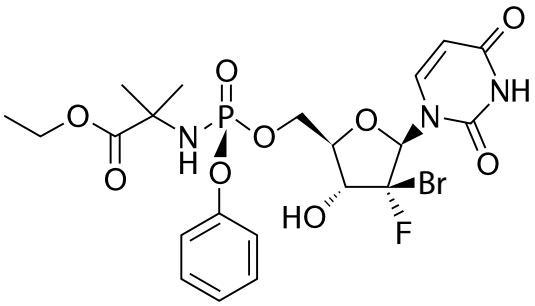
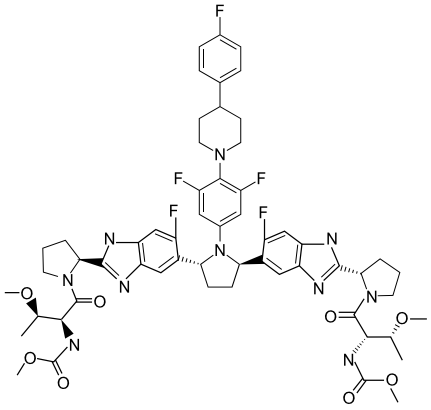
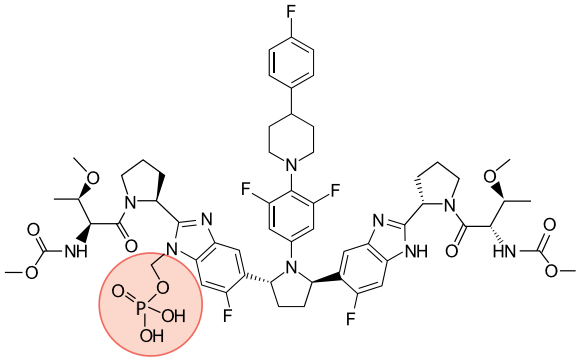


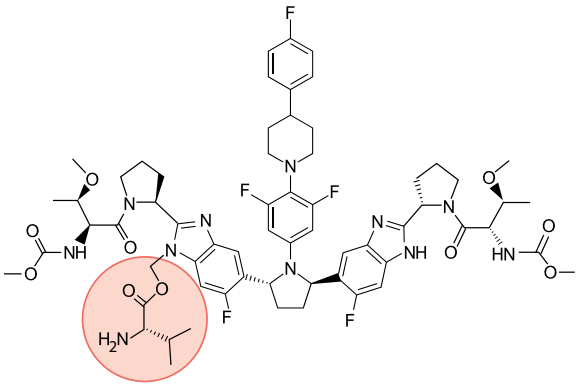
FIGURE A2.2.
Molecular Structure of Pibrentasvir and Some Examples of Related Prodrugs Described in WO 2018/093717



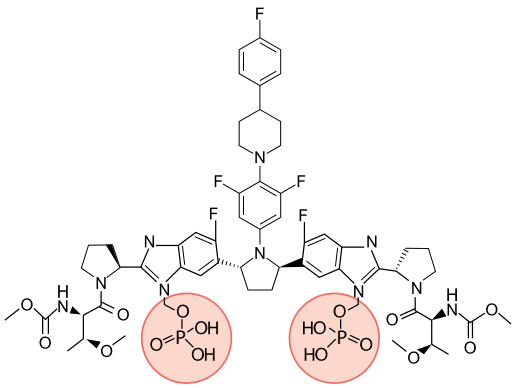
Pibrentasvir (compound 2a)



Prodrug of Pibrentasvir (compound 2b)



Prodrug of Pibrentasvir (compound 2c)



Prodrug of Pibrentasvir (example 3-3)

TABLE A2.1.
Detailed Information of the Method of Treatment Claimed in WO 2018/093717

Compounds involved	Method of treatment	Population*	Duration	Dose
Compound 1 + pibrentasvir Compound 1 + prodrugs of pibrentasvir Compound 1 + pibrentasvir + glecaprevir Compound 1 + prodrugs of pibrentasvir + glecaprevir	A method of treating HCV infection wherein said pharmaceutical composition is administered once daily, without either interferon or ribavirin	Patients are infected with HCV genotype 1, 2, 3, 4, 5, or 6. (claims 13–18) The patient can be: without cirrhosis or with compensated cirrhosis; patient is a treatment-naive patient or treatment-experienced. (claims 19–22) The patient can have end stage renal disease or severe renal impairment. (claims 34 and 35)	4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks (claims 10–12)	Compound 1: 80 mg 90 mg 100 mg 60–100 mg 70, 75, 80, 85, 90, 95, or 100 mg once daily (claims 23–32)

*The language adopted for the target population is the one adopted in the patent application analyzed.

TABLE A2.2.
Analysis of Updated Patents/Applications Related to the Combination of Glecaprevir and Pibrentasvir and Methods of Treatment

International publication number	Compounds involved	Method of treatment	Population*	Duration	Dose
WO 2017/007934 (17 claims)	Glecaprevir + Pibrentasvir Glecaprevir + Pibrentasvir + Sofosbuvir Pibrentasvir + Sofosbuvir (claim 1)	A method for treatment of HCV involving **at least two DAA** and where the treatment **does not involve** either **interferon** or **ribavirin**, lasting for 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks (claim 1)	Patients infected with HCV genotypes 1, 1a, 2, 3, 4, 5, and 6 (claims 7–13) Patients without cirrhosis or with compensated cirrhosis (claims 14–15) Treatment-naive patients (claim 16) Interferon non-responder patients (claim 17)	4, 6, 8, 10, or 12 weeks (claims 2–6)	-
WO 2018/057919 (26 claims)	Glecaprevir + Pibrentasvir (claims 1, 13, and 25)	A method of treating patients infected with hepatitis C virus having an **independent comorbid condition**, comprising co-administering to said patients glecaprevir and pibrentasvir once daily, together with a concomitant drug** for treating the comorbid condition. **The established dose of said drug is dose-adjusted prior to administering glecaprevir and pibrentasvir** to said patient. (claims 1, 13, 25). The administration of the glecaprevir and the pibrentasvir is **not recommended or contraindicated** for a concomitant treatment with a drug selected from a group consisting of atazanavir, rifampin, carbamazepine, Hypericum perforatum, efavirenz, ethinyl estradiol containing medications, darunavir, lopinavir, ritonavir, atorvastatin, lovastatin, and simvastatin. (claims 12 and 24)	Patients infected with HCV genotypes 1, 2, 3, 4, 5, and 6 (claims 4 and 16) Patient is treatment-naive, treatment-experienced, or has cirrhosis (claims 5 and 17)	8, 12, or 16 weeks (claims 2 and 15)	Glecaprevir 300 mg and pibrentasvir 120 mg once a day
	Digoxin pravastatin rosuvastatin fluvastatin pravastatin cyclosporin* (claims 6, 18, and 25)				**Digoxin:** dose is reduced by 50% of the established dose **Pravastatin:** dose is reduced by 50% of the established dose **Rosuvastatin:** dose is no more than 10 mg per day **Cyclosporine:** dose is no more than 100 mg per day **Fluvastatin or pitavastatin:** dose is reduced to lowest approved dose or lowest necessary dose (claims 7–11, 19–23, 26)

WO 2019/074507 (24 claims)	Glecaprevir + Pibrentasvir + Sofosbuvir Ribavirin	A method for **re-treating patients with HCV who have previously failed glecaprevir and pibrentasvir combination treatment**, comprising administering at least three direct-acting antiviral agents (DAAs) and ribavirin to an HCV patient, wherein said treatment does not include administration of interferon to said patient, and said treatment lasts for 4, 5, 6, 7, 8, 9, 10, 11, 12, or 16 weeks. (claim 1)	Patients infected with HCV genotypes 1, 1a, 2, 3, 4, 5, and 6 (claims 8–14) Patients without cirrhosis or with compensated cirrhosis (claims 15–16) Patient is treatment-naive, treatment-experienced, interferon non-responder, or has resistance-related substitutions comprising of a group consisting of NS3 alone, NS5A alone, and a combination of NS3 and NS5A substitutions (claims 17–20)	4, 6, 8, 10, 12, or 16 weeks (claims 2–7, 24)	**Glecaprevir:** 300 mg once a day **Pibrentasvir:** 120 mg once a day **Sofosbuvir:** 400 mg once a day **Ribavirin:** 1000–1200 mg twice a day, based on weight (claims 21–23)
WO 2019/027694	Glecaprevir + Pibrentasvir	A method of treating or preventing a HCV genotype 1–6 infection **in a transplant recipient receiving a solid organ from an HCV-infected donor** comprising administering two direct-acting antiviral agents (DAAs) to the recipient once daily for a duration of no more than 16 weeks, **without interferon or ribavirin**. (claim 1)	Donor is infected with HCV genotypes 1, 2, 3, 4, 5, or 6 (claim 5)	8 or 12 weeks for kidney transplant (claim 2)	**Glecaprevir:** 300 mg once a day **Pibrentasvir:** 120 mg once a day **Beginning of the administration:** before or simultaneously with transplant surgery (claims 3–4)
		A method of treating a HCV genotype 1–6 infection in a **transplant recipient** comprising administering two direct-acting antiviral agents (DAAs) to the recipient once daily for a duration of no more than 16 weeks, without interferon or ribavirin. (claim 6)	Transplant recipient was HCV-free prior to receiving a solid organ from an HCV-infected donor (claim 7) Transplant recipient are either a liver or a kidney transplant recipient (claims 11–12) Transplant recipient is without cirrhosis (claim 14)	8, 12, or 16 weeks	**Glecaprevir:** 300 mg once a day **Pibrentasvir:** 120 mg once a day **Beginning of the administration:** after transplant surgery or one year after transplant surgery (claims 8–9, 13)

		A method of genotype 1–6 infection in a **treatment-experienced patient** comprising administering two direct-acting antiviral agents (DAAs) to the patient once daily for a duration of no more than 16 weeks, **without interferon or ribavirin**. (claims 15)	Treatment-experienced patient is: a. NS5A inhibitor-experienced patient infected with HCV genotype 1; or b. NS3/4A protease inhibitor-experienced patient infected with HCV genotype 1; or c. an interferon-, pegylated interferon-, ribavirin-, and/or sofosbuvir-experienced patient infected with HCV genotype 3; or, d. an interferon-, pegylated interferon-, ribavirin-, and/or sofosbuvir-experienced patient infected with HCV genotype 1, 2, 4, 5, or 6 (non-cirrhotic or has compensated cirrhosis)	According to the population: 16 weeks 12 weeks 16 weeks 8 weeks for non-cirrhotic patients and 12 weeks for patients with compensated cirrhosis	-
WO 2019/046569	Glecaprevir + Pibrentasvir	A method of **preventing a HCV genotype 1–6 infection in a transplant recipient receiving a solid organ from a HCV -infected donor**, comprising administering two direct-acting antiviral agents (DAAs) to the recipient once daily for a duration of no more than 16 weeks, **without either interferon or ribavirin** (claim 1)	The donor is: • infected with HCV genotype 1, 2, 3, 4, 5, or 6; • without cirrhosis. • The solid organ is kidney (claims 2–4, 7–8)	4, 6, and 8 weeks (claims 2–4)	**Glecaprevir:** 300 mg once a day **Pibrentasvir:** 120 mg once a day **Beginning of the administration:** before or simultaneously with transplant surgery (claims 5 and 6)
		A method of **preventing** or treating a HCV genotype 1–6 infection **in a transplant recipient**, comprising administering two direct-acting antiviral agents (DAAs) to the recipient once daily for a duration of no more than 16 weeks, **without either interferon or ribavirin**	The recipient is: • liver transplant recipient • kidney transplant recipient • without cirrhosis • (claims 17–18, 20)	4, 6, 8, and 12 weeks (claims 14–16)	**Glecaprevir:** 300 mg once a day **Pibrentasvir:** 120 mg once a day **Beginning of the administration:** before or simultaneously with transplant surgery, or after transplant surgery or more than one year after transplant surgery (claims 11–13 and 19)

WO 2020/106835	Glecaprevir + Pibrentasvir	A method for **treatment for acute** HCV, comprising administering two direct-acting antiviral agents (DAAs) to said HCV patient, **without either interferon or ribavirin**, and said treatment lasts for **6 weeks**	Patient can be: • HCV-HIV co-infected; • without cirrhosis; • with compensated cirrhosis; • a treatment-naive patient; • an interferon non-responder; • kidney or liver transplant patient; • any degree of renal impairment; • pis infected with HCV genotype 1, 1a, 2, 3, 4, 5, or 6. (claims 2–15)	6 weeks	-

*The language adopted for the target population is the one adopted in the patent applications analyzed.
**Drugs that are substrates of Organic Anion Transporting Polypeptide, P-glycoprotein, and Breast Cancer Resistance Protein. (claim 1)

APPENDIX 3. DETAILED ANALYSIS OF UPDATED PATENTS/APPLICATIONS RELATED TO BEDAQUILINE

TABLE A3.1.
Analysis of Pharmaceutical Composition Claims From WO 2019/012100 (Long-Acting Formulation)

Components of the pharmaceutical composition	Type	Amount/size
Composition	A pharmaceutical composition for **administration by intramuscular or subcutaneous injection**, comprising a therapeutically effective amount of bedaquiline, or a pharmaceutically acceptable salt thereof, in the form of a **suspension** of micro- or nanoparticles comprising: (a) **bedaquiline**, or a pharmaceutically acceptable salt thereof, in **micro- or nanoparticle form**, and a **surface modifier**; and (b) a pharmaceutically acceptable aqueous carrier. (claim 1)	Weight based on the total volume of the composition: (a) from 10% to 70% (w/v), or from 20% to 60% (w/v), or from 20% to 50% (w/v), or from 20%> to 40%> (w/v) of bedaquiline (or pharmaceutically acceptable salt thereof; but where the w/v is calculated on the basis of its non-salt form); (b) from 0.5% to 20%, or from 2% to 15% or 20% (w/v), or from 5% to 15% (w/v) of a wetting agent; (c) from 0% to 10%, or from 0% to 5%, or from 0% to 2%, or from 0% to 1% of one or more buffering agents; (d) from 0% to 20 %, or from 2% to 15% or 20% (w/v), or from 5% to 15% (w/v) of a isotonizing agent (e) from 0%> to 2% (w/v) preservatives; and (f) water for injection q.s. ad 100%. (Claim 7)
Surface modifier	Selected from the group of poloxamers, a-tocopheryl polyethylene glycol succinates, polyoxyethylene sorbitan fatty acid esters, and salts of negatively charged phospholipids. (claim 2) Specific type: Selected from Pluronic™ F108, Vitamin E TGPS, Tween™ 80, and Lipoid™ EPG. (claim 4)	
Bedaquiline	Bedaquiline is in its non-salt or **free form** or in the form of a **fumarate salt**. (claim 3)	**Particle size** of the bedaquiline, or a pharmaceutically acceptable salt thereof, micro- or nanoparticles is: • below about **50 μιη**, in particular below about **200 nm** • average size is **130 nm** (claims 5 and 6)

Process for preparing the pharmaceutical composition	(a) obtaining bedaquiline, or a pharmaceutically acceptable salt thereof, in micronized form; (b) adding the micronized bedaquiline, or a pharmaceutically acceptable salt thereof, to a liquid medium to form a premix/predispersion; (c) and subjecting the premix to mechanical means in the presence of a grinding medium to reduce the average effective particle size. (claim 14)	

TABLE A3.2.
Analysis of Use Claims From WO 2019/012100 (Long-Acting Formulation)

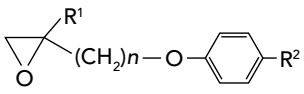
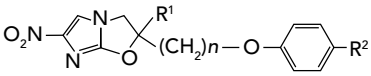
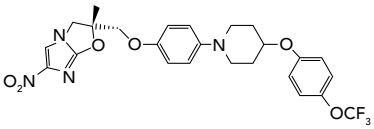
Product	Use	Administration of the treatment	Interval of the treatment
Pharmaceutical composition of bedaquiline (as described in claims 1–7)	**Use** of a pharmaceutical composition for the manufacture of a medicament for the **long-term treatment** of a pathogenic mycobacterial infection: • *Mycobacterium tuberculosis* (such as the **latent/dormant form**) • *Mycobacterium leprae* (claims 8 and 9)	Administration by intramuscular or subcutaneous injection (claim 10)	Composition is administered: • intermittently at a time interval of one week to two years; • at an interval of at least one month to one year; • at a time interval that is in the range of one week to one month, or in the range of one month to three months, or in the range of three months to six months, or in the range of six months to twelve months, or in the range of 12 months to 24 months; • once every two weeks, or once every month, or once every three months. (claims 1–13)

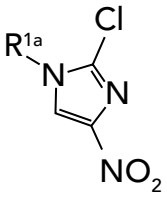
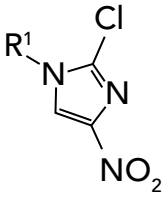
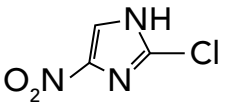
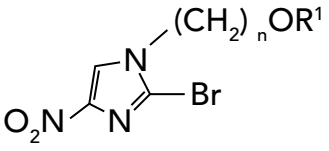
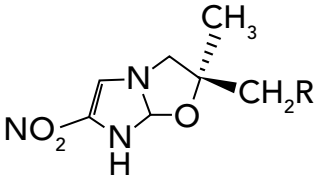
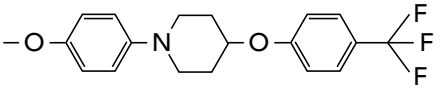
TABLE A3.3.
Analysis of Claims From WO 2020/144197

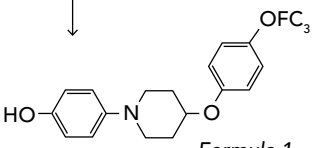
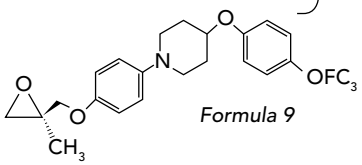
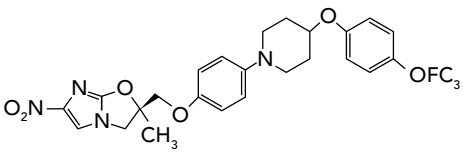
Product	Method of treatment/use	Disease	Treatment regimen	Process for preparing the combination
A combination comprising: • bedaquiline • a macrolide (e.g., clarithromycin or azithromycin) • ethambutol (Claim 1)	A combination for use in the treatment of a disease associated with nontuberculous mycobacteria (NTM) A method of treating a disease associated with NTM in a patient, comprising administering an effective amount of a combination of: (i) bedaquiline; (ii) a macrolide (e.g. clarithromycin or azithromycin); and (iii) ethambutol (Claim 2 and 3)	Disease associated with nontuberculous mycobacteria (NTM) is NTM-PD (pulmonary disease) Disease is NTM-PD in which the isolates of the NTM are not macrolide-resistant (Claims 9 and 10)	Administration of: • **bedaquiline:** Weeks 1–2: 400 mg once daily (or"qd"); Weeks 3–24 (and optionally up to 52 weeks, i.e., Weeks 3–52): 200 mg three times per week (or "tiw") (with at least 48 hours between doses); • **macrolide:** for instance, when it is clarithromycin, 1000 mg per day, for instance 500 mg twice daily (i.e., 500 mg "bid") and when it is azithromycin, 250 mg per day; • **ethambutol:** using the dosing 15 mg/kg per day. Total treatment regimen is about 52 weeks Combination of antibacterial drugs may be co-administered, sequentially administered, or administered substantially simultaneously. (Claims 4–7, 11)	A process for preparing a combination, which comprises: • bringing into association each of the components (e.g., as separate pharmaceutical formulations) of the combination product and co-packaging (e.g., as a kit of parts) or indicating that the intended use is in combination (with the other components); and/or bringing into association each of the components in the preparation of a pharmaceutical formulation comprising such components.

APPENDIX 4. DETAILED ANALYSIS OF SOME UPDATED PATENTS/ APPLICATIONS RELATED TO DELAMANID

TABLE A4.1.
Analysis of the Updated Patents/Applications Related to Synthetic Processes of Key-Intermediates of Delamanid

International publication number	Products	Processes	Comments
WO 2008/140090	Epoxy compounds or salts represented by the following Formula 2:  (claims 1 and 2)	• Methods for manufacturing epoxy compounds of Formula 2 (claim 3) • Method for manufacturing an oxazole compound (Formula 1) (by reacting with epoxy compounds):  (claim 4)  In order to achieve delamanid structure, substituents of Formula 1 should be: R^1: CH_3 n: 1 R^2: 4-[4-(Trifluoromethoxy)phenoxy] piperidine	Epoxy compounds are key-intermediates for the synthesis of oxazole compounds disclosed by WO2004/033463, WO2004/035547, and WO2005/042542, which are useful as an antitubercular agent. These are Patents 1, 2, and 9 from Unitaid report related, respectively, to the API of delamanid and key-intermediate of nitroimidazole compounds. Delamanid is one of the possible compounds covered by compound of Formula 1. **Conclusion**: this patent covers (a) key-intermediates for the synthesis of delamanid; (b) the process for synthesis of such key-intermediates.

WO 2019/146113	Compounds of Formula Ia:  wherein R^{1a} is selected from C 1-6 alkoxymethyl, C 1-6 alkoxycarbonyl, phenyloxymethyl, and tetrahydropyranyl, each of which may be optionally substituted with at least one halogen atom, ethoxymethyl, tert-butoxycarbonyl, 3-Cl-phenyloxymethyl, and tetrahydropyranyl (claims 15 and 16).	A process for preparing compound of Formula I:  (Claims 1–14)	This patent application consists of 16 claims. Claims 1–14 are process claims to obtain key nitroimidazole intermediates (uses of different activating agents, etc.). Claims 15–16 are compound claims where the applicant is trying to protect specific key-intermediates that are also covered by some of the process claims 1–14. It refers, among other background references, to WO2006035960, WO2010021409, and WO2005077913 (Patent 8 from Unitaid report) related to key-intermediates for tuberculosis agents. In particular, compound of Formula Ia (with some of the possible R1a substituents) are similar to the intermediates used in WO2016158737, WO2008140090.
WO 2006/035960	A process for production of 2-chloro-4-nitroimidazole represented by the Formula:  comprising a reaction of l-alkoxyalkyl-2-bromo-4-nitroimidazole represented by the general Formula:  wherein R^1 represents a lower alkyl group, and n represents an integer of 1 to 3, with hydrogen chloride.		2-chloro-4-nitroimidazole is a key-intermediate for the synthesis of delamanid. Patent/application WO2005077913 (Patent 8 from Unitaid report) also discloses a process to produce such key-intermediate.
WO 2010/021409	The process to produce 2-halo-4-nitroimidazoles (claims 1–12). Claim 13 aims to protect a process to produce an antituberculosis agent to produce the compound of Formula VIII.  Where R is: 		This claim includes the option of 2-chloro-4-nitroimidazole, which is a key-intermediate for the synthesis of delamanid. Patent/application WO2005077913 (Patent 8 from Unitaid report) also discloses a process to produce such key-intermediate. Compound of Formula VIII (claim 13), resultant of this process, is very similar to the molecular structure of Delamanid, with one slight difference: the substituent of the phenoxy group is a trifluoromethyl, instead of trifluoromethoxy as in Delamanid. The present application refers to delamanid on the description, but claims only the referred compound VIII (trifluoromethyl instead of trifluoromethoxy).

WO 2016/158737	It is possible to identify three main compounds on the synthesis process: **Claims 1–4**  *Formula 1* 3 Methods: B1 – Steps c2, c3 B2 – Steps c1, c2, c3 B3 – Step b1 **Claims 9–11**  *Formula 9* Step b2, b3 **Claims 5–8**  *Formula 12* Differences on process claimed from compound 1 to compound 9. **B1** **Claims 6, 9** *Formula 1* c2 *Formula 14* c3 *Formula 15* *Formula 9* **B2** **Claims 7, 10** *Formula 1* c1 *Formula 13* c2 *Formula 14* c3 *Formula 15* *Formula 9* **B3** **Claims 8, 11** *Formula 1* c3 *Formula 8* *Formula 9*	Compound of Formula 1 is a key-intermediate for the synthesis of delamanid. Compound of Formula 12 is delamanid (claim 5). Processes claimed in claims 6, 7, and 8 are mainly the same with the *minor* differences. Among other references as background, it cites WO2005092832 (Patent 9 from Unitaid report).

Source: Authors, based on some of the analysis developed by Dr. María Lorena Bacigalupo and Dr. Maria Florencia Pignataro.
Disclaimer: Considering the WO documents were in Japanese, the authors made the analysis on the US equivalent patents for WO 2008/140090 and WO 2016/158737. The limitation of this approach though is the potential changes in the language of claims.

TABLE A4.2.
Detailed Analysis of Claims of WO 2019/240104

Components of the pharmaceutical composition	Type	Specific type	Amount/size
Composition	(A) delamanid particles and (B) a surface stabilizer (claim 1). Pharmaceutical oral solid preparation obtained from the granular composition (tablet or capsule) (claims 11–14).	(B-1) polymer (B-2) surfactant (claim 2)	100 parts by weight (B-1) 2 ~ 20 parts by weight of component (B-2) 2 ~ 55 parts by weight of components (claim 6) (A) 100 parts by weight (B-1) 2 ~ 20 parts by weight of component (B-2) 2 to 15 parts by mass of sucrose fatty acid ester and 2 to 40 parts by mass of dioctylsodium sulfosuccinate with respect to 100 parts by mass of the component (claim 7) 100 parts by weight (B-1) 2 ~ 20 parts by weight of component (B-2) 2 ~ 55 parts by weight of components (C) sugar and/or sugar alcohol (claim 8) 100 parts by mass of (A) component 2 to 20 parts by mass of (B-1) component 2 to 55 parts by mass of (B-2) component 30 to 200 parts by mass of sugar and / or sugar alcohol (claim 9) 2 to 15 parts by mass of sucrose fatty acid ester 2 to 40 parts by mass of dioctylsodium sulfosuccinate, 30 to 200 parts by mass of mannitol with respect to 100 parts by mass of the component (claim 10)
Surfactant	At least a nonionic surfactant and/or an anionic surfactant (claim 4)	sucrose fatty acid ester and/or diester of alkyl alcohol and sulfosuccinic acid or a salt thereof (claim 5)	
Polymer	At least hydroxypropyl cellulose (claim 3)		
Delamanid particles	Submicron particles		Average particle size of the delamanid particles is 350 nm or less (claim 13)

Source: Authors.

APPENDIX 5. PATENT STATUS IN SELECT HIGH-BURDEN HCV AND TB COUNTRIES

1. Glecaprevir

	Patent 1	Patent 2	Patent 3
Title (description)	Macrocyclic proline derived HCV serine protease inhibitors	Methods for treating HCV	Crystal Forms
Applicant	Enanta Pharm Inc	AbbVie	AbbVie
International publication number (publication date)	WO 2012/040167 (29/03/2012)	WO 2015/061742 (30/04/2015)	WO 2015/188045 (10/12/2015)
Australia	2011305695 Granted (01/09/2016) 2016204491 Elapsed (29/06/2016)	Not filed	AU2015269306 (A1) Granted (05/06/2015)
Belarus	EA201390425 Granted (29/04/2016) Patent No. EA023009 EA201500728 Granted (28/02/2018) Patent No.EA029145	Not filed	Not filed
Brazil	BR112013006693 Pending (14/07/2020)	Not filed	BR 11 2016 027366 4 Pending (06/10/2020)
Burkina Faso	Not filed	Not filed	Not filed
Cambodia	Not filed	Not filed	Not found
Canada	CA 2812261 Granted (21/02/2017)	CA2925328 Abandoned (24/10/2016)	CA 2948902 Pending
Côte d'Ivoire	Not filed	Not filed	Not filed
DRC	Not filed	Not filed	Not filed
Ethiopia	Not filed	Not filed	Not filed
EU (EPO)	EP2618831 (A1) Granted (09/12/1992) EP2618831 (A4) Granted (06/01/2016) EP2618831 (B1) Granted (06/01/2016) EP3020723 (A1)	EP3060216 Withdrawn (18/05/2018)	Not filed
Ghana	Not filed	Not filed	Not filed
India	IN2891DELNP2013 Pending (29/06/20)	Not filed	Not filed

Indonesia	W00201301596 Pending	Not filed	Not filed
Kazakhstan	EA201390425 Granted (29/04/2016) Patent No. EA023009 EA201500728 Granted (28/02/2018) Patent No.EA029145	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed
Kyrgyzstan	EA201390425 Granted (29/04/2016) Patent No. EA023009 EA201500728 Granted (28/02/2018) Patent No.EA029145	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed
Mexico	MX/a/2013/003230 Granted (31/10/2016)	MX/a/2016/005393 Withdrawn	MX/a/2016/016127 Granted (20/05/2020)
Morocco	Not filed	Not filed	EP15803592 Application deemed to be withdrawn: dispatch of communication + time limit (26/10/2020)
Mozambique	Not field	Not filed	Not filed
Nigeria	Not filed	Not filed	Not filed
Pakistan	Granted	Not filed	Not found
Peru	000545-2013/DIN Granted 15/06/2017 (INDECOPI)	Not Filed	Not Filed
Russia	EA201390425 Granted (29/04/2016) Patent No. EA023009 EA201500728 Granted (28/02/2018) Patent No.EA029145	Not filed	Not found
Rwanda	Not field	Not filed	Not filed
Senegal	Not filed	Not filed	Not found
South Africa	ZA201308655B Granted ZA201302317 Granted	Not filed	Not filed
Tajikistan	EA201390425 Granted (29/04/2016) Patent No. EA023009 EA201500728 Granted (28/02/2018) Patent No.EA029145	Not filed	Not found
Tanzania	Not field	Not filed	Not filed
Turkey	EP11827336 Granted EP15202935 Withdrawn	Not filed	EP15803592 Pending
Uganda	Not field	Not filed	Not filed
Ukraine	UAa201305119 Granted (25/04/2018) Patent No. UA116616	Not filed	Not found

US (USPTO)	US 20120070416 A1 (Application #13/237,120) Granted (22/01/2014) US2014194350 (A1) (Application #14/146,161) Granted (12/09/2015) US2016145298 (A1) (Application #14/946,866) Withdrawn US2017088583 (A1) (Application #15/287,042) Withdrawn US2018162905 (A1) (Application #15/839,249) Withdrawn US2019263860 (A1) (Application #16/142,087) Withdrawn US2020270303 (A1) (Application #16/724,677) Pending (28/05/2020) US8648037 (B2) (Application #13/237,120) Granted (22/01/2014)	US20150119400 (A1) (Application #14/523,692) Granted (25/02/2015) Withdrawn (2017)	US2015/0353600(A1) (Application #14/731,765) Granted (06/04/2016) Patent No. US9,321,807 US2016/0220487(A1) (Application #15/095,474) Granted (18/01/2017) Patent No.US9,561,181 (B2)
Uzbekistan	Not filed	Not filed	Not found
Vietnam	VN1-2013-01552 Pending (26/08/2019)	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed

2. Pibrentasvir

	Patent 1	Patent 2	Patent 3	Patent 4
Title (description)	Antiviral compounds	Antiviral compounds	Methods for treating hepatitis C	Crystal forms
Applicant	AbbVie	AbbVie	AbbVie	AbbVie
International publication number (publication date)	WO 2012/051361	WO 2012/116257	WO 2014/047039	WO 2015/171993
Australia	AU2011316506 (B2) Granted (12/10/2011)	Not filed	AU2013318302 (A1) Granted (21/06/2018) AU2013318302 (B2) AU2018203608 (A1) Granted (02/04/2020) AU2018203608 (B2)	AU2015255784 (A1) Lapsed (08/05/2015) AU2020203494 (divisional) Pending
Belarus	EA201390538 Granted (31/08/2016) Patent No.EA024100 EA201301158 Granted (30/09/2019) Patent No. EA033332	Not filed	Not filed	Not filed

Brazil	BR 11 2013 005701 7 Pending (13/10/2020)	Not filed	BR112015006037 Pending (20/03/2018)	Not filed
Burkina Faso	Not filed	Not filed	Not filed	Not filed
Cambodia	Not filed	Not found	Not found	Not found
Canada	CA 2807847 (A1) Granted (20/09/2016)	CA 2828495 Withdrawn (26/02/2018)	CA 2884539 Pending	CA 2945205 (A1) Pending
Côte d'Ivoire	Not filed	Not filed	Not filed	Not filed
DRC	Not filed	Not found	Not found	Not found
Ethiopia	Not filed	Not found	Not found	Not found
EU (EPO)	EP2627651 (A1) Withdrawn (17/04/2015) EP2692346 (A1) Granted (05/02/2014) EP2692346 (B1) Granted (02/12/2015) EP2692726 (A1) Refusal of Application (22/02/2019) EP3438106 (A1) Pending	EP2678334 Granted (22/03/2017)	EP2897611 (A1) Granted (24/07/2019) EP2897611 (B1) Granted (24/07/2019) EP3597190 (A1) Pending	EP3140284 (A1) Pending
Ghana	Not filed	Not filed	Not filed	Not filed
India	IN1310/DELNP/2013 Pending (03/12/2018) IN20180821052 Pending (17/09/20)	Not filed	Not filed	Not filed
Indonesia	W00201301506 Granted (26/09/2016) Patent No. IDP000042760	Not filed	Not filed	Not filed
Kazakhstan	EA201390538 Granted (31/08/2016) Patent No.EA024100 EA201301158 Granted (30/09/2019) Patent No. EA033332	Not filed	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	EA201390538 Granted (31/08/2016) Patent No.EA024100 EA201301158 Granted (30/09/2019) Patent No. EA033332	Not filed	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed	Not filed
Mexico	MX2013/004150 Granted (05/12/2016) Patent No. MX344092 B	MX/a/2013/009763 Granted (13/03/2017)	MX/a/2015/003501 Granted (06/09/2019)	MX/a/2016/014459 Pending
Morocco	Not filed	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed	Not filed
Nigeria	Not filed	Not filed	Not filed	Not filed
Pakistan	Pending	Not found	Not found	Not found

Peru	000057-2014/DIN Granted (13/08/2018) 000838-2013/DIN Granted (31/03/2017) (INDECOPI)	Not Filed	Not Filed	Not Filed
Russia	EA201390538 Granted (31/08/2016) Patent No.EA024100 EA201301158 Granted (30/09/2019) Patent No. EA033332	Not filed	RU2015114543 (Appl. No) Granted Patent No. RU2665365	Not filed
Rwanda	Not filed	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed	Not filed
South Africa	ZA201306888 Granted ZA201705519 (divisional of ZA201302269) Granted ZA201302269 Granted ZA201903284 Granted	Not filed	ZA201501752 Granted	Not filed
Tajikistan	EA201390538 Granted (31/08/2016) Patent No.EA024100 EA201301158 Granted (30/09/2019) Patent No. EA033332	Not filed	Not Filed	Not filed
Tanzania	Not filed	Not filed	Not filed	Not filed
Turkey	EP18196401 Filed EP11773371 Withdrawn EP13191049 Filed EP13191041 Granted	Not found	EP13773463 Granted EP19187747 Pending	EP15803592 Pending
Uganda	Not filed	Not filed	Not filed	Not filed
Ukraine	UAa201305877 Granted (12/12/2016)	Not found	Not found	Not found

US (USPTO)	US 2017-0157105 (A1) (Application #15/434,789) Granted (04/07/2018) Patent No. US 10,028,937 (B2) US 2017-0157104 (A1) (Application #15/431,069) Granted (18/07/2018) Patent No. US10,039,754 (B2) US2012/0004196 (A1) (Application #13/100,827) Granted (30/12/2014) Patent No. US8,937,150 (B2) US 2015/0087618 (A1) (Application #14/558,318) Granted (15/02/2017) Patent No. US9,586,978 (B2) US 2019/0015402 (A1) (Application #16/042,447) Withdrawn (30/03/2020)	US2012/0172290 (A1) (Application #13/328,848) Granted (29/06/2016) Patent No. US9,394,279 (B2) US 2012/0220562 (A1) (Application #13/404,429) Withdrawn	US20140080868 (A1) (Application #14/029,302) Withdrawn (08/07/2016)	US205/0322047 (A1) (Application #14/707,433) Granted (22/02/2017) Patent No. US 9,593,078
Uzbekistan	Not filed	Not filed	Not found	Not found
Vietnam	VN 1-2013-01449 Granted (15/08/2016) Patent No. VN 1-0015857-000	Not filed	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed	Not filed

	Patent 5	**Patent 6**	**Patent 7**
Title (description)	Solid forms of antiviral compounds	Compositions and methods for treating HCV Infection	Process for manufacturing pibrentasvir active drug substance
Applicant	AbbVie	AbbVie	AbbVie
International patent publication number (publication date)	WO 2016/053869	WO 2018/093717 (24/05/2018)	WO 2020/047182 (05/03/2020)
Australia	Not filed	Not filed	AU2019331459
Belarus	Not filed	Not filed	Not filed
Brazil	Not filed	Not filed	BR1120210037241 Pending
Burkina Faso	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found
Canada	Not filed	Not filed	Application # CA3110519 Pending
Côte d'Ivoire	Not filed	Not filed	Not filed
DRC	Not found	Not found	Not found
Ethiopia	Not found	Not found	Not found

EU (EPO)	Not filed	Not filed	Application # EP3843712 Pending
Ghana	Not filed	Not filed	Not filed
India	Not filed	Not filed	Not filed
Indonesia	Not filed	Not filed	Not filed
Kazakhstan	Not filed	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed
Kyrgyzstan	Not filed	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed
Mexico	Not found	Not found	Not filed
Morocco	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed
Nigeria	Not filed	Not filed	Not filed
Pakistan	Not found	Not found	Not found
Peru	Not filed	Not filed	Not filed
Russia	Not filed	Not filed	Not filed
Rwanda	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed
South Africa	Not filed	Not filed	Not filed
Tajikistan	Not filed	Not filed	Not filed
Tanzania	Not filed	Not filed	Not filed
Turkey	Not found	Not found	Not found
Uganda	Not filed	Not filed	Not filed
Ukraine	Not found	Not filed	Not filed
US (USPTO)	US2016/0090373 (A1) (Application #14/867,785) Withdrawn (04/09/2016)	US2019/0358214 (A1) (Application #16/461,823) Withdrawn (9/10/2020)	Application # 17/267885 Pending
Uzbekistan	Not filed	Not filed	Not filed
Vietnam	Not filed	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed

3. Glecaprevir + Pibrentasvir

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
Title (description)	Combinations of Two Antivirals for Treating hepatitis C	Combination of Direct-Acting Antiviral Agents and Ribavirin for Treating HCV Patients	Methods for Treating HCV	Methods for Treating HCV	Combinations Useful to Treat Hepatitis C Virus
Applicant	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie
International publication number (publication date)	WO 2014/152514 (A1) (2014-09-25)	WO 2014/152635 (A1) (2014-09-25)	WO 2015/153792 (A1) (2015-10-08)	WO 2015/153793 (A1) (2015-10-08)	WO 2016/134058 (A1) (2016-08-25)
Australia	AU2014239563 (A1) Granted (14-03-2014) Patent No. AU2014239563 (B2 AU2016202823 (A1) Granted (14-03-2014) Patent No. AU2016202823 (B2)	AU2014239322 (A1) Granted (02-08-2018) AU2014239322 (B2 AU2018202581 (A1) Granted (02-04-2020) Patent No. AU2018202581 (B2) AU2020201656 (A1) Pending	AU2015240753 (A1) Granted (14-05-2020) AU2015240753 (B2) AU2020202560 (A1) Lapsed (23-07-2020)	AU2015240754 (A1) Granted (08-10-2020) Patent No. AU2015240754 (B2)	Not Filed
Belarus	EA201591702 Granted (30/09/2019) Patent No. EA033257 EA201991174 Pending (31/01/20)	EA201591701 Granted (31/08/2018) Patent No. EA030482 EA201890507 Pending (31/07/2018)	Not filed	Not filed	Not filed
Brazil	BR112015023017 Pending (27/02/2018)	BR112015020918 Pending (27/02/2018)	BR 11 2016 022858 8 Pending (15/10/2019)	BR 11 2016 022976 2 Pending (15/10/2019)	Not filed
Burkina Faso	Not filed	Not filed	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found	Not found	Not found
Canada	CA 2901810 (A1) Granted (08/01/2019) Patent No. CA 2901810 (B2)	CA 2901818 (A1) Pending	CA 2943054 (A1) Pending	CA 2942823 (A1) Pending	Not filed
Côte d'Ivoire	Not filed	Not filed	Not filed	Not filed	Not filed
DRC	Not found	Not found	Not found	Not found	Not found
Ethiopia	Not found	Not found	Not found	Not found	Not found

EU (EPO)	EP2968301 (A1) Granted (19/04/2017) EP3213750 Granted (12/08/2020)	EP2968302 (A1) Revocation of Patent (07/10/2020) EP2968302 (B9) Revocation of Patent (07/10/2020) EP3318258 (A1) Revocation of Patent (18/11/2020)	EP3125890 (A1) Pending	EP3125889 (A1) Pending	Not filed
Ghana	Not filed	Not filed	Not filed	Not filed	Not filed
India	Not filed	Not filed	Not filed	Not filed	Not filed
Indonesia	Not filed	Not filed	Not found	Not found	Not found
Kazakhstan	EA201591702 Granted (30/09/2019) Patent No. EA033257 EA201991174 Pending (31/01/20)	EA201591701 Granted (31/08/2018) Patent No. EA030482 EA201890507 Pending (31/07/2018)	Not filed	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	EA201591702 Granted (30/09/2019) Patent No. EA033257 EA201991174 Pending (31/01/20)	EA201591701 Granted (31/08/2018) Patent No. EA030482 EA201890507 Pending (31/07/2018)	Not filed	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed	Not filed	Not filed
Mexico	MX/a/2015/012538 Granted (28/01/2019)	MX/a/2015/012536 Pending (22/02/2016)	MX/a/2016/012722 Pending (13/01/2017)	MX/a/2016/012799 Pending (13/01/2017)	Not filed
Morocco	Not found	Not found	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed	Not filed	Not filed
Nigeria	Not filed	Not found	Not filed	Not filed	Not filed
Pakistan	Not found	Not found	Not found	Not found	Not found
Peru	Not Filed	Not Filed	Not Filed	Not Filed	Not Filed
Russia	EA201591702 Granted (30/09/2019) Patent No. EA033257 EA201991174 Pending (31/01/20)	EA201591701 Granted (31/08/2018) Patent No. EA030482 EA201890507 Pending (31/07/2018)	Not filed	Not filed	Not filed
Rwanda	Not filed	Not filed	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed	Not filed	Not filed

South Africa	ZA201505880 Granted	ZA201705080 Granted ZA201506031 Granted	Not filed	Not filed	Not filed
Tajikistan	EA201591702 Granted (30/09/2019) Patent No. EA033257 EA201991174 Pending (31/01/20)	EA201591701 Granted (31/08/2018) Patent No. EA030482 EA201890507 Pending (31/07/2018)	Not filed	Not filed	Not filed
Tanzania	Not filed	Not filed	Not filed	Not filed	Not filed
Turkey	Not found	Revoked	Not found	Not found	Not found
Uganda	Not filed	Not filed	Not filed	Not filed	Not filed
Ukraine	Not found	Not found	Not found	Not found	Not found
US (USPTO)	US 2014-0275099 A1 (Application #14/210,870) Withdrawn (06/06/2016)	US 2014-0274934 A1 (Application #14/210,858) Withdrawn (01/04/2016)	US2015283199 (A1) (Application #14/676,378) Pending US2016317603 (A9)	US 2015-0283198 A1 (Application# 14/676,370) Granted (24/04/2019) Patent No. US10286029 (B2) US2019336565 (A1) (Application #16/405,029) Rejected (02/04/2020)	USPTO filed US1618327 Pending
Uzbekistan	Not found	Not found	Not filed	Not filed	Not found
Vietnam	Not filed	Not filed	Not filed	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed	Not filed	Not filed

	Patent 6	Patent 7	Patent 8	Patent 9	Patent 10
Title (description)	Solid pharmaceutical compositions for treating HCV	Methods for treating HCV	Solid pharmaceutical compositions for treating HCV	Methods for treating HCV	Dose adjustment
Applicant	AbbVie	AbbVie	AbbVie	AbbVie	AbbVie
International publication number (publication date)	WO 2016/210273 (29/12/2016)	US201715431906 (WO not found) US20170151238 (Granted Number)	WO 2017/015211 (26/01/2017)	WO 2017/007934 (12/01/2017)	WO 2018/057919 (A1) (2018/03/29)
Australia	AU2016283018 (A1) Pending	AU2018201011 (A1) Pending	AU2016296709 (A1) Pending	AU2016291154 (A1) Pending	AU2017332771 (A1) Pending
Belarus	EA201890160 Pending (29/06/2018)	Not found	EA201890334 Pending (29/06/2018)	Not filed	Not filed
Brazil	BR112017028185 Pending (01/10/2019)	BR102018002956 (A2) Pending	BR112018000982 Pending (01/10/2019)	BR112018000383 Pending (15/10/2019)	BR112019005725 Pending (09/07/2019)
Burkina Faso	Not filed	Not filed	Not filed	Not filed	Not filed
Cambodia	Not filed	Not found	Not filed	Not found	Not found

Canada	CA2990855 (A1) Pending	CA 2994496 (A1) Pending	CA2992722 (A1) Pending	CA2991417 (A1) Pending	CA3037719 (A1) Pending
Côte d'Ivoire	Not filed	Not filed	Not filed	Not filed	Not found
DRC	Not filed	Not found	Not filed	Not found	Not found
Ethiopia	Not filed	Not found	Not filed	Not found	Not found
EU (EPO)	EP3313378 (A1) Pending	EP3360555 (A1) Pending	EP3324941 (A1) Pending	EP3319604 (A1) Pending	EP3515442 (A1) EP3515442 (A4) Pending
Ghana	Not filed	Not filed	Not filed	Not filed	Not filed
India	IN201817002543 Pending (24/02/20)	Not filed	IN201817004313 Pending (20/07/20)	Not filed	Not filed
Indonesia	P00201800608 Pending Publication No: ID2018/07530	Not filed	P00201801161 (Appl. No) Pending Publication No: ID2018/10306	Not filed	Not found
Kazakhstan	EA201890160 Pending (29/06/2018)	Not found	EA201890334 Pending (29/06/2018)	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	EA201890160 Pending (29/06/2018)	Not found	EA201890334 Pending (29/06/2018)	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed	Not filed	Not filed
Mexico	MX/a/2018/000218 Pending (05/04/2018)	MX2018001905 (A1) Pending	MX2018000746 (A) Pending	MX2018000240 (A) MX/a/2018/000240 Pending (05/04/2018)	MX/a/2019/003366 Pending (21/08/2019)
Morocco	Not filed	Not found	Not filed	Not found	Not found
Mozambique	Not filed	Not filed	Not filed	Not filed	Not filed
Nigeria	Not filed	Not filed	Not filed	Not filed	Not filed
Pakistan	Not filed	Not found	Not filed	Not found	Not found
Russia	RU2018102809 Pending EA201890160 Pending (29/06/2018)	Not filed	RU2018105849 Pending EA201890334 Pending (29/06/2018)	Not filed	Not filed
Rwanda	Not filed	Not filed	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed	Not filed	Not filed
South Africa	ZA201800533 Granted ZA201801082 Granted	Not filed	ZA201800533 Granted ZA201801082 Granted	ZA201505880 Pending	Not filed
Tajikistan	EA201890160 Pending (29/06/2018)	Not found	EA201890334 Pending (29/06/2018)	Not filed	Not filed
Tanzania	Not filed	Not filed	Not filed	Not filed	Not filed
Turkey	EP16738291 Pending EP16745584 Pending	EP18156337 Pending	EP16738291 Pending EP16745584 Pending	Not found	Not found
Uganda	Not filed	Not filed	Not filed	Not filed	Not filed

Ukraine	UAa201800702 Pending	Not found	UAa201801549 Pending	Not filed	Not found
US (USPTO)	US2016375087 (A1) (Application # 16/227,994) Withdrawn (13/02/2020) US2019216882 (A1) (Application #16/654,433) Pending: Docketed New Case: US2020282004 (A1)	US2017151238 (A1) (Application # 15/431,906) Pending (27/01/2021)	USPTO file US1642806 Pending	US2018177779 (A1) (Application #15/738,773) Pending	US2018085330 (A1) (Application #15/713,137) Rejected (18/05/2020)
Uzbekistan	Not filed	Not found	Not filed	Not filed	Not filed
Vietnam	VN 1-2018-00320 Pending (25/12/2018)	Not found	VN 1-2018-00634 Pending (24/12/2018)	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed	Not filed	Not filed

	Patent 11	Patent 12	Patent 13	Patent 14
Title (description)	Methods for treating HCV	Methods for treating HCV	Methods for treating HCV	Methods for treating acute HCV
International publication number (publication date)	WO 2019/074507 (A1) (18/04/2019)	WO 2019/027694 (07/02/2019)	WO 2019/046569 (07/03/2019)	WO 2020/106835 (A1) (28/05/2020)
Australia	AU2017435897 (A1) Pending	AU2017248487 (A1) Pending AU2018311684 (A1) Pending	Not filed	AU2019384793 Pending
Belarus	Not filed	EA202090412 Pending	Not filed	Not filed
Brazil	BR 112020007292 3 Pending	BR102017022849 BR11202002308 Pending	Not filed	Not filed
Burkina Faso	Not filed	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found	Not found
Canada	CA3078939 (A1) Pending	CA2981993 (A1) Pending CA3072026 (A1) Pending	Not filed	CA3120686 Pending
Côte d'Ivoire	Not filed	Not filed	Not filed	Not filed
DRC	Not found	Not filed	Not filed	Not filed
Ethiopia	Not found	Not found	Not found	Not found
EU (EPO)	EP3694512 (A1) Pending	EP3437643 (A1) Pending	Not filed	EP3883569 Pending
Ghana	Not filed	Not filed	Not filed	Not filed
India	Not filed	Not filed	Not filed	Not filed
Indonesia	Not found	Not found	Not filed	Not filed
Kazakhstan	Not filed	EA202090412 Pending	Not filed	Not filed

Kenya	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	Not filed	EA202090412 Pending	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed	Not filed
Mexico	Not filed	MX/a/2020/001422 Pending	Not filed	Not filed
Morocco	Not found	Not found	Not found	Not filed
Mozambique	Not filed	Not filed	Not filed	Not filed
Nigeria	Not filed	Not found	Not filed	Not filed
Pakistan	Not found	Not found	Not found	Not found
Peru	Not filed	Not filed	Not filed	Not filed
Russia	Not filed	EA202090412 Pending	Not filed	Not filed
Rwanda	Not filed	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed	Not filed
South Africa	Not filed	Not filed	ZA201505880 Pending	Not filed
Tajikistan	Not filed	EA202090412 Pending	Not filed	Not filed
Tanzania	Not filed	Not filed	Not filed	Not filed
Turkey	Not found	Not found	Not found	Not found
Uganda	Not filed	Not filed	Not filed	Not filed
Ukraine	Not filed	Not filed		Not filed
US (USPTO)	USPTO file US1756298 Pending	US2020222397 (A1) (Application #16/635,813) Pending	US 2020-0330460 A1 (Application #16/643,069) Pending	USPTO file US1962407 Pending
Uzbekistan	Not found	Not found	Not found	Not filed
Vietnam	Not filed	Not filed	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed	Not filed

4. Isoniazid + Rifapentine

	Patent 1	Patent 2	Patent 3
Title (description)	Antituberculosis stable pharmaceutical composition in the form of a coated tablet comprising granules of isoniazid and granules of rifapentine and its process of preparation	Antituberculosis stable pharmaceutical composition in the form of dispersible tablet comprising granules of rifapentine and its process of preparation	Use of rifapentine in the treatment of tuberculosis in patients infected with the HIV/ Acquired Immune Deficiency Syndrome (AIDS) and treated with antiretroviral combination
Applicant	Sanofi SA	Sanofi SA	Sanofi SA
International publication number (publication date)	WO 2015/011161 (A1) (29/01/2015)	WO 2015/011162 (A1) (29/01/2015)	WO 2014/037121 (A1) (13/03/2014)
Australia	AU2014295098 (A1) Revoked 10/03/2020 AU2014295098 (B2) Revoked 10/03/2020	AU2014295099 (A1) Patent No. AU2014295099 (B2) Revoked 10/03/2020	Not filed
Belarus	Not filed	Not filed	Not filed
Brazil	BR 11 2016 001531 2 A2 Withdrawn (10/03/2020)	BR 11 2016 001559 2 A2 Withdrawn	Not filed

Burkina Faso	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found
Canada	CA2918827 (A1) Withdrawn 04/02/2020	CA2918528 (A1) Withdrawn 04/02/2020	Not filed
Côte d'Ivoire	Not filed	Not filed	Not filed
DRC	Not filed	Not filed	Not filed
Ethiopia	Not found	Not found	Not found
EU (EPO)	EP3024443 (A1) Withdrawn 12/02/2020	EP3024444 (A1) Withdrawn 12/02/2020	EP2705840 (A1) Withdrawn 25/03/2015
Ghana	Not filed	Not filed	Not filed
India	IN3341/CHE/2013 Withdrawn (23/05/2019) IN201637002757 Withdrawn (05/02/20)	IN201637002758 Withdraw (05/02/20)	Not filed
Indonesia	P00201601205 Withdrawn	P00201601207 (Appl. No.) Publication No.ID2017/12721 Withdrawn	Not filed
Kazakhstan	Not found	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed
Kyrgyzstan	Not found	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed
Mexico	MX2016001154 (A) Withdrawn	MX2016001155A Withdrawn	Not filed
Morocco	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed
Nigeria	NG/PT/C/2016/1720 Pending	NG/PT/C/2016/1719 Pending	Not filed
Pakistan	Not found	Not found	Not found
Peru	000096-2016/DIN Rejected	000090-2016/DIN Withdrawn	Not filed
Russia	RU2016106384 Withdrawn	RU2016106328 Patent No. RU2694056 Withdrawn	Not filed
Rwanda	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed
South Africa	ZA201600109B Granted	ZA201600110B Withdrawn	Not filed
Tajikistan	Not filed	Not filed	Not filed
Tanzania	Not filed	Not filed	Not filed
Turkey	EP14741646 Withdrawn	EP14741647 Withdrawn	Not found
Uganda	Not filed	Not filed	Not filed
Ukraine	Not filed	Not found	Not found
US (USPTO)	US2016158157 (A1) Withdrawn 11/02/2020	US2016184231 (A1) (Application #14/906,885) Granted 25/10/2017 Patent No. US9814680 (B2)	Not filed
Uzbekistan	Not found	Not found	Not found
Vietnam	VN 1-2016-00462 (25/11/2019) Rejected	VN1201600462 Rejected	Not filed
Zimbabwe	Not filed	Not filed	Not filed

5. Bedaquiline

	Patent 1	Patent 2	Patent 3	Patent 4
Title (description)	Quinoline derivatives and their use as mycobacterial inhibitors	Use of substituted quinolone derivatives for the treatment of drug-resistant mycobacterial diseases	Quinoline derivatives for the treatment of latent tuberculosis	Process for preparing (alpha S, beta R)-6-bromo-alpha- [2-(dimethyllamino) ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quinolineethanol
Applicant	Janssen Pharmaceutica NV	Janssen Pharmaceutica NV and others	Janssen Pharmaceutica NV and others	Janssen Pharmaceutica NV and others
International publication number (publication date)	WO 2004/011436A1 (05/02/2004)	WO 2005/117875A1 (15/12/2005)	WO 2006/067048A1 (29/06/2006)	WO 2006/125769A1 (30/11/2006)
Australia	AU2003262529 (A1) Granted (04/032010) Patent No. AU2003262529 (B2)	AU2005249231 (B2) Granted (24/02/2011)	AU2005242138 (B2) Granted (08/09/2011)	AU2006251208 (B2) Granted (14/03/2013)
Belarus	EA200500257 Granted (26/10/2007) Patent No. EA008937	EA200602260 Granted (30/10/2008) Patent No. EA010651	Not filed	EA200702611 Granted (30/06/2009) Patent No. EA011770
Brazil	BR0312927-6 Granted (10/07/2018)	BR0510414-9 Rejected (19/11/2019) Appealed (28/01/2020)	BR0506400-7 Pending (29/09/2020)	BR0611166-1 Pending (23/06/2020)
Burkina Faso	OA1200500019 Granted	OA1200600407 Granted	OA1200700252 Granted	Not Filed
Cambodia	Not Filed	Not Filed	Not Filed	Not Found
Canada	CA2493225 (A1) Granted (20/03/2012) Patent No. CA2493225 (C)	CA2566544 (A1) Granted (17/04/2012) Patent No. CA2566544 (C)	CA2529265 (A1) Granted (11/02/2014) Patent No. CA2529265 (C)	CA2606675 (A1) Granted (19/02/2013) Patent No. CA2606675 (C)
Côte d'Ivoire	OA1200500019 Granted	OA1200600407 Granted	OA1200700252 Granted	Not Filed
DRC	OA1200500019 Granted	Not Filed	Not Filed	Not Filed
Ethiopia	Not Filed	Not Filed	Not Filed	Not Found
EU (EPO)	EP1527050 (B1) Granted (07/04/2010) EP2301544 (B1) Granted (19/09/2012)	EP1753427 (A1) Granted (02/04/2008) Patent No. EP1753427 (B1)	EP1830850 (A1) Granted (16/03/2011) Patent No. EP1830850 (B1)	EP2086940 (A1) Granted (16/05/2012) Patent No. EP2086940 (B1)
Ghana	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed
India	IN220/DELNP/2005 Granted (23/11/2009) Patent No. 236811	IN6315/DELNP/2006 Granted (17/01/2015) Patent No.264718	IN5213/DELNP/2007 Rejected (29/10/2015)	IN9746/DELNP/2007 Granted (23/07/2015) Patent No. 267540
Indonesia	ID042.530 Granted (11/02/2014) Patent No. IDP000035543 ID051.1478 Granted (06/12/2016) Patent No. IDP000043709	Publ. No ID046.4391 W00200603351 (Appl. No) Granted (02/07/2009) Patent No. IDP000023726	Not Filed	Publ. No. ID048.0974 W00200703858 Granted (21/12/2015) Patent No. IDP000040025

Kazakhstan	EA200500257 Granted (26/10/2007) Patent No. EA008937	EA200602260 Granted (30/10/2008) Patent No. EA010651	Not filed	EA200702611 Granted (30/06/2009) Patent No. EA011770
Kenya	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed
Kyrgyzstan	EA200500257 Granted (26/10/2007) Patent No. EA008937	EA200602260 Granted (30/10/2008) Patent No. EA010651	Not filed	EA200702611 Granted (30/06/2009) Patent No. EA011770
Malawi	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed
Mexico	MXPA05001052 (A) Granted	MXPA06013888 (A) PA/a/2006/013888 Granted	Not filed	MX2009005909 (A) Granted (11/12/2012)
Morocco	Not Filed	Not Filed	Not found	Not found
Mozambique	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed
Nigeria	OA1200500019 Granted	Not Filed	Not filed	Not filed
Pakistan	PK20061114 Granted PK20061113 Granted PK20030640 Granted	PK20050467 Pending	PK735/2011 Granted PK1163/2005 Granted	Not Found
Peru	Not Filed	Not Filed	Not Filed	Not Filed
Russia	EA200500257A1 Granted – Term Extension Patent No. EA008937B1	EA200602260 Granted – Term Extension Patent No. EA010651B1	EA200500802A1 Granted	EA200702611 Granted
Rwanda	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337	AP200704054 Granted Patent No. AP2327A	Not Filed
Senegal	OA1200500019 Granted	OA1200600407 Granted	OA1200700252 Granted	Not Found
South Africa	ZA200500680B Granted	ZA200705160B Granted	ZA200705160B Granted	ZA200710150B Granted
Tajikistan	EA200500257 Granted (26/10/2007) Patent No. EA008937	EA200602260 Granted (30/10/2008) Patent No. EA010651	Not filed	EA200702611 Granted (30/06/2009) Patent No. EA011770
Tanzania	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed
Turkey	EP10154018 Granted EP03771115 Granted	EP05743054 Granted	TR200504892 Withdrawn EP05815816 Granted	EP06755275 Granted
Uganda	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed
Ukraine	UA2005001778 Granted Patent No. UA82198	UAA200611048 Granted Patent No. UA90267	UAA200511766 Granted Patent No. UA88766C2	UAA200711767 Granted Patent No. UA92484

US (USPTO)	US2005148581 (A1) (Application #11/007,026) Granted (11/02/2009) Patent No. US7498343 (B2)	US2007249667 (A1) (Application #11/569,681) Withdrawn (14/01/2013) US2010168133 (A1) (Application #12/719,221) Withdrawn (04/06/2012)	US2006142279 (A1) (Application #11/296,992) Withdrawn (21/09/2010)	US2008200683 (A1) (Application #11/915,204) Granted (28/09/2011) Patent No. US8039628 (B2) US2011319623 (A1) (Application #13/225,647) Granted (18/12/2012) Patent No. US8350040 (B2)
Uzbekistan	Not Filed	Not Filed	Not Found	Not Found
Vietnam	VN 1-2004-01363 Granted (12/11/2012) Patent No. 1-0010819-000	VN 1-2006-01723 Granted (18/02/2014) Patent No. VN 1-0012414-000	VN 1-2007-02216 Granted (15/07/2013) Patent No. VN 1-0011586-000	VN 1-2009-00771 Granted (17/12/2012) Patent No. VN 1-0010953-000
Zimbabwe	AP2005003210 Granted Patent No. AP2421A	AP200603828 Granted Patent No. AP2337A	AP200704054 Granted Patent No. AP2327A	Not Filed

	Patent 5	Patent 6	Patent 7	Patent 8	Patent 9
Title (description)	Fumarate salt of (alpha S, beta R)-6-bro-mo-alpha- [2-(dimethyllamino) ethyl]-2-me-thoxy-alpha -1-naphthalenyl -beta-phe-nyl-3-quino-lineethanol	Dispersible compositions	Combination antibacterial composition and short-course antibacterial regimen	Long-acting formulations	Combination in the treatment of nontuberculous mycobacterial diseases
Applicant	Janssen Pharmaceutica NV and others	Janssen Pharmaceutica	Janssen Pharmaceutica NV and others	Janssen Pharmaceutica NV [BE]	Janssen Pharmaceutica
International publication number (publication date)	WO 2008/068231 (A1) (12/06/2008)	WO 2016/120258 (A1) (04/08/2016)	WO 2017/066053 (20/04/2017)	WO 2019/012100 (A1) (17/01/2019)	WO 2020/144197 (A1) (16/07/2020)
Australia	AU2007328945 (A1) Granted (17/07/2014) Patent No. AU2007328945 (B2)	AU2018298855 (A1) Pending	AU 2016338637 (A1) Filed (05/10/2016) Pending	AU2018298855 (A1) Pending	Not filed
Belarus	EA200970532 Granted (28/09/2012) Patent No. EA017091	EA201791701 Pending (30/11/2017)	EA201890614 Pending	EA202090287 Pending (12/05/2020)	Not filed
Brazil	BR0719693-8 Pending (14/07/2020)	BR112017015784-5 Pending (15/10/2019)	BR112018007625 Pending	BR112020000687-4 Pending (14/07/2020)	Not filed

Burkina Faso	OA1200900177 Granted	OA1201700283 Granted	Not Found	OA/1/2020/000018 (Appl. No) Granted (10/06/2020) Patent No. 019392	Not filed
Cambodia	Not found	Not found	Not Found	Not found	Not found
Canada	CA2668512 (A1) Granted (24/03/2015) Patent No. CA2668512 (C)	CA2973301 (A1) Pending (07/07/2017)	CA 3001309 Filed (06-04-2018) Pending	CA3069069 (A1) Pending (06/01/2020)	Not filed
Côte d'Ivoire	OA1200900177 Granted	OA1201700283 Granted	Not Found	OA/1/2020/000018 (Appl. No) Granted (10/06/2020) Patent No. 019392	Not filed
DRC	Not found	Not found	Not Found	OA/1/2020/000018 (Appl. No) Granted (10/06/2020) Patent No. 019392	Not filed
Ethiopia	Not found	Not found	Not Found	Not found	Not found
EU (EPO)	EP2086940 (A1) Granted (16/05/2012) Patent No. EP2086940 (B1)	EP3250182 (A1) Pending (03/06/2020)	EP336206 (A1) Pending	EP3651736 (A1) Pending (25/08/2020)	Not filed
Ghana	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
India	IN1220/ MUMNP/2009 Pending (19/12/2019)	N264/MUM/2015 Withdraw (30/03/2016) IN201727030045 Pending (09/07/2020)	IN201817014361 Pending	IN202017005443 Pending	Not filed
Indonesia	Publ. No ID049.2264 W00200901493 (Appl. No) Granted (08/02/2013) Patent No. IDP000032913	Publ. No. ID2018/04122 PID201704901 (Appl. No.) Pending (21/10/2020)	Not Filed	Not found	Not found
Kazakhstan	EA200970532 Granted (28/09/2012) Patent No. EA017091	EA201791701 Pending (30/11/2017)	EA201890614 Pending	EA202090287 Pending (12/05/2020)	Not filed
Kenya	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
Kyrgyzstan	EA200970532 Granted (28/09/2012) Patent No. EA017091	EA201791701 Pending (30/11/2017)	EA201890614 Pending	EA202090287 Pending (12/05/2020)	Not filed

Malawi	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
Mexico	MX2009005909 (A) Granted (11/12/2012)	MX2017009681 (A) MX/a/2017/009681 Pending	Not Filed	MX/a/2020/000461 Pending	Not filed
Morocco	Not found	EP16701516 Pending	EP16855973 Pending	Not found	Not found
Mozambique	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
Nigeria	Not found	Not found	Not Found	OA/1/2020/000018 (Appl. No) Granted (10/06/2020) Patent No. 019392	Not filed
Pakistan	PK1403/2007 Pending	Not found	Not Found	Not found	Not found
Peru	Not filed	001255-2017/DIN Pending	Not Filed	000033-2020/DIN Pending	Not filed
Russia	EA200970532A1 Granted – Term Extension Patents No. EA017091B1 EA017091B9	EA201791701 Pending	EA201890614A1 Pending	EA202090287 Pending	Not filed
Rwanda	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
Senegal	OA1200900177 Granted	OA1201700283 Granted	Not Found	Not Found	Not filed
South Africa	ZA200903907B Granted	ZA200903907 Pending	Not Filed	AZ2020/00215 Pending	Not filed
Tajikistan	EA200970532 Granted (28/09/2012) Patent No. EA017091	EA201791701 Pending (30/11/2017)	EA201890614A1 Pending	EA202090287 Pending (12/05/2020)	Not filed
Tanzania	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
Turkey	EP07847697 Granted	EP1670151 Pending	EP16855973 Pending	Not found	Not found
Uganda	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending (13/07/2018)	Not filed
Ukraine	UAA200904218 Granted Patent No. UA97813	UAa201708632 Pending	Not Found	UAA202000901 Pending (27/04/2020)	Not Filed

US (USPTO)	US2010028428 (A1) (Application #12/515,986) Granted (11/09/2013) Patent No. US8546428 (B2)	US2018000810 (A1) (Application #15/545,524) Pending	US201615765310 (A1) Pending US20180280401A1 (Application #15/765,310) Pending US2020/0237770A1 (Application #16/843,946) Pending	US20210085620 Pending	USPTO file US17421546 Pending
Uzbekistan	Not found	Not found	Not Found	Not found	Not filed
Vietnam	VN 1-2009-00771 Granted (17/12/2012) Patent No. VN 1-0010953-000	Not filed	Not Filed	Not filed	Not filed
Zimbabwe	AP2009004870 Granted Patent No. AP2498A	AP/P/2017/010050 Pending	Not Found	AP/P/2019/012115 Pending 13-07-2018	Not filed

6. Delamanid

	Patent 1	Patent 2	Patent 3	Patent 4
Title (description)	2,3-dihydro-6-nitroim-idazo [2,1-b]oxazoles	2,3-dihydro-6-nitroimidazo [2, 1-b] oxazole compounds for the treatment of tuberculosis	Pharmaceutical composition comprising 2,3-dihydro-6-nitroimidazo [2, 1-b] oxazole derivatives	Antituberculous composition comprising oxazole compounds
Applicant	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.
International publication number (publication date)	WO 2004/033463 (22/04/2004)	WO 2005/042542 (12/05/2005)	WO 2007/013477 (01/02/2007)	WO 2007/043542 (19/04/2007)
Australia	AU2003272979 (A1) Granted (05/11/2009) Patent No. AU2003272979 (B2)	AU2004285811 (A1) Granted (25/09/2008) Patent No. AU2004285811 (B2) Lapsed (22/05/2014)	AU2006273355 (A1) Granted (03/05/2012) Patent No. AU2006273355 (B2)	AU2006300320 (A1) Granted (09/12/2010) Patent No. AU2006300320 (B2) Lapsed (18/04/2017) AU2010241497 (A1) Withdrawn (22/11/2013)
Belarus	Not filed	a200660534 Granted (30/06/2011)	a20080226 Granted (30/04/2011)	a20080575 Granted (30/04/2015)
Brazil	BR0314344-9 Granted (26/11/2019)	BR0414909-2 Lapsed (02/09/2014)	BR0613883-7 Pending (01/10/2019)	BR0616659-8 Pending (08/05/2018)
Burkina Faso	Not filed	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found	Not found

Canada	CA2497569 (A1) Granted (24/05/2011) Patent No. CA2497569 (C)	CA2539335 (A1) Withdrawn (13/05/2014)	CA2610749 (A1) Granted (04/06/2013) Patent No. CA2610749 (C)	CA2624497 (A1) Granted (11/18/2014) Patent No. CA2624497 (C) Lapsed (10/04/2017) CA2862193 (A1) Granted (06/07/2016) Patent No. CA2862193 (C) Lapsed (10/04/2017)
Côte d'Ivoire	Not filed	Not filed	Not filed	Not filed
DRC	Not filed	Not filed	Not filed	Not filed
Ethiopia	Not found	Not found	Not found	Not found
EU (EPO)	EP1555267 (A1) Granted (16/01/2013) Patents No. EP1555267 (B1) EP2570418 (A2) Pending	EP1678185 (A1) Granted (08/10/2008) Patent No. EP1678185 (B1)	EP1906926 (A1) Granted (01/12/2010) Patent No. EP1906926 (B1)	EP1931425 (A1) Pending EP2269694 (A2) EP2269694 (A3) Pending
Ghana	Not filed	Not filed	Not filed	Not filed
India	IN600/KOLNP/2005 Granted (16/01/2012) Patent No. 250365 IN1647/KOLNP/2007 Rejected (29/12/2016)	IN824/KOLNP/2006 Withdrawn (17/10/2017)	IN9790/DELNP/2007 Granted (08/08/2012) Patent No. 253642	IN1255/KOLNP/2008 Granted (12/08/2015) Patent No. 268015
Indonesia	ID043.084 Granted (01/10/2014) Patent No. IDP000036869	Publ. No. ID046.2086 W00200601160 (Appl. No) Granted (08/12/2011) Patent No. IDP000029726	Publ. No. ID048.2242 W00200800233 (Appl. No) Granted (26/03/2012) Patent No. IDP000030491	Publ. No. ID048.2262 W00200801089 (Appl. No.) Granted (23/09/2011) Patent No. IDP000029196 Lapsed Publ. No. ID051.4644 W00201103024 (Appl. No) Granted (28/11/2013) Patent No. IDP000035064 Lapsed
Kazakhstan	Not filed	Not filed	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	Not filed	Not filed	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed	Not filed
Mexico	MXPA05003674 (A) Granted (12/02/2008)	PA/a/2006/004064 Granted (01/07/2009) Patent No. 267920	MX2008001210 (A) Granted (13/01/2011)	MX/a/2008/004256 Granted (13/11/2013)
Morocco	Not Found	Not found	Not found	Not found
Mozambique	Not Filed	Not filed	Not filed	Not filed
Nigeria	Not Filed	Not filed	Not found	Not found
Pakistan	Not found	Not found	Not Found	PK20060826 Pending
Peru	Not filed	Not filed	Not filed	Not filed
Russia	RU2005114017 Granted Patent No. RU2326121	RU2006118794 Granted (27/08/2009) Patent No. RU2365593	RU2008107595 Granted Patent No. RU2413504	RU2008117427 Withdrawn
Rwanda	Not filed	Not filed	Not filed	Not filed

Senegal	Not filed	Not filed	Not filed	Not filed
South Africa	ZA200501033 Granted	ZA200602184B Withdrawn	ZA200710404B Granted	ZA200802883B Granted
Tajikistan	Not Filed	Not filed	Not filed	Not filed
Tanzania	Not Filed	Not filed	Not filed	Not filed
Turkey	EP12193820 Withdrawn EP03754085 Granted	EP04793412 Withdrawn	EP06781620 Granted	EP06811551 Withdrawn EP10182000 Withdrawn
Uganda	Not filed	Not filed	Not filed	Not filed
Ukraine	UA2005004391 Granted Patent No. UA83200	UAA200605975 Lapsed Patent No. UA91822	UAA200802496 Granted Patent No. UA95251	UAA200805407 (Appl. No) Withdrawn Patent No. UA93888
US (USPTO)	US2006094767 (A1) (Application #10/530,429) Granted (08/08/2007) Patent No. US7262212 (B2)	US2008119478 (A1) (Application #10/574,597) Patent No. US8163753 (B2) Lapsed (10/06/2020)	US2010130508 (A1) (Application #11/996,699) Granted (27/04/2011) Patent No. US7943623 (B2)	US2009275528 (A1) (Application #12/088,867) Patent No. US8,987,304 (B2) Lapsed (29/04/2019) US2015224099 (A1) (Application #14/622,700) Withdrawn (30/09/2016)
Uzbekistan	Not found	Not found	Not found	Not found
Vietnam	VN 1-2005-00622 (Appl. No.) Granted (13/04/2009) Patent No. VN 1-0007644-000	VN 1-2006-00645 Granted (20/07/2009) Patent No. VN1-0007850-000	VN 1-2008-00490 Granted (17/10/2012) Patent No. VN 1-0010752-000	Not filed
Zimbabwe	Not filed	Not filed	Not filed	Not filed

	Patent 5	**Patent 6**	**Patent 7**	**Patent 8**
Title (description)	Medicinal composition showing improved drug absorbability	Synthetic intermediate of oxazole compound and method for producing the same	1-Substituted 4-nitroimidazole compound and process for producing the same	Method for producing 4-nitroimidazole compound
Applicant	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.
International publication number (publication date)	WO 2007/052738 (10/05/2007)	WO 2011/093529 (04/08/2011)	WO 2004/035547 (29/04/2004)	WO 2005/077913 (25/08/2005)
Australia	Not filed	AU2011211311 (A1) Withdrawn Lapsed	AU2003301282 (A1) Lapsed (29/04/2013) Patent No. AU2003301282 (B2)	AU2005212093 (A1) Lapsed (29/08/2013) Patent No. AU2005212093 (B2)
Belarus	Not filed	EA201290681 Pending (28/02/2013)	a20050456 Granted	a20060909 Granted
Brazil	Not filed	BR112012018069-0 Lapsed (14/03/2017)	BR0313566-7 Lapsed (22/04/2014)	BR0507777-0 Lapsed (29/04/2014)
Burkina Faso	Not filed	Not Filed	Not filed	Not filed
Cambodia	Not found	Not Found	Not found	Not found

Canada	Not filed	CA2787246 (A1) Withdrawn (30/01/2017)	CA2494710 (A1) Granted Patent No. CA2494710 (C) Lapsed (15/10/2013)	CA2555372 (A1) Withdrawn (30/07/2013)
Côte d'Ivoire	Not filed	Not Filed	Not filed	Not filed
DRC	Not filed	Not Filed	Not filed	Not filed
Ethiopia	Not found	Not Found	Not found	Not found
EU (EPO)	Not filed	EP2528896 (A1) Granted (27/08/2014) Patent No. EP2528896 (B1)	EP1553088 (A1) Withdrawn EP1553088 (A4) Withdrawn EP2644599 (A1) Granted (10/12/2014) Patent No. EP2644599 (B1)	EP1720838 (A1) Granted (04/07/2007) Patent No. EP1720838 (B1)
Ghana	Not filed	Not Filed	Not filed	Not filed
India	Not filed	IN201918054211 IN7240/DELNP/2012 Granted (07/02/2020) Patent No. 331646	IN605/KOLNP/2005 Granted (09/05/2008) Patent No. 219525	IN2205/KOLNP/2006 Granted (05/07/2011) Patent No. 248249
Indonesia	Not filed	Publ. No. ID048.2262 W00200801089 (Appl. No.) Granted (23/09/2011) Cancellation (status) Patent No. IDP000029196 Publ. No ID051.4644 W00201103024 (Appl. No) Granted (28/11/2013) Cancellation (status) Patent No. IDP000035064	ID043.086 W00200500908 (Appl. No) Granted (20/02/2018) Patent No. IDP000020577	ID046.3417 W00200602294 (Appl. No) Granted (19/03/2009) Patent No. IDP000022977
Kazakhstan	Not filed	EA201290681 Pending (28/02/2013)	Not filed	Not filed
Kenya	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	Not filed	EA201290681 Pending (28/02/2013)	Not filed	Not filed
Malawi	Not filed	Not filed	Not filed	Not filed
Mexico	Not filed	MX2012008501 (A) Granted (11/11/2013)	MXPA05002414 (A) Granted (11/11/2013)	PA/a/2006/009262 Granted (11/11/2008) Patent No. 262077
Morocco	Not found	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed	Not filed
Nigeria	Not filed	Not filed	Not found	Not filed
Pakistan	PK200601314 Pending	Not found	Not found	Not found
Peru	Not filed	Not filed	Not filed	Not filed
Russia	Not filed	EA201290681 Pending (28/02/2013)	RU2005114534 Granted (20/05/2008) Patent No. RU2324682	RU2006133312 Granted (01/27/2009) Patent No. RU2345071
Rwanda	Not filed	Not filed	Not filed	Not filed
Senegal	Not filed	Not found	Not filed	Not filed

South Africa	Not filed	ZA201204802B Granted	Granted Patent No. ZA200500918- Lapsed	Granted Patent No. ZA2006/06332 Lapsed
Tajikistan	Not filed	EA201290681 Pending (28/02/2013)	Not filed	Not filed
Tanzania	Not filed	Not filed	Not filed	Not filed
Turkey	EP06811551 Withdrawn EP10182000 Withdrawn	EP11706939 Granted	Not found	Not found
Uganda	Not filed	Not filed	Not filed	Not filed
Ukraine	Not found	UAA201210058 Withdrawn Patent No. UA108092	UA200503528 Granted Patent No. UA80839	UA20060010008 Granted Patent No. UA82773
US (USPTO)	US2009/0227630 A1 (Application #12/084,483) Granted (05/08/2014) Patent No. US8,796,309B1 Lapsed (10/09/2018)	US2012302757 (A1) (Application #13/574,546) Granted (13/11/2013) Patent No. US8598358 (B2)	US2006079697 (A1) (Application #10/523,008) Lapsed (06/06/2016) US2008097107 (A1) (Application #11/905,446) Lapsed (13/04/2020) US2008200689 (A1) (Application #12/007,776) Lapsed (03/11/2014) US2012130082 (A1) (Application #13/362,646) Withdrawn (29/07/2013)	US2007161802 (A1) (Application #10/589,864) Lapsed (04/09/2017)
Uzbekistan	Not found	Not found	Not found	Not found
Vietnam	Not filed	Not filed	VN 1-2005-00461 Granted (17/08/2010) Patent No. VN 1-0008693-000	VN 1-2006-01519 Granted (14/10/2008) Patent No. VN 1-0007311-000
Zimbabwe	Not filed	Not field	Not filed	Not filed

	Patent 9	**Patent 10**	**Patent 11**	**Patent 12**
Title (description)	Method of producing aminophenol compounds	Epoxy compound and method for manufacturing the same	Method for producing 1-(4-hydroxy-phenyl)-4-(4-trifluo-romethoxyphenoxy) piperidine or salt thereof	Process for production of 2-chloro-4-nitroimid-azole derivatives
Applicant	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.
International publication number (publication date)	WO 2005/092832 (06/10/2005)	WO 2008/140090 (20/11/2008)	WO 2016/158737 (06/10/2016)	WO 2019/146113 (01/08/2019)
Australia	AU2005226409 (A1) Patent No. AU2005226409 (B2) Lapsed (10/10/2016)	AU2008250097 (A1) Granted (27/10/2011) Patent No. AU2008250097 (B2) Lapsed (21/11/2016)	Not filed	Not filed

Belarus	a20061039 Granted	a20091744 Granted (28/02/2014)	EA201792154 Pending (28/02/2018)	EA202091799 Pending
Brazil	BR0509095-4 Lapsed (23/05/2017)	BR0810780-7 Lapsed (27/06/2017)	Not filed	Not filed
Burkina Faso	Not filed	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found	Not found
Canada	CA2559488 (A1) Granted (12/06/2012) Patent No. CA2559488 (C) Lapsed (27/03/2017)	CA2686092 (A1) Granted (24/04/2015) Patent No. CA2686092 (C) Lapsed (10/05/2017)	Not filed	Not filed
Côte d'Ivoire	Not filed	Not filed	Not filed	Not filed
DRC	Not filed	Not filed	Not filed	Not filed
Ethiopia	Not found	Not found	Not found	Not found
EU (EPO)	EP1727782 (A1) Granted (22/08/2012) Patent No. EP1727782 (B1) Lapsed (29/07/2016)	EP2144899 (A1) Granted (07/12/2011) Patent No. EP2144899 (B1)	EP3275862 (A1) EP3275862 (A4) Granted (12/08/2020) Patent No. EP3275862 (B1)	EP3746423 Pending
Ghana	Not filed	Not filed	Not filed	Not filed
India	IN2585/KOLNP/2006 Granted (30/12/2010) Patent No. 244643	N7174/DELNP/2009 Granted (05/06/2018) Patent No. 297401	IN201717034109 Pending (10/08/20)	IN202047035396 Pending (17/08/20)
Indonesia	Publ. No. ID047.0174 W00200602656 (Appl. No) Granted (24/12/2014) Patent No. IDP000037513 Lapsed	Publ. No. ID049.4551 W00200903097 (Appl. No) Granted (04/12/2012) Patent No. IDP000032450 Lapsed	Not filed	Not filed
Kazakhstan	Not filed	Not filed	EA201792154 Pending (28/02/2018)	EA202091799 Pending
Kenya	Not filed	Not filed	Not filed	Not filed
Kyrgyzstan	Not filed	Not filed	EA201792154 Pending (28/02/2018)	EA202091799 Pending
Malawi	Not filed	Not filed	Not filed	Not filed
Mexico	PA/a/2006/010967 Granted (19/04/2010)	MX2009011888 (A) Granted (22/09/2011)	Not filed	Not filed
Morocco	Not found	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed	Not filed
Nigeria	Not found	Not filed	Not filed	Not filed
Pakistan	Not found	Not found	Not found	Not found
Peru	Not filed	Not Filed	Not filed	Not filed
Russia	RU2006137563 Granted (12/20/2009) Patent No. RU2376280	RU2009145273 Granted (27/08/2012) Publication No. RU2459822	EA201792154 Pending (28/02/2018)	EA202091799 Pending
Rwanda	Not filed	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not found	Not filed
South Africa	ZA2006/07640 Granted	ZA2009/07755 Pending	Not filed	Not filed
Tajikistan	Not filed	Not filed	EA201792154 Pending (28/02/2018)	EA202091799 Pending
Tanzania	Not filed	Not filed	Not filed	Not filed

Turkey	Not found	Not found	Not found	Not found
Uganda	Not filed	Not filed	Not filed	Not filed
Ukraine	UAA200611248 Granted Patent No. UA87301	UAa200911599 Granted (27/08/2012) Patent No. UA99455	Not filed	Not filed
US (USPTO)	US2007219374 (A1) (Application #10/593,968) Granted (20/09/2007) Patent No. US7750156 (B2) Lapsed (06/08/2018)	US2010217005 (A1) (Application #12/599,214) Granted (12/12/2012) Patent No. US8344148 (B2) US2013072683 (A1) (Application #13/677,727) Granted (18/09/2013) Patent No. US8552188 (B2)	US2018065931 (A1) (Application #15/561,602) Granted (20/03/2019) Patent No. US10252995 (B2)	US 2021-0053925 A1 (Application #16/965,464) Pending
Uzbekistan	Not found	Not found	Not found	Not found
Vietnam	VN 1-2006-01751 Granted (27/07/2010) Patent No. VN 1-0008635-000	VN 1-2009-02637 Granted (06/09/2012) Patent No. VN 1-0010623-000	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed	Not filed

	Patent 13	**Patent 14**	**Patent 15**
Title (description)	Process for production of 2-chloro-4- nitroimidazole	Methods for the production of 2-halo-4-nitroimidazole and intermediates thereof	Delamanid-containing composition
Applicant	Otsuka Pharmaceutical Co., Ltd.	Dynamit Nobel Gmbh Explosivstoff - Und Systemtechnik, Asahi Kasei Chemicals Corporation, Otsuka Pharmaceutical Co., Ltd.	Otsuka Pharmaceutical Co., Ltd.
International publication number (publication date)	WO 2006/35960 (06/04/2006)	WO 2010/021409 (25/02/2010)	WO 2019/240104 (19/12/2019)
Australia	AU 2005288086 (A1) Lapsed	Not filed	AU 2019287313 (A1) Pending
Belarus	a20070483 Withdrawn	Not filed	a202092952 Pending
Brazil	BR0516009-0 Withdrawn	Not filed	Not filed
Burkina Faso	Not filed	Not filed	Not filed
Cambodia	Not found	Not found	Not found
Canada	CA 2580139 (A1) Withdrawn	Not filed	CA 3103642 Pending
Côte d'Ivoire	Not filed	Not filed	Not filed
DRC	Not filed	Not filed	Not filed
Ethiopia	Not found	Not found	Not found
EU (EPO)	EP2323990 Granted	EP2323990 Lapsed	EP2019819975 Pending
Ghana	Not filed	Not filed	Not filed
India	1229/DELNP/2011 Granted Patent No. 277705	1229/DELNP/2011 Granted Patent No. 277705	IN202017054538 Pending

Indonesia	Not filed	Not filed	Not filed
Kazakhstan	Not filed	Not filed	202092952 Pending
Kenya	Not filed	Not filed	Not filed
Kyrgyzstan	Not filed	Not filed	202092952 Pending
Malawi	Not filed	Not filed	Not filed
Mexico	MX/a/2007/003257 Pending	Not filed	Not filed
Morocco	Not found	Not found	Not found
Mozambique	Not filed	Not filed	Not filed
Nigeria	Not found	Not filed	Not filed
Pakistan	Not found	Not found	Not found
Peru	Not filed	Not filed	Not filed
Russia	2007115892 Pending	Not filed	202092952 Pending
Rwanda	Not filed	Not filed	Not filed
Senegal	Not filed	Not filed	Not filed
South Africa	ZA2007/02426B Granted	Not filed	ZA021/00070 Pending
Tajikistan	Not filed	Not filed	202092952 Pending
Tanzania	Not filed	Not filed	Not filed
Turkey	Not found	Not found	Not found
Uganda	Not filed	Not filed	Not found
Ukraine	Withdrawn	Not found	a202100047 Pending
US (USPTO)	US 2009-0082575 A1 (Application #11/663,724) Withdrawn	US 2011-0178308 A1 (Application #13/059,333) Granted	US2021/0251902 (A1) (Application #16/973,530) Pending
Uzbekistan	Not found	Not found	Not found
Vietnam	1-2007-00651 Rejected	Not filed	Not filed
Zimbabwe	Not filed	Not filed	Not filed

Endnotes

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refers to G/P in a fixed-dose combination form. There is no other clause in the main licence or sublicence agreement to specify whether the sublicensee can work on the single formulation of GLE or PIB; or develop fixed-dose combinations containing GLE or PIB and other approved DAA compounds"…"Moreover, the license does not provide for potential development of a long-acting injectable formulation, which could dramatically improve patient adherence, possibly reduce treatment to one dose and reduce costs." Médecins Sans Frontières Access Campaign. Médecins Sans Frontières Access Campaign Technical Briefing - MPP licence agreement with AbbVie for Glecaprevir/Pibrentasvir (G/P). Updated analysis and recommendations; 2019 August, p. 3. Available from: https://msfaccess.org/sites/default/files/2019-03/HCV_TechnicalBrief_MPPLicenceAgreementAbbVieForGP_ENG_2019.pdf. (Accessed February 15, 2021).

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40 Patent Cooperation Treaty opinion for the following patent applications:

- WO 2017/015211: lack of inventive step (claims 1–14)
- WO 2017/007934: lack of novelty and inventive step (claims 1–17)
- WO 2018/057919: lack of inventive step (claims 1–26)
- WO 2019/074507: lack of novelty (claims 1–17; 21–24) and inventive step (claims 1–24)
- WO 2019/027694: lack of inventive step (for claims 1–6; 8; 10–13; 15–22)
- WO 2019/046569: lack of inventive step (claims 1–20)
- WO 2020/106835: suggestive to lack novelty and inventive step (based on International Search Report).

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91 1- (4-hydroxyphenyl) -4- (4-trifluoromethoxyphenoxy) piperidine.

92 2-chloro-4-nitroimidazole derivatives.

93 1 micron (μm)=1000 nanometers (nm). Nanoparticles are submicron particles with a size smaller than 1 μm.

94 1- (4-hydroxyphenyl) -4- (4-trifluoromethoxyphenoxy) piperidine.

95 2-chloro-4-nitroimidazole derivatives.

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