medicines patent pool

Unitaid
Innovation in Global Health

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INTELLECTUAL PROPERTY REPORT ON LONG-ACTING TECHNOLOGIES

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Acronyms and abbreviations

ARIPO	African Regional Intellectual Property Organization (19 States)[1]
BR	Brazil
BY	Belarus
CN	China
EAPO	Eurasian Patent Organization (8 States[2] including Russia)
EP	European Patent Organization (38 member states[3])
GT	Guatemala
HIC	High income countries
ID	Indonesia
IN	India
KZ	Kazakhstan
LAI	Long-acting injection
PrEP	Pre-exposure prophylaxis (of HIV infection)
LMICs	Low- and middle-income countries
MA	Morocco
OAPI	Organisation Africaine de la Propriété Intellectuelle (17 States)[4]
RU	Russian Federation
UA	Ukraine
US	United States of America
VN	Vietnam
ZA	Republic of South Africa

Patent Status

-	No filing
C	Challenged patent or patent application (e.g. opposition, invalidation)
F	Patent application pending
G	Granted patent
N	Not in force (abandoned, expired, withdrawn)
u	Status unknown
Blue shading	International patent application in the international phase. Filing status will be available upon entry into the national phase[5].

[1] ARIPO States are: Botswana, The Gambia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Sierra Leone, Liberia, Rwanda, São Tomé and Príncipe, Somalia, Sudan, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe

[2] EAPO States are: Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Russia, Tajikistan, Turkmenistan

[3] EPO States: in addition to 38 member states, European patents can for example be validated in Morocco if filed on or after 1 March 2015, in Tunisia if filed on or after 1 December 2017 or Cambodia if filed on or after 1 March 2018)

[4] OAPI States are: Benin, Burkina Faso, Cameroun, Centrafrique, Comores, Cogo, Côte d'Ivoire, Gabon, Guinée, Guinée Bissau, Guinée équatoriale, Mali, Mauritanie, Niger, Sénégal, Tchad, Togo

[5] National phase entry: When an international patent application is filed, under the Patent Cooperation Treaty (PCT), administered by the World Intellectual Property Organization (WIPO), it is considered as filed in all the PCT contracting states on the date of filing. WIPO carries the international search, provides a written opinion on patentability and publishes the application during what is known as the International Phase or PCT stage. After the end of this phase, usually at 30 months from the priority date, the applicant decides in which countries he wishes to proceed further with the international patent application and starts to pursue the grant of patents directly before the national or regional patent offices concerned entering thereby into the National or Regional phase.

Contents

Foreword

Long-acting technologies herald a potentially exciting new era in modern medicine. In high-income countries, weekly, monthly and less frequent long-acting injectable drug formulations are already leading to significantly improved adherence and treatment outcomes in areas as diverse as anti-psychotic treatment for schizophrenia, the management of severe, chronic asthma, osteoporosis and opioid substitution therapy. In sub-Saharan Africa, long-acting injectable hormonal contraception is becoming the method of choice for women of reproductive age who have access to it.

While not yet approved for prevention or treatment of HIV, tuberculosis, malaria or hepatitis C, several long-acting formulations are now being explored for such indications, along with innovative methods of delivering them, including a wide range of implants, patches, rings and capsules. Research and development underway in this area offer hope that the benefits of long-acting technologies already seen in other disease areas could also be achieved for the treatment and prevention of major diseases in low- and middle-income countries.

Despite their promise, developing a healthy market for long-acting products in low- and middle-income countries will be more challenging than for conventional, oral medications. Intellectual property issues for long-acting technologies are likely to be particularly complex, requiring attention to the three dimensions of the drugs themselves, the technologies needed to manufacture them, and new delivery devices. Significant investments and technology transfer are also likely to be needed for generic manufacturers to enter the market. To help better understand these issues, Unitaid and the Medicines Patent Pool have worked together to develop this report. It provides a brief overview of the intellectual property status of long-acting drugs, formulation processes and delivery devices for major infectious diseases that are in pre-clinical or later stages of development as of October 2018.

The report is intended as a companion to a compendium of materials exploring the broader science and market landscape on long-acting technologies to be published online by Unitaid in November 2018.

Lelio Marmora

Unitaid

Charles Gore

Medicines Patent Pool

Introduction

Although significant advances have been made in the treatment and prophylaxis of infectious diseases that disproportionately affect low and middle-income countries, adherence to daily oral treatment or prophylactic regimens remain challenging in diseases such as tuberculosis (TB) or malaria and particularly in infections such as HIV that require lifelong treatment. Further, stigma and/or logistical challenges in resource-limited settings are amongst the factors that also impact on retention in care, timely access to medicines as well as adherence. Poor treatment compliance and treatment interruption or cessation in turn contribute to suboptimal drug exposure and the emergence of drug resistance, which could undermine global progress in scaling-up access to treatment as well as preventive therapies in low and middle-income countries (LMICs).

Long-acting (LA) platform technologies could contribute to removing some of these challenges; approved and new, investigational drugs could be developed into oral, parenteral or implantable depots. Such LA products could offer extended drug release, thereby enabling less frequent administration. Recent years saw an increase in the number of innovative LA products being developed for a variety of diseases. In relation to infectious diseases, the pipeline is most dynamic for the prevention and/or treatment of HIV infection.

Key Findings

First, LA products are typically technologically intensive to manufacture, and also relatively complex in terms of patent protection. For instance, an LA product may involve multilayered patent protection, such as patents on the molecule, the formulation of the drug reservoir (often using nanotechnology), the device, and the process of manufacturing each component.

Second, patents specific to the long-acting formulations often provide additional years of exclusivity beyond the expiry of the compound patents. The tables on specific products below illustrate that in a number of cases.

Third, in terms of nanoformulations, the patent landscape appears particularly complex with potential for multiple overlapping patents, depending on the process of preparing nanoparticles (such as homogenization, granulation and spray drying), as well as the selection of polymers and excipients constituting the nanoformulation of an active substance. A number of nanotechnology platforms are owned by drug formulation companies that develop new formulations incorporating such technologies under contract. Such patent holders often grant a licence specific to a given product that incorporates its proprietary technology, but not to the technology platform as a whole. The technology platforms are often being applied to multiple products and are covered by extensive intellectual property protection. The above complexity may present challenges to the freedom-to-operate of future LA products, be it generic or originating from the patent holders themselves.

Fourth, the geographical scope of patent protection varies by product and by technology. Apart from the high-income countries, certain middle-income countries, where many of the leading generic manufacturers are based, are often covered in patent filings. For example, smaller corporations and academic institutions often file in less LMICs compared with major pharmaceutical companies. However, key manufacturing countries such as China and India are generally covered in the patenting strategy.

Methodology

The current report on the patent landscape of LA technologies was compiled by the MPP and Unitaid, for the purpose of illustrating the complexities of IP protection for select LA products marketed or under development for HIV, Hepatitis C Virus (HCV), TB, malaria and opioid substitution therapy. These products have been highlighted in recent workshops such as the NIH Long-Acting/Extended-Release Antiretroviral Resource Program, and are featured in the Unitaid Compendium of Technical and Market Information on Long-Acting Technologies for the Prevention and Treatment of Major Infectious Diseases and the recent Unitaid consultation on this topic. This report does not include all potential LA options that may have been developed or could be developed for the above therapeutic areas.

Information concerning the main patents and patent applications for the selected products was collected from sources such as the FDA Orange Book (for FDA-approved products), regional or national patent office databases, and the originator's website or financial statements, as the case may be. The stage of clinical development was verified against the NIH Clinical Trials Registry (clinicaltrials.gov). Other information such as preclinical development and potential contractual arrangements was drawn from scientific literature, conference proceedings or press releases.

With respect to patent expiry dates, it is assumed in this report that most patents expire in most countries 20 years after the filing of the patent application. However, the exact date of expiry may vary from country to country as a result of differences in national patent laws or the existence of patent term extensions, which are possible in some countries.

Limitations

It should be noted that this report may not be comprehensive and should not be interpreted as a freedom-to-operate analysis, for which further detailed analysis would be required. For example, the report may not cover all granted patents or patent applications for a given product, particularly where no patent applications have been made public for the more recent innovations. Finally, the MPP patent searches were limited to a number of sample countries, including countries where a number of leading generic manufacturers are located (e.g. Brazil, China, India, South Africa, Thailand), relevant regional patent offices (ARIPO, EAPO and OAPI) and an illustrative sample of LMICs from other regions (e.g. Guatemala, Indonesia, Morocco, Ukraine and Vietnam).

Summary of Patent Status by Product/Technology

Part A. Long-Acting Technologies as applied to specific drugs

A1. Cabotegravir Long-Acting Injectable (LAI)

Therapeutic area	 **HIV**
Name and formulations	Cabotegravir (CAB): oral and LAI
Originator	ViiV Healthcare (some patents owned by GSK)
Stage of development	• Phase III: CAB-LAI for HIV PrEP • Phase III: CAB-LAI combined with rilpivirine LAI for HIV treatment / maintenance therapy

Patent Summary	• ViiV's patent families cover:
	  • Cabotegravir (CAB), dolutegravir (DTG) and analogues having inhibitory activity on HIV integrase; granted or pending in CN, EAPO, ID, MA, ZA, UA, VN; BR, IN (with opposition), but not filed in ARIPO, GT, OAPI & TH. Expected expiry in 2026 (except term extension in some EAPO countries)
	  • CAB-LAI, including its combination with RPV-LAI; granted or pending in CN, EAPO, ZA, UA; BR and IN, but not filed in ARIPO, GT, ID, MA, OAPI, TH & VN. Expected expiry in 2031
	  • GSK has additional filings covering CAB-LAI and GSK-2838232 (a Phase II maturation inhibitor) and combinations thereof
	• The Univ. of Nebraska has also filed for patent applications concerning other formulations of CAB-LAI and DTG-LAI in the US and Europe, but not in the majority of LMICs mentioned above.

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
CAB, DTG and analogues having inhibitory activity on HIV integrase WO 2006/116764 A1 WO 2006/088173 A1 WO 2007/049675 A1	Shionogi & Co Ltd (with ViiV and/or GSK as joint assignees in some cases)	2026*	-	F	G	G*	-	F/C	G	G	-	G	-	G	G	G	G
Long-acting parenteral CAB; includes RPV-LAI combination WO 2012/037320 A2	GSK (ViiV in some filings)	2031	-	F	G	G	-	F	-	-	-	G	-	G	-	F	F
CAB or DTG nanoformulations WO 2015/127437 A1	University of Nebraska	2035	-	-	-	-	-	-	-	u	u	-	-	-	-	F	F

** Patent term extension in some EAPO countries until 2028*

A2. Rilpivirine Long-Acting Injectable and implant

Therapeutic area	 **HIV**
Name and formulations	Rilpivirine (RPV): oral, LAI and implant
Originator	Janssen Pharmaceutica
Stage of development	• Phase III: RPV-LAI combined with CAB-LAI for HIV treatment / maintenance therapy • Clinical investigation for HIV PrEP was discontinued in Phase IIa[6]

Patent Summary	• Janssen's leading RPV-LAI formulation incorporated Alkermes' proprietary NanoCrystal® technology (see B6 for further details)[7]. The licensing arrangement between Janssen and Alkermes is not in the public domain
	• AstraZeneca owns a patent family on the general formula covering RPV. Patent granted or pending in CN, ZA; BR, but not filed in ARIPO, EAPO, GT, IN ID, TH, UA and VN. The status in MA and OAPI is unknown. Expected expiry in 2021.
	• Janssen owns patent families covering:
	  • Rilpivirine (RPV) compound, its salts and polymorphic forms. Patent granted or pending in ARIPO, CN, EAPO, IN (with opposition), ID, OAPI, UA, VN, ZA; BR and TH, but not filed in GT. The filing status in MA is unknown. Expected expiry in 2022 (except term extension in some EAPO countries)
	  • Solid oral composition of RPV salts, its N-oxide or isomeric form and wetting agent. Patents granted or pending in ARIPO, CN, EAPO, IN, ID, OAPI, UA, VN, ZA; BR, but not filed in GT, MA & TH. Expected expiry in 2025. Several filings on parenteral formulations (intramuscular or subcutaneous) of RPV or its salt for the prevention and/or treatment of HIV infection. Patent granted or pending in ARIPO, EAPO, ID, OAPI, UA, ZA; BR, CN, IN, TH and VN, but not filed in GT or MA. Expected expiry 2026-2027.
	  • Freeze-dried nanosuspension of RPV with a steric stabilizer, and compositions for injection. Patent granted or pending in RU; BR, CN, IN, but not filed in ARIPO, other EAPO countries, GT, ID, MA, OAPI, TH, UA, VN and ZA. Expected expiry in 2032.
	  • Various filings on subcutaneous biodegradable implants for sustained release of HCV or HIV inhibitors, including RPV. Patent granted or pending in CN, RU, UA; BR, IN, ZA, but not filed in ARIPO, other EAPO countries, GT, ID, MA, OAPI, TH and VN. Expiry 2029-2030
	• Additional Janssen patents on RPV polymorphic form and salt which are not contained in the marketed products are not mentioned here

[6] McGowan, I (2017) An open label multiple dose Phase 1 assessment of long acting rilpivirine, presented during the 9th IAS Conference on HIV Science, July 23-26, 2017, Paris.

[7] Williams, PE *et al* (2015) Curr Opin HIV AIDS, 10: 233-238

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs													HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
RPV product, general formula of pyrimidine derivatives covering RPV WO 2001/064656	AstraZeneca	2021	-	F	G	-	-	-	-	u	u	G	-	-	-	G	G
RPV, including salts and polymorphic forms WO 2003/01630	Janssen	2022 (25-27*)	G	F	G	G*	-	F/C	G	u	G	G	F	G	G	G*	G*
Solid oral composition of RPV salts, its N-oxide or isomeric form and wetting agent WO 2006/024667 A1 WO 2006/024668 A1	Janssen	2025	G	F	G	G	-	G	G	-	G	G	-	G	G	F	G
Parenteral (IM or SC) formulation comprising RPV or its acid-addition salt for long-term prevention of HIV infection WO 2006/106103 A2	Tibotec / Janssen	2026	G	F	F	G	-	F	G	-	G	G	F	G	F	F	G
Suspension of micro- or nanoparticles of RPV, its salt or stereoisomer(s) as IM or SC injection for the long-term treatment or prevention of HIV infection WO 2007/147882 A2	Tibotec / Janssen	2027	G	F	F	G	-	G	F	-	G	F	F	G	F	F	G
Parenteral (IM or SC) formulation of RPV or its salt for HIV treatment WO 2007/082922 A8	Tibotec/ Janssen	2027	G	F	F	G	-	F/C	G	-	G	F	F	G	F	F	G

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
RPV implant (biodegradable, biocompatible) with release-enhancing agents WO 2010/072844 A1	Janssen	2029	-	F	G	(G in RU)	-	F	-	-	-	F	-	F	-	F	G
SC implant (Sustained release, degradable, removable) for HCV or HIV inhibitor, including RPV WO 2011/080141 A2	Janssen	2030	-	F	G	(G in RU)	-	F	-	-	-	F	-	G	-	G	G
Freeze dried nanosuspension of RPV and a steric stabilizer, and composition for SC or IM injection WO 2012/140220 A1	Janssen	2032	-	F	F	(G in RU	-	F	-	-	-	-	-	-	-	F	F

** Patent Term extension in some EAPO, EP countries or the US*

A3. EfdA (MK-8591) Long-Acting Injection and implant

Therapeutic area	 **HIV**
Name and formulations	EfdA (MK-8591): oral, LAI and implant (under development)
Originator	Merck Sharp & Dohme (MSD)
Stage of development	• Phase II: Oral EfdA combined with doravirine for HIV treatment • Preclinical: EfdA LAI and implant for HIV PrEP and/or treatment[8]

Patent Summary	• MSD has worldwide exclusive licence to Yamasa's IP on EfdA[9], which has compound patents granted in the US and Europe expiring 2025-2026 but was not filed in the LMICs mentioned above
	• MSD owns the following patent families, for which national phase entry[10] is due and has not yet been made public
	  • Oral or parenteral administration of EfdA for the prophylaxis or treatment of HIV infection. Expected to expire in 2037
	  • EfdA implant delivery systems for the prevention or treatment of HIV infection. Expected to expire in 2037
	• Note EfdA implant is also covered in another patent family filed by Oak Crest (see B2 below)

[8] Grobler, J, Friedman, E and Barrett, SE et al (2016) Long-acting oral and parenteral dosing of MK-8591 for HIV treatment or prophylaxis, presented at CROI 2016

[9] Available from: https://www.mrknewsroom.com/press-release/research-and-development-news/merck-signs-two-deals-novel-hiv-drug-candidates-and-init

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
4'-C-substituted-2-haloadenosine derivatives including the EfdA and their use for treating AIDS WO 2005/090349 A1	Yamasa Corporation (Exclusive worldwide licence to MSD)	n/a in LMIC 2025 in US, EP	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G
EfdA for the treatment or prophylaxis of HIV infection, as oral or parenteral administration WO 2017/139519 A1	Merck Sharp & Dohme (MSD)	2037														F	F
Implant drug delivery system (subdermal) of EFdA comprising a biocompatible nonerodible polymer, and its use for the prevention or treatment of HIV infection WO 2017/196697 A1	MSD	2037															
Implant drug delivery system (subdermal) of EFdA compring a biocompatible bioerodible polymer, and its use for the prevention or treatment of HIV infection WO 2017/222903 A1	MSD	2037															

A4. VRC family of broadly neutralizing antibodies

Therapeutic area	 **HIV**
Name and formulations	VRC family of broadly neutralizing antibodies (bNAbs)
Originator	US National Institute of Health (NIH); University of Washington
Stage of development	• Phase II: VRC01 for HIV PrEP and treatment • Phase I: VRC01LS, VRC07-523LS for HIV PrEP and treatment
Patent Summary	• The US Government as represented by the DHHS owns a patent family covering neutralizing monoclonal antibodies against HIV gp120, including VRC01, VRC02, VRC03 etc and their expression vectors, for use in preventing or treating HIV infection or for testing a potential vaccine. Patents granted or pending in CN; IN and ZA, but not filed in other LMICs mentioned above. Expected expiry in 2030 • Univ. of Washington, and the US Government as represented by the DHHS own a patent family covering VRC01-like mAbs such as VRC07 and their expression vectors, for use in preventing or treating HIV infection or for detecting HIV. Patents granted or pending in CN; IN and ZA, but not filed in other LMICs mentioned above. Expected expiry in 2032 • Xencor Inc. owns the Xtend Technology that has been applied to VRC01LS (VRC01 with Xtend) and VRC07-523LS (VRC07 with Xtend)[11]. Patents covering the Xtend Technology are granted or pending in CN, RU, IN; BR, but are not filed in the other LMICs mentioned above. Expected expiry 2025-2028, earlier than the above VRC patents • Contractual or licensing arrangement between Xencor and DHHS (or NIH) is not in the public domain

[11] Available from: https://investors.xencor.com/news-releases/news-release-details/national-institutes-health-initiates-phase-1-trial-vrc01ls-anti

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Neutralizing monoclonal antibody against HIV gp120: VRC01, 02, 03 etc, the expression vector encoding the corresponding nucleic acid molecules, method of preparation, and use in preventing or treating HIV infection or for testing a potential vaccine WO 2011/038290 A8	The United States of America, as represented by the Secretary, Department of Health and Human Services (DHHS); University of Washington	2030	-	-	G	-	-	F	-	-	-	F	-	-	-	G	F
VRC01-like neutralizing monoclonal antibody against HIV gp120 such as VRC07; the expression vector encoding the corresponding nucleic acid molecules, method of preparation, and use in detecting HIV from a biological sample, preventing or treating HIV infection; the use of combination of two or more of said antibody, antigen-binding fragment, scaffold protein, nucleic acid molecule and expression vector to inhibit or prevent HIV infection WO 2013/086533 A1	The United States of America, as represented by the Secretary, Department of Health and Human Services (DHHS)	2032	-	-	G	-	-	F	-	-	-	F	-	-	-	G	G
Antibody, immunoadhesin or polypeptide comprising a variant Fc region comprising specific amino acid substitutions for increasing serum half-life; method of production WO 2006/053301 A9 WO 2009/058492 A2 WO 2009/086320 A1	Xencor, Inc	2025-2028	-	F	G	(G in RU)	-	G	-	-	-	-	-	-	-	G	G

A5. GS-9131

Therapeutic area	 **HIV**
Name and formulations	GS-9131 (a prodrug of GS-9148): oral and possibly long-acting formulation
Originator	Gilead Sciences, Inc.
Stage of development	• Phase II: oral GS-9131

Patent Summary	• Patent families cover:
	  • GS-9131, its salts and analogues for the treatment or prevention of HIV infection, and method of preparation. Patents granted or pending in ARIPO, CN, EAPO, IN, ID, OAPI, UA, VN, ZA; BR and TH, but not filed in GT or MA. Expiry 2025-2029
	  • GS-9148 or its salts for treating HIV infection. Patent granted in CN and EAPO, application lapsed in BR, no filing in the majority of LMICs mentioned above (the status in MA and OAPI is unknown).
	  • Oral dosage form combining GS-9131 + bictegravir + darunavir + cobicistat. National phase entry due in 2019. Expected to expire in 2037
	• Other patent families covering GS-9148 for anticancer purpose are not mentioned here
	• Although no patent filings were found yet on long-acting formulations of GS-9131 at the time of this Report, the MPP will continue to monitor the patent status

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
GS-9131 and analogues for treating HIV; composition and method of preparation WO 2006/015261 A2 WO 2006/110157 A2	Gilead Sciences, Inc.	2025	G	F	G	G	-	G	G	-	G	G	F	G	G	G	G
Citrate, succinate or malonate salt of GS-9131, and its use for the treatment or prevention of HIV infection WO 2010/005986 A1	Gilead Sciences, Inc.	2029	G	F	G	G	-	F	G	-	G	G	-	G	F	G	G
GS-9148 or its salts, composition and method of use for treating viral infections such as HIV WO 2004/096286 A2	Gilead Sciences, Inc.	2024	-	N	G	G	-	-	-	u	u		-	-	-	G	G
Solid oral dosage form comprising specific percentages of GS-9131 + bictegravir + darunavir + COBI WO 2018/064071 A1	Gilead Sciences, Inc.	2037														F	

A6. GS-6207 (GS-CA2)

Therapeutic area	 **HIV**
Name and formulations	GS-6207 (also known as GS-CA2, an analogue of GS-CA1): possibly oral and long-acting formulation
Originator	Gilead Sciences, Inc.
Stage of development	• Phase I (according to the Gilead Pipeline, though study is not yet shown in clinical trials registry)

Patent Summary	• Patent families cover:
	  • General formula of amide derivatives covering GS-CA2 product or it salts, pharmaceutical compositions and their use for treating HIV infection, alone or in combination with other HIV treating agents.Patent granted or filed in CN, OAPI; ARIPO, BR, EAPO, IN, ID, ZA, TH, UA & VN. There may be unpublished applications in GT and MA. Expected expiry in 2034
	  • GS-CA2 product or its salt specifically, and its use for the treatment of HIV alone or in combination with other drugs for HIV; Pharmaceutical composition of GS-CA2 for oral formulation, or parenteral formulation (intramuscular, subcutaneous). National phase entry not due until Feb 2019, so there may be yet unpublished patent applications. Expected expiry in 2037
	  • The same patents apply to the analogue GS-CA1.

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
General formula of amide derivatives covering GS-CA2 product or it salts, pharmaceutical compositions and their use for treating HIV infection, alone or in combination with other HIV treating agents. WO 2014/134566 A2	Gilead Sciences, Inc.	2034	F	F	G	F	u	F	F	u	G	F	F	F	F	G	G
GS-CA2 product or its salt specifically, and its use for the treatment of HIV alone or in combination with other drugs for HIV; compositions for oral or parenteral administration. WO 2018/035359 A1	Gilead Sciences, Inc.	2037														G	F

A7. Elsulfavirine

Therapeutic area	 **HIV**
Name and formulations	Elsulfavirine (VM-1500): daily oral, with clinical development plans for oral weekly dosing. A long-acting injectable formulation of elsulfavirine's prodrug (VM-1500A) is currently in preclinical development [12]
Originator	Viriom (exclusively licensed elsulfavirine from Roche)[12]
Stage of development	• Approved in Russia on June 30, 2017[13] • Not yet approved by FDA or EMA

Patent Summary	• Patent families cover:
	  • Elsulfavirine and its salts, metabolites etc (including in combination with other HIV drugs) for treating HIV infection. Patent granted or pending in CN, IN, RU; BR, ID and TH, but not filed in the majority of LMICs mentioned above (the status in MA and OAPI in unknown). Expected expiry in 2029
	  • Elsufavirine sodium polymorphic forms. Patent granted or pending in CN, EAPO (3 countries only, lapsed in others), UA; BR and IN, but not filed in other LMICs mentioned above. Expected expiry in 2029
	• One patent covering a long-acting formulation of VM1500A was granted in Russia (no counterparts were found). Expected expiry date in 2037

[12] Available from: https://www.viriom.com/pipeline
[13] Available from: http://pharmstd.com/archivedetails_64_2753.html

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Elsulfavirine and its metabolites, hydrates, solvates and salts and their use for treating HIV infection; this patent family also covers the combination use of elsulfavirine with other HIV drugs WO 2005/102989 A1	Roche (exclusively licensed to Viriom)	2025	-	F	G	(G in RU)	-	G	F	u	u	-	F	-	-	G	G
Polymorphic crystalline forms (I to IX, with specific x-ray powder diffraction patterns) of elsulfavirine sodium, and process for preparation; for the therapeutic and/or prophylactic treatment of HIV-associated diseases WO 2010/028968 A2	Roche (exclusively licensed to Viriom)	2029	-	F	G	G (BY, KZ, RU)	-	F/C	-	-	-	-	-	G	-	G	F
Long acting pharmaceutical suspension of VM1500A to be used as an injectable preparation for long-term maintenance therapy for HIV infection RU2665383	Nikolaj Savchuk et al. (Viriom)	2037	-	-	-	(G RU)	-	-	-	-	-	-	-	-	-	-	-

A8. Ivermectin long-acting

Therapeutic area	 **MALARIA**
Name and formulations	Ivermectin: oral, long-acting oral, long-acting injectable
Originator	Ivermectin long-acting injectable: Merck Sharp & Dohme (MSD), Boehringer Ingelheim, Biogenesis S.A. Ivermectin long-acting oral: Lyndra
Stage of development	• Ivermectin has been in use since the 1980s • Ivermectin long-acting injectable is marketed for veterinary use, but not yet for humans
Patent Summary	• Ivermectin compound is off patent • No patent application was found in relation to the NIH-sponsored research at Colorado State University on the use of ivermectin for malarial control[14] • See B5 (Lyndra) which covers long-acting oral ivermectin • MSD and Merial LLS (acquired by Boehringer Ingelheim) own a patent family on long-acting injectable parasiticide formulations covering ivermectin for the prevention and treatment of parasitic infestation in a host. The granted/pending patents in CN, EAPO, ZA and BR shall expire at the end of 2018. • Biogenesis S.A., Argentina owns another patent family on long-acting injectable parasiticide formulations covering ivermectin and process for preparation, for treating animals. Patents granted in BR and ZA expired in 2018

[14] Available from: Kolbylinski, KC et al (2011) The American Journal of Tropical Medicine and Hygiene, 85 (1) 3 - 5

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Long-acting injectable parasiticide formulation comprising specific weight ranges of ivermectin and certain excipients and adjuvants; process for its preparation. The patent family covers use in treating parasites in animals N/A - European publication EP0867186	Biogenesis S.A, Argentina	(Expired)	-	N	-	-	-	-	-	-	-	N	-	-	-	N	N
Long-acting injectable parasiticide formulation comprising specific excipients and therapeutic agent such as ivermectin, for various use including the prevention and treatment of parasitic infestation in a host WO 99/27906 A1	Merck Sharp & Dohme Corp; and Merial LLS (acquired by Boehringer Ingelheim)	2018 (oct-dec)	-	N	N	N	-	-	-	-	-	G	-	-	-	N	G

A9. GSK2878175 LAI

Therapeutic area	 **HCV**
Name and formulations	GSK2878175: oral and long-acting injectable
Originator	GlaxoSmithKline (GSK)
Stage of development	• Phase II: GSK2878175-LAI in combination with RG-101 (now discontinued)[15]

Patent Summary	• Patent families cover:
	  • GSK2878175 compound, its salts, intermediates and analogues for treating or preventing HCV infections. Patent granted or pending in CN, MA; BR, EAPO, IN, ID, TH, UA, VN and ZA, but not filed in ARIPO or GT. The status in OAPI is unknown. Expected expiry in 2032
	  • GSK2878175 compound, its salts, intermediates and analogues GSK2878175 LAI for treating HCV infection, including in combination with one or more HCV drugs such as other DAAs or RG-101. Patent pending in BR, CN, EAPO, IN, ID, MA (EP), TH, UA, VN and ZA, but not filed in ARIPO, GT, MA or OAPI. Expected expiry in 2035

[15] Available from: https://www.reuters.com/article/brief-regulus-says-plans-to-discontinue-idUSFWN1J908U

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
GSK2878175, its salt and intermediates and their use for treating or preventing viral infections like HCV infection WO 2013/028371 A1	Glaxo Group Limited	2032	-	F	G	F	-	F	F	G	u	F	F	F	F	G	F
GSK2878175 and analogues and their salts in combination with other HCV inhibitors such as a DAA, interferon, ribavirin or immunomodulator etc, and their use for treating HCV WO 2013/025992 A1	GlaxoSmith Kline LLC	2032	-	F	G	G	-	F	F	G	u	G	F	G	F	G	F
Long acting parenteral (LAP; as IM injection) composition of GSK-2878175 or its salt, for the treatment of HCV infection; including in combination with one or more HCV drugs, such as other DAAs, or anti-miR-122 oligonucleotides like RG-101 (covered in WO'583). WO'584 covers the combination of anti-miR-122 oligonucleotides such as RG-101 in combination with other LAP HCV agent WO 2016/075582 A1 WO 2016/075583 A1 WO 2016/075584 A1	GlaxoSmith Kline	2035	-	F	F	F	-	F	F	F (EP)	u	F	F	F	F	F	F

A10. Bedaquiline long-acting

Therapeutic area	 **TB**
Name and formulations	Bedaquiline (BDQ): oral (as BDQ fumarate); Long-acting injectable is currently in preclinical research
Originator	Janssen
Stage of development	• Conditional approval by FDA (2012) and EMA (2014) • Preclinical: BDQ-LAI[16]

Patent Summary	• Patent families on BDQ and oral formulation:
	  • BDQ compounds family. Patent granted in ARIPO, BR, CN, EAPO, IN, ID, OAPI, ZA, TH, UA but not filed in GT or MA. Expected expiry in 2023 (except term extension in RU until 2028)
	  • BDQ fumarate salt. Patent granted or pending in ARIPO, EAPO, ID, OAPI, TH, ZA, UA, VN; BR, CN and IN (opposition) but not filed in GT or MA. Expected expiry in 2027 (except term extension in RU until 2028)
	  • A method for preparing/isolating bedaquiline from a mixture of stereoisomeric forms. Patent granted or pending in CN, EA, IN, ZA, UA, VN; BR and ID but not filed in ARIPO, GT, MA, OAPI and TH. Expected expiry in 2026
	  • BDQ to treat latent TB infection. Patent granted or pending in ARIPO, CN, EAPO, ID, OAPI, ZA, TH, UA, VN; BR and TH but not filed in GT, MA. Application abandoned in US and rejected in IN. Expected expiry in 2025
	  • BDQ to treat MDR-TB. Patent granted or pending in ARIPO, CN EAPO, IN, ID, OAPI, ZA, UA & VN; BR and TH but not filed in GT or MA. Expected expiry in 2025
	• Although no patent filings were found on long-acting formulations of BDQ at the time of this Report, the MPP may continue to monitor the patent status

[16] Ammerman, N et al (2018) Evaluation of a long-acting bedaquiline formulation in a mouse model of latent tuberculosis infection. Presented during the 49th TB Union Conference, October 25, 2018

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Quinoline derivatives including Bedaquiline WO 2004/011436 A1	Janssen Pharmaceutica N.V	2023-2028* (EP, RU)	G	G	G	G*	-	G	G	-	G	G	G	G	G	G	G*
Use of substitutes quinoline derivatives in general and bedaquilline specifically for the treatment of drug resistant mycobacterial diseases WO2005117875A1	Janssen Pharmaceutica N.V	2025-2028* (RU)	G	F	G	G*	-	G	G	-	G	G	F	G	G	N	G
Bedaquilline fumarate salt and its use to treat or prevent a mycobacterial infection, especially TB; solid compositions of BDQ fumarate and manufacturing processes. WO 2008/068231 A1	Janssen Pharmaceutica NV	2027 -2028* (RU)	G	F	F	G*	-	F/C	G	-	G	G	G	G	G	G	G
Use of bedaquiline generically for the manufacture of a medicament for the treatment of latent tuberculosis. WO 2006/067048 A1	Janssen Pharmaceutical N.V	2025	G	F	G	G	-	N	G	-	G	G	F	G	G	N	G
A process for preparing/isolating bedaquilline from a mixture of d stereoisomeric forms WO2006/125769 A1	Janssen Pharmaceutical N.V	2026	-	F	G	G	-	G	F	-	-	G	-	G	G	G	G

** Patent term extension in some EAPO or EP countries*

A11. RBP-6000: buprenorphine LAI

Therapeutic area	**OPIOID SUBSTITUTION THERAPY**
Name and formulations	RBP-6000 (Sublocade™): buprenorphine extended-release subcutaneous injection, given monthly
Originator	Indivior (rebranded from Reckitt Benckiser Healthcare - the original assignee of the patents - post demerger)[17]
Stage of development	• FDA approved Sublocade™ on Nov 30, 2017 • Buprenorphine has been in use since the 1980s and has been formulated as tablets and films
Patent Summary	• Buprenorphine compound is off patent, but various pharmaceutical compositions of buprenorphine remain patent-protected • Indivior owns patent families covering Sublocade™ composition and its approved indications and dosage regimens. Patents granted or pending in CN, ID, RU, ZA; BR and IN. Expiry in 2031. National phase filings have yet to be made public regarding a more recent patent family, which is expected to expire in 2035 • Tolmar Therapeutics Inc (formerly Atrix Labs, QLT) owns the extended release Atrigel Technology which is used in Sublocade™.[18] Some patent families were not filed in LMICs, but other patents were granted or filed in CN, EAPO, IN and ZA, and national phase filings have yet to be made concerning other LMICs. Expected expiry in 2036 • The contractual or licensing arrangement between Indivior and Tolmar is not in the public domain

[17] Available from: http://www.indivior.com/investor-news/reckitt-benckiser-pharmaceuticals-inc-announces-plans-to-rebrand-under-indivior-plc-following-demerger/
[18] Available from: https://www.sublocade.com/hcp/

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
This patent and family covers the Atrigel® technology from Tolmar which is used in the Sublocade and biocompatible polymer used in composition. A polymeric composition for forming a controlled-release "implant" that is insoluble in acqueous/body fluids, biocompatible and biodegradable, comprising biologically active agent such as antibacterials, antifungals or narcotic antagonists WO 2000/024374 A1	Tolmar Therapeutics Inc (formerly Atrix Labs, QLT)	2019 is EP, 2023 US	-	-	-	-	-	-	-	u	u	-	-	-	-	G	G
This application covers the Atrigel Technology. A liquid polymer composition comprising biodegradable liquid polyester, biocompatible organic solvent, and an active pharmaceutical agent (such as hormones), for the delivery of extended-release administration; also claims method for forming an "implant" in situ, and delivery system including syringe(s) WO 2017/024027 A1	Tolmar Therapeutics Inc (formerly Atrix Labs, QLT)	2036			F	F		F				F					F

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
This patent and family covers the Sublocade™ composition and approved indications and dosage regimen. An injectable composition comprising buprenorphine (its metabolite or prodrug) and biodegradable thermoplastic polymers in specific weight percentages, and the composition is transformed into a biodegradable "implant" in situ; for the treatment of medical condition comprising administering buprenorphine, opioid addiction or chronic pain WO 2011/154724 A9	Indivior UK Limited (rebranded from RECKITT BENCKISER HEALTHCARE - original assignee - post demerger)	2031	-	F	G	(G in RU)	-	F	G	-	-	G	-	-	-	G	G
This application covers the Sublocade™ composition for approved indication (moderate to severe addiction (dependence) to opioid). A method of treating opioid dependence or pain comprising administering buprenorphine long-acting injectable compositions and dosage regimens WO 2016/071767 A1	Indivior UK Limited (rebranded from RECKITT BENCKISER HEALTHCARE - original assignee - post demerger)	2035														F	F

A12. CAM 2038: buprenorphine LAI

Therapeutic area	**OPIOID SUBSTITUTION THERAPY**
Name and formulations	CAM2038: buprenorphinelong-acting subcutaneous injection, given weekly or monthly
Originator	Braeburn Pharmaceuticals, Inc.
Stage of development	• Approved by the European Commission on Nov 22, 2018 • Resubmitted to the FDA after a Complete Response Letter, with a new target date of Dec 26, 2018[19] • Buprenorphine has been in use since the 1980s and has been formulated as tablets and films
Patent Summary	• Buprenorphine compound is off patent, but various pharmaceutical compositions of buprenorphine remain patent-protected • CAM2038 uses Camurus' proprietary FluidCrystal® injection depot technology[20] and is covered by several patent families describing controlled release injectable buprenorphine formulations and preformulations (which form a depot upon injection and contact with aqueous fluid *in vivo*). Patents granted or filed in CN, EAPO (some patents only active in RU), ZA; BR, IN, ID, TH, but are not filed in other LMICs mentioned above. Expected expiry 2032-2035 • Camurus owns additional patents covering controlled release formulations for parenteral or non-parenteral use. These patents are granted or filed in CN, IN, RU, ZA; and BR. Expected expiry in 2025 • The licensing arrangement between Camurus and Braeburn is not in the public domain • Tolmar Therapeutics Inc (formerly Atrix Labs, QLT) owns the patent on syringe device for CAM2038 as well as process for its filling and use. The patent was not filed in the majority of the LMICs mentioned above (the status in MA, GT and OAPI is unknown).

[19] Available from: https://braeburnrx.com/working-toward-common-goal-cam2038-pdufa/
[20] Available from: https://www.camurus.com/cam2038-opioid-dependence/

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs														HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
This patent covers Camurus' proprietary FluidCrystal® injection depot technology, and claims the low viscosity, non-liquid crystalline pre-formulation comprising active agent such as buprenorphine and specific biocompatible excipients, which forms a depot upon injection (a liquid crystalline phase upon contact with aqueous fluid in vivo) providing continuous release of the active agent, the process of preparation, and the method of treatment or prophylaxis WO 2013/083460 A1	Camurus AB	2032	-	F	G	G (RU)	-	F	-	-	-	G	-	-	-	G	G
This patent describes a depot precursor formulation comprising buprenorphine and its salts, controlled release matrix and organic solvent; its administration for the sustained delivery of buprenorphine, for the treatment of pain or opioid dependence etc WO 2014/016428 A1	Camurus AB	2033	-	F	F	F	-	F	F	-	-	F	F	-	-	G	F
A controlled release injectable buprenorphine formulation comprising lipid controlled release matrix and other specific excipients, for treatment and prophylaxis such as opioid dependence WO 2016/066655 A1	Camurus AB	2035	-	F	F	F	-	F	F	-	-	F	F	-	-	F	F

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Low viscosity, non-liquid crystalline pre-formulations comprising active agent such as buprenorphine and specific excipients and organic solvent, and is capable of forming a liquid crystalline phase upon contact with aqueous fluid in vivo; method for preparing the pre-formulation and the liquid crystalline composition; a kit including injection device; and method of treatment or prophylaxis using the pre-formulations WO 2016/102683 A1	Camurus AB	2035	-	F	F	F	-	F	-	-	-	F	-	-	-	F	F
This patent family covers low viscosity, non-liquid crystalline pre-formulation comprising bioactive agent and specific excipients, its non-parenteral formulation, as well as parenteral/injectable formulation that forms a depot (a liquid crystalline phase upon contact with aqueous fluid in vivo), providing continuous release of active agent WO 2016/102683 A1	Camurus AB	2025	-	F	G	(G in RU)	-	G	-	-	-	G	-	-	-	G	G

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs													HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
This patent family covers particulate composition comprising active agent and specific excipients, its formulations for parenteral or non-parenteral administration, a kit for the preparation and the method of treatment of inflammation and/or irritation WO 2005/117830 A1	Camurus AB	2025	-	-	G	-	-	G	-	-	-	-	-	-	-	G	F
Lipid formulations comprising bioactive agent, thiolated antioxidant and optionally, chelating agent WO 2010/020794 A1	Camurus AB	n/a in LMIC 2031 in US, 2029 in EP	-	-	-	-	u	-	-	u	u	-	-	-	-	G	G
These patents cover syringe device for CAM 2038, as well as processes for their filling and use; the syringe assembly maintains sterility WO 01/72356 A2	Artix Laboratories Inc/ Tolmar Therapeutics, Inc	n/a in LMIC 2020 in US, 2021 in EP	-	-	-	-	u	-	-	u	u	-	-	-	-	G	G

A13. Probuphine: buprenorphine implant

Therapeutic area	**OPIOID SUBSTITUTION THERAPY**
Name and formulations	Probuphine: buprenorphine implant, given every 6 months
Originator	Braeburn Pharmaceuticals, Inc.
Stage of development	• FDA approved Probuphine on May 26, 2016 • Buprenorphine has been in use since the 1980s and has been formulated as tablets and films
Patent Summary	• Buprenorphine compound is off patent, but various pharmaceutical compositions of buprenorphine remain patent-protected • Titan owns patent families covering the Probuphine subdermal implant (based on the ProNeura™ implant technology[21]) and indication. These patents were not filed in majority of LMICs mentioned above (the status in MA, GT and OAPI is unknown). The US exclusivity related to New Product is set to expire on May 26, 2019 • The contractual or licensing arrangement between Titan and Braeburn is not in the public domain

[21] Available from: https://www.titanpharm.com/technology

Patent landscape

			LMICs													HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Implantable device and approved indication of Probuphine® (buprenorphine subdermal implant based on ProNeura™ implant technology) and Implant delivery mechanism and buprenorphine release profile form the implant. WO 2003/101358 A1	Titan Pharmaceuticals, Inc	2023	-	-	-	-	-	G	-	-	-	-	-	-	-	G	G
This application covers the implantable device for the controlled release of buprenorphine, for the treatment of pain WO 2007/139744 A2	Titan Pharmaceuticals, Inc	n/a	-	-	-	-	u	-	-	u	u	-	-	-	-	N	-
This application claims the approved indication for Probuphine®. (US2014271765)	Titan Pharmaceuticals, Inc	n/a	-	-	-	-	u	-	-	u	u	-	-	-	-	N	-

Part B. Long-Acting Technology Platforms

A number of nanotechnology platforms are owned by formulation companies that develop new formulations incorporating such technologies under contract. Some examples of industry platform technologies include NanoCrystal®, Medisorb®, BEPO®, NanoPure® and IDD-P®, to name just a few. Such platforms often have extensive IP protection. It is often the case that a patent holder may grant a licence specific to a given product that incorporates its proprietary technology, but not necessarily to the technology as a platform applicable to other products.

In addition, there are various different devices and platforms in the pipeline for long-acting delivery of medicines. We have included here a few examples of platform technologies to illustrate the diversity across platforms. This list is not exhaustive and does not include all potential long-acting options that may have been developed or are under development.

B1. Solid drug nanoparticleLong-Acting Injectables for HIV,malaria and other areas

Therapeutic area	 **HIV**  **MALARIA**  **OTHER AREAS**
Name and formulations	Solid drug nanoparticle (SDN) long-acting injectable of atovaquone, tenofovir, or emtricitabine (FTC); this technology platform may be applicable to other compounds and therapeutic areas
Originator	University of Liverpool, and Johns Hopkins University
Stage of development	• Preclinical, pending first-in-human study • FDA 505b(2) regulatory pathway might be applicable

Patent Summary	• The following compound patents have already expired: atovaquone (standalone), TDF (standalone), FTC (standalone)
	• All patent families below are currently in PCT stage. Decisions for national phase filings have yet to be made, and might cover certain LMICs. Expected to expire in 2037-2038:
	  • The two universities jointly own patent families on SDN formulations of atovaquone as LAI for the prevention of malaria, and its process for preparation
	  • The two universities jointly own patent families on novel prodrugs of emtricitabine (FTC) and their SDN formulations as LAI
	  • Liverpool has also filed for patent application of tenofovir-LAI using the SDN technology
	• Liverpool has signed a Collaboration & Licence Agreement with the Medicines Patent Pool in 2015 for specific patents and know-how concerning SDN-ARVs, but the above-mentioned IP has not yet been included[22]

[22] Available from: https://medicinespatentpool.org/licence-post/solid-drug-nanoparticle-technology/

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs														HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
This patent application covers solid drug nanoparticle formulations of atovaquone, the process for preparation, and use in long-acting injectables as monotherapy or part of combination therapy, for the prevention of malaria WO 2017/216564	Univ. Liverpool; Johns Hopkins Univ.	2037																
Methods for the preparation of a liquid composition for long-acting injectables of tenofovir solid drug nanoparticles PCT/GB2018/050887 (no WO # yet)	Univ. Liverpool	2038																
Novel pro-drugs of emtricitabine, and their solid drug nanoparticle formulations for long-acting intramuscular injectables PCT/GB2018/050888 (no WO # yet)	Univ. Liverpool; Johns Hopkins Univ.	2038																

B2. Intarcia Medici implant

Therapeutic area	 **HIV**  **DIABETES**  **OTHER AREAS**
Name and formulations	Intarcia Medici Drug Delivery System™: an osmotic mini-pump as subcutaneous implant for exenatide, or ARV; this technology platform may be applicable to other compounds and therapeutic areas
Originator	Intarcia Therapeutics (formerly BioMedicines Inc)[23]
Stage of development	• Phase III (on clinical hold): ITCA650, an exenatide implant that received FDA Complete Response Letter in Sept 2017[24] • Preclinical: ARV implant for HIV prevention in collaboration with the BMGF[25]
Patent Summary	• Intarcia's Medici drug delivery system, its technology and compositions are extensively protected in several patents of Alza Corporation (now part of Johnson & Johnson) and Intarcia/ BioMedicines Inc. • Patent landscape on other osmotic implantable drug delivery technologies will also need to be assessed in the future • Our patent search revealed a large number of patents and patent applications. Only some of these filings are named below to illustrate the extent of patent coverage in LMICs. • By way of example, Intarcia's patent families covering implantable osmotic delivery system flow modulator has patents granted or pending in CN and IN, but not filed in other LMICs mentioned above. Expected expiry in 2027

[23] Available from: https://www.biospace.com/article/releases/-b-biomedicines-inc-b-announces-name-change-to-b-intarcia-therapeutics-inc-b-/
[24] Available from: https://www.reuters.com/article/brief-intarcia-therapeutics-says-fda-has/brief-intarcia-therapeutics-says-fda-has-issued-a-crl-for-itca-650-idUSFWN1M80SB
[25] Available from: https://www.intarcia.com/media/media-archive/press-releases/intarcia-secures-second-close-of-the-series-ee-equity-financing-.html

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
An implantable, osmotic delivery system flow modulator comprising i) two pieces (outer shell & inner core) and ii) internal fluid channel being adapted for delivery of active agent formulation (containing one or more active agents such as interferon) from the reservoir of the osmotic delivery system. The patent family further describes the method of making the delivery systems, as well as stable non-aqueous suspension of various active agents WO 2007/140416 A2 (An osmotic delivery system flow modulator) WO 2006/083761 A2 (Non-aqueous active agent suspension)	Alza Corp/ BioMedicines Inc (now Intarcia Therapeutics)	2027	-	-	G	-	-	F	-	-	-	-	-	-	-	G	G

B3. Auritec implant

Therapeutic area	 **HIV**  **OTHER AREAS**
Name and formulations	ARV implants, especially TAF implant for HIV prevention; this technology platform may be applicable to other compounds and therapeutic areas
Originator	Auritec; Oak Crest Institute of Science
Stage of development	Preclinical

Patent Summary	• Auritec Pharmaceuticals and Oak Crest collaborate on TAF implant for HIV prophylaxis, as well as intravaginal rings[26]. Licence status is unclear, but there is litigation between Auritec and Oak Crest Institute[27]
	• Auritec owns patent families concerning the method for producing microparticles of drugs for parenteral administration, for which no patent filings were found in the majority of the above mentioned LMICs (the status in MA, GT and OAPI is unknown)
	• Oak Crest has filed for subdermal implant for water soluble drugs such as TAF, FTC, 3TC or EfdA, for which national phase entry is due and has not yet been made public. Expected expiry in 2036
	• pSivida Inc (now EyePoint Pharmaceuticals)[28] owns several patent families as follows, and it is unclear which ones may have been licensed to Auritec:
	  • Extensive filings by Control Delivery Systems (acquired by pSivida Inc[29]) on sustained release implant or injectable device comprising drug reservoirs of antibiotics, adrenergic agents, fluocinolone acetonide, proteins or peptides etc. Patent granted or pending in BR, CN, RU, IN, ZA; other EAPO countries, but not filed in ARIPO, GT, ID, TH, UA and VN. The status in MA and OAPI is unknown. Expected expiry in 2024
	  • Two other patent families covering implants comprising porous silicon body and drug reservoirs. Patent granted or pending in China, and Russia, but not filed in other LMICs mentioned above. Expected expiry in 2030, 2034

[26] Available from: http://www.oak-crest.org/oakcrest-news/oak-crest-receives-20-million-grant-for-hiv-prevention-research/
[27] Available from: https://www.prnewswire.com/news-releases/auritec-pharmaceuticals-announces-judgment-against-oak-crest-institute-of-science-300712368.html
[28] Available from: http://investors.eyepointpharma.com/investor-relations
[29] Available from: https://www.businesswire.com/news/home/20060103005138/en/pSivida-Completes-Acquisition-Control-Delivery-Systems

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
These patent families cover sustained release implant delivery systems or injectable devices comprising drug reservoirs of antibiotics, adrenergic agents, fluocinolone acetonide, proteins or peptides etc WO 2001/80825 A2 WO 2003/094888 A9 WO 2004/043435 A2 WO 2004/066979 A2 WO 2004/066980 A2 WO 2004/066983 A2 WO 2005/000268 A2 WO 2005/002625 A2 WO 2005/051234 A2	Control Delivery Systems (acquired by pSivida Inc - now EyePoint Pharmaceuticals)	2021 - 2024	-	G	G	G (RU)	-	G	-	u	u	G	-	-	-	G	G
A biodegradable implant system comprising porous silicon body and drug reservoir for sustained release of therapeutic agents such as fluocinolone acetonide WO 2010/129545 A2	pSivida Inc (now EyePoint Pharmaceuticals)	2030	-	-	F	-	-	-	-	u	u	-	-	-	-	G	F

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
A device (and method of making the device) containing a shell filled with particles that are porous silicon-based carriers, and beneficial substances (such as bevacizumab or ranibizumab) deposited within the pores; the description, but not the claims, covers antivirals such as nucleoside or non-nucleoside antivirals including those for HIV infection, and antibacterials such as TB drugs WO 2014/165097 A1	pSivida Inc (now EyePoint Pharmaceuticals)	2034	-	-	G	(G in RU)	u	-	-	u	u	-	-	-	-	G	G
Sustained release delivery system (subdermal implant) for water soluble drugs such as TAF, FTC, 3TC, EfdA WO 2016/149561 A1	Oak Crest Institute Of Science	TBD (might be 2036)															
'222: Method for producing and isolating pressure-fused microparticles comprising active pharmaceutical ingredient; '223: Pharmaceutical preparation of sustained-release polymeric coated microparticles of drugs for parenteral administration WO 2004/058222 A1 WO 2004/058223 A1	Auritec Pharmaceuticals	n/a in LMICs	-	-	-	-	u	-	-	u	u	-	-	-	-	G	G

B4. Microneedle patch

There are various types of microneedle patches. These include: (i) dissolvable microneedles, which are essentially nanoformulated drug reservoirs that dissolve (either immediate or sustained release) upon insertion into the skin, or (ii) non-dissolvable microneedles, typically composed of polymers or inert materials, through which the drug is channeled from a reservoir to enable sustained release.

Example of type (i) microneedle patch

Therapeutic area	 **HIV**  **OTHER AREAS**
Name and formulations	Microneedle patches with ARV (also known as microarray or microprotrusion patch); this technology platform may be applicable to other compounds and therapeutic areas
Originator	The Queen's University of Belfast
Stage of development	Preclinical
Patent Summary	• Patent families cover microprotrusion array delivery device for transdermal delivery of active agents. Patent granted or pending in China and India, but not filed in other LMICs mentioned above. Expected expiry in 2028. A more recent patent application disclosed use of HIV drugs in the description and national phase filings have yet to be made public (expected to expire in 2037) • Belfast has additional patent applications on microneedle patches specific to compounds unrelated to HIV and are not mentioned here • Patent search has revealed applications for similar microneedle technologies by other entities such as the Georgia Technology Research Corporation[30] and Nanyang Technological University[31], which are not mentioned here.

[30] Available from: http://drugdelivery.chbe.gatech.edu/gallery_microneedles.html
[31] Than, A, Liu, C and Chang, H et al (2018) Nature Communications, 9: 4433

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs													HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
Microprotrusion array delivery device for transdermal or intravessel delivery of an active agent across a biological barrier This patent covers broad MAP technology and is not drug specific. WO 2009/040548 A1	The Queen's University of Belfast	2028	-	-	G	-	-	F	-	-	-	-	-	-	-	G	G
Transdermal delivery device comprising a microneedle array and reservoir portion, containing hydrophobic active agent(s) Use of HIV drug is disclosed in the description (not claims) WO 2017/191457 A1	The Queen's University of Belfast	2037															

B5. Lyndra long-acting oral / gastric residence system

Therapeutic area	 **HIV**  **MALARIA**  **OTHER AREAS**
Name and formulations	Long-acting oral system (also known as gastric residence system) for ivermectin[32]; this technology platform may be applicable to other compounds and therapeutic areas (e.g. currently explored: HIV, Alzheimer's disease….)
Originator	Lyndra Inc (a spinout from Massachusetts Institute of Technology)
Stage of development	Preclinical
Patent Summary	• Lyndra owns several patent families on long-acting gastric residence systems comprising therapeutic agents such as ivermectin, antimalarials, antivirals, antimicrobials, antifungals etc. National phase filings have not yet been made in most cases. Expected to expire in 2036-2037 • MIT, Brigham & Women's Hospital, and Tokitae LLC own another patent family covering star shaped gastric residence structure loaded with therapeutic agents such as ARVs, ivermectin or other antimalarial agents. Patent pending in BR, CN, IN, RU and ZA. Expected expiry in 2035. Note rights to the US patents have been assigned to the US Government, NIH and DHHS. No information was found on contractual or licensing arrangement with Lyndra.

[32] Available from: http://www.malariaeradication.org/mesa-track/oral-ultra-long-acting-ivermectin-malaria-elimination

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs														HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
A multi-armed star shaped gastric residence structure loaded with therapeutic agent such as ARVs, ivermectin, or anti-malarial agent etc; the linkers would degrade over time, causing the structure to disassemble; the residence time period is at least 24 hours WO 2015/191920 A8 WO 2015/191922 A1 WO 2015/191925 A8	MIT; Brigham & Women's Hospital; Tokitae LLC (Note rights to US patents have been assigned to USG, NIH and DHHS)	2035	-	F	F	(F in RU)	-	F	-	-	-	F	-	-	-	F	F
Gastric residence system comprising therapeutic agent or its salt, such as doxycycline, ivermectin, adamantane-class of drugs (including neuropsychiatric agent for HIV-associated dementia or for viral infection) etc; the residence time period is at least about 24 hours. WO 2017/070612 A1 WO 2018/064630 A1 (specific to adamantane-class of drugs)	Lyndra Inc	2036															F
Asterisk shaped gastric residence system comprising therapeutic agent or its salt; the residence time period is at least about 24 hours. WO 2017/100367 A1	Lyndra Inc	2036										F				F	F
Gastric residence system comprising therapeutic agent or its salt, such as antivirals, antimicrobials, antifungals, antimalarials etc WO 2017/205844 A2	Lyndra Inc	2037															

B6. NanoCrystal® technology

Therapeutic area	 **HIV**  **NEUROPSYCHIATRIC**  **DIABETES**  **OTHER AREAS**
Name and formulations	NanoCrystal® technology, both oral and injectables
Originator	Élan Drug Technologies (now Alkermes)
Stage of development	NanoCrystal® has been incorporated in a number of FDA-approved medicines including Rapamune, Emend, Tricor, Megace ES, Invega Sustenna and more recently, Aristada[33]. Janssen's leading RPV-LAI formulation has also used the NanoCrystal® technology[34], though the details of the licence arrangement are not in the public domain
Patent Summary	• Our patent search revealed a large number of patents and patent applications. • According to Alkermes[35], the basic patent on NanoCrystal technology expired in 2011, however there are a large number of patents and applications covering variously (i) therapeutic categories (ii) routes/methods of administration, (iii) approaches to making and stabilizing nanoparticulates, and (iv) milling apparatus and systems exist. • Patent families are listed below to illustrate the extent of patent coverage. The families sampled show filings mainly in Europe and US or US only. However, there may be other patents on the technology as applied to specific products that are not listed below.

[33] Available from: http://www.alkermes.com/products/us-products-using-alkermes-technologies
[34] Williams, PE et al (2015) Curr Opin HIV AIDS, 10: 233-238
[35] Available from: http://investor.alkermes.com/ mobile.view?c=92211&v=202&d=3&id=aHR0c DovL2FwaS50ZW5rd2l6YXJkLmNvbS9maWxpbmcueG1sP2lwYWdlPTc3NDM5OTgmRFNFUT0xJlNFUT0xNDgmU1FERVNDPVNFQ1RJT05fUEFHRSZleHA9JnN1YnNpZD01Nw%3D%3D

Patent landscape

			LMICs														HICs	
Description **Int'l patent application publication #**	**Patent holder**	**Expected expiry date**	**ARIPO**	**Brazil**	**China**	**EAPO**	**Guatemala**	**India**	**Indonesia**	**Morocco**	**OAPI**	**South Africa**	**Thailand**	**Ukraine**	**Vietnam**	**USA**	**EPO**
Basic patent on NanoCrystal Technology covering dispersible particles (nanopartilculates) consisting of a crystalline drug substance having a surface modifier adsorbed on the surface US5145684	Elan corp.	2011	-	-	N	(N in RU)	-	-	-	-	-	-	-	-	-	N	N
A small-scale or micro media-mill and a method of milling materials or products, especially pharmaceutical prod WO0072973	Elan Pharma/ Nanosystem LLC	2020	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G
Solid dose nanoparticulate compositions comprising a synergistic combination of a polymeric surface stabilizer and dioctyl sodium sulfosuccinate WO0224163	Elan Pharma	2021	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G
Milling of materials using magnetic drive for preparing drug particles WO02098565	Elan Pharma	2022	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G
Nanoparticulate fenofibrate compositions and treatment methods relating to the approved drug Tricor US7320802	Elan Pharma	2023	-	-	-	-	-	-	-	-	-	-	-	-	-	G	-
Nanoparticulate megestrol formulations and methods of treatment relating to the approved drug Megace US9101540	Elan Pharma	2024	-	-	-	-	-	-	-	-	-	-	-	-	-	G	-
Reduction of flake-like aggregation in nanoparticulate active agent compositions WO2010138539	Alkermes	2030	-	-	-	-	-	-	-	-	-	-	-	-	-	G	G

B7. BEPO® technology

Therapeutic area	 **HIV**  **MALARIA**  **NEUROPSYCHIATRIC**  **OTHER AREAS**
Name and formulations	BEPO® technology (formerly known as MedinGelTM), subcutaneous or intra-articular injectables
Originator	MedinCell
Stage of development	Varies by product: mdc-IRM is in Phase 3 study for schizophrenia; mdc-CWM is in Phase 2 for pain and inflammation; other candidates such as ivermectin are in preclinical or formulation development
Patent Summary	• MedinCell owns a patent family on biodegradable drug delivery compositions covering the BEPO® Technology with patents granted in CN, EAPO, IN, ID, MA, ZA, UA, CN, RU, IN, ZA and pending in BR and TH with an expected expiry date in 2031. • A second patent family on biodegradable drug deliver compositions with an expected expiry date in 2033 had been granted in CN, ZA, UA and VN as is pending in BR, EAPO, IN, ID, MA and TH. • A more recent filing on a method for morselizing a biodegradable drug delivery composition and targeting synovial tissue using claimed triblock and diblock copolymers is pending in IN and EP (MA) only. The expected expiry date is 2036.

Patent landscape

Description Int'l patent application publication #	Patent holder	Expected expiry date	LMICs														HICs	
			ARIPO	Brazil	China	EAPO	Guatemala	India	Indonesia	Morocco	OAPI	South Africa	Thailand	Ukraine	Vietnam	USA	EPO
Biodegradable drug delivery composition covering BEPO® technology WO 2012/090070	MedinCell	2031 (2033 in the US)	-	F	G	G	-	G	G	G	-	G	F	G	G	G	G
Biodegradable drug delivery composition comprising triblock polymer (PLAv-PEGw-PLAx) and diblock polymer (mPEGy-PLAz) with specific range of repeat units (v, w, x, v, z) WO 2014/001904 A1 WO 2014/001905 A1	MedinCell	2033	-	F	G	F	-	F	F	F	-	G	F	G	G	F	F
Method for morselizing a biodegradable drug delivery composition and targeting synovial tissue using claimed triblock and diblock copolymers WO 2017/085561 A1	MedinCell	2036	-	-	-	-	-	F	-	F (EP)	-	-	-	-	-	-	F

Unitaid Secretariat

Global Health Campus - 5th Floor
Chemin du Pommier, 40
1218 Grand-Saconnex, Geneva
Switzerland

T +41 22 791 12 00
F +41 22 791 48 90
unitaid@who.int

www.unitaid.org

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