

Bogotá D.C agosto 04 de 2025.

Superintendencia de Industria y Comercio

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

REFERENCIA:	EXPEDIENTE NACIONAL NC2025/0004675
TITULO:	Patente PCT “MÉTODO PARA TRATAR VIH CON CABOTEGRAVIR Y RILPIVIRINA EN PACIENTES PEDIÁTRICOS” “FAMILIA”: PCT/EP2023/075264 -WO/2024/056789.
SOLICITANTE(S) DE PATENTE:	JANSSEN SCIENCES IRELAND UNLIMITED COMPANY. - VIIV HEALTHCARE UK (NO.3) LIMITED
OPOSITOR:	FUNDACIÓN IFARMA
ACTUACIÓN:	Oposición inicial, con solicitud del plazo para sustentar de conformidad a lo previsto en el artículo 42 de la Decisión 486 de 2000.

1. ENCABEZADO

Harold Humberto Silva Carvajal, identificado con C.C. No. **1.022.433.355** de Bogotá, Abogado, portador de la T.P. **391454** del Consejo Superior de la Judicatura, en mi condición de abogado apoderado de la Fundación Ifarma, mediante el presente escrito, presento oposición con solicitud de plazo la solicitud de patente del expediente: Titulada: “**MÉTODO PARA TRATAR VIH CON CABOTEGRAVIR Y RILPIVIRINA EN PACIENTES PEDIÁTRICOS**”. Presento solicitud del plazo para sustentar oposición prevista de acuerdo con lo establecido en el artículo 42 de la Decisión 486 de 2000. Todo lo anterior con el debido respeto al apoderado, a los solicitantes y a la SIC. De llegar a ser necesario, dado el caso, solicito dar aplicación a lo previsto en la circular única de la SIC, versión de marzo de 2025¹.

¹ Circular Única de la SIC, Título X:

<https://sedeelectronica.sic.gov.co/sites/default/files/normativa/Titulo%20X%20-%20Versi%C3%B3n%2010-03-2025.pdf>

“Si la oposición se presenta por intermedio de apoderado y no se aporta el poder con el escrito de oposición, o por intermedio de agente oficioso, la Superintendencia procederá a requerir el documento según lo establecido en el artículo 17 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo”.

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2. OPORTUNIDAD

La solicitud de patente objeto de oposición fue publicada en la Gaceta No. 1066 de 8 de mayo de 2025. Para lo cual los sesenta (60) días hábiles para radicar el presente escrito vencen en agosto 4 de 2025. De acuerdo con lo establecido en el artículo 42 de la Decisión 486 de 2000. Por lo tanto, esta solicitud de oposición con petición de plazo adicional es oportuna y procedente. El nuevo plazo para sustentar detalladamente la oposición sería el 30 de octubre de 2025.

3. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente NC2025/0004675, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

4. LEGITIMACIÓN

Del mismo modo, de acuerdo con lo establecido en el artículo 42 de la Decisión 486 de 2000, la **FUNDACIÓN IFARMA**, representada por JULIANA LÓPEZ MÉNDEZ, acredita su legítimo interés para actuar en razón a su amplia trayectoria como organización en la defensa y promoción de asuntos relacionados con el acceso a medicamentos, la propiedad intelectual y demás asuntos conexos. Dónde su enfoque ha sido desde su creación el acceso a medicamentos en Colombia con lo cual han contribuido al análisis y a la toma de decisiones en temas de salud pública.² Lo anterior de conformidad con el desarrollo del objeto social de la fundación:

“Contribuir al crecimiento social y económico de Colombia y de otros países, a través del trabajo especializado en la investigación, el mejoramiento y el desarrollo de los aspectos relativos a la formulación y ejecución de políticas, la administración, la gestión y el uso adecuado de los medicamentos en particular y la salud y la seguridad social en general. La fundación, para cumplir con su objeto social, utilizara el conocimiento, la experiencia y la experticia de profesionales nacionales e internacionales ampliamente acreditados. Buscará recopilar las experiencias existentes nacional e internacionalmente en los temas de su objeto social. La fundación igualmente buscará actuar como un soporte del sistema de seguridad social en salud y de la prestación de servicios de salud, especialmente pero no exclusivamente, en los temas relativos a la oferta suficiente y competitiva de los recursos terapéuticos que la población requiere. Ello sin incluir en su objeto social la prestación de servicios de salud. Igualmente fomentará el debate, el análisis y la investigación en todos los temas relativos a su objeto, con el propósito de generar e innovar líneas de acción y

² <https://www.ifarma.org/historia.html>

desarrollo, para lo cual buscará y promoverá la acción conjunta con los organismos nacionales e internacionales que tienen similares objetivos. La fundación utilizará los medios que estime convenientes para comunicar y difundir el conocimiento generado por su accionar. La fundación podrá desarrollar planes, proyectos y programas de investigación, asistencia técnica, asesoría y consultoría, e innovación tecnológica en los campos de la salud, la seguridad social y el desarrollo social. (...)”

Sobre la acreditación del legítimo interés asociado a la debida observancia de la normatividad aplicable por parte de la administración, es pertinente citar a Xavier Gómez Velasco, que, estudiando la figura del legítimo interés para oponerse a una solicitud de patente de invención a la luz de la jurisprudencia comunitaria andina, señala que:

“el fundamento de una oposición no se limita exclusivamente a la titularidad de un derecho subjetivo, como sería el caso del solicitante previo del privilegio de patente o el titular de una patente previamente otorgada, sino que se extiende, en principio, a cualquier norma jurídica que regule la actuación prescrita para que la Administración otorgue el derecho solicitado...”.

Nuestro interés como persona jurídica especializada en estos asuntos, también tiene sustento, entre otros, en pronunciamientos del Tribunal Andino de Justicia – TJCA tales como el Proceso 69-IP-2005, GOAC No. 1304, de 7 de marzo de 2006, pp. 10-11, del cual cito un extracto pertinente, que deja en claro que las personas jurídicas pueden presentar oposiciones sin que sea necesario que sean competidores de la solicitante de la patente. A continuación, transcribo el apartado del pronunciamiento:

*“De conformidad con el artículo 25, cuya interpretación ha sido solicitada, dentro de los treinta días hábiles siguientes a la publicación, quien tenga interés, podrá presentar observaciones fundamentadas que puedan desvirtuar la patentabilidad de la invención. **Se entiende que tienen legítimo interés para presentar observaciones:** el titular de una patente ya registrada, el titular de una solicitud de patente que goce de prioridad, **cualquier persona natural o jurídica** que considere que una patente es contraria al orden público, a la moral o a las buenas costumbres o que sean evidentemente contrarias a la salud o a la vida de las personas o de los animales, a la preservación de los vegetales o a la preservación del medio ambiente. Igualmente se podrá presentar observaciones cuando se intente patentar especies y razas animales y procedimientos esencialmente biológicos para su obtención, invenciones sobre las materias que componen el cuerpo humano y sobre la identidad genética del mismo y las invenciones relativas a productos farmacéuticos que figuren en la lista de medicamentos esenciales de la Organización Mundial de la Salud”.* Proceso 69-IP-2005, GOAC No. 1304, de 7 de marzo de 2006, pp. 10-11.” (Resaltado para la presente actuación)

Como se ve, el TJCAN, reconociendo la importancia que tienen las patentes para el orden público, la salud y la vida de las personas y los animales, ha determinado que el interés legítimo en la oposición de una patente puede encontrar sus argumentos, no solamente en el ámbito de lo privado y lo directamente económico, sino también en la protección de los valores y bienes de carácter público, como lo es la vida y la salud de las personas.

Consecuentemente, en caso de que la SIC considere apartarse de esos lineamientos del Tribunal andino, estaría desconociendo la jurisprudencia del Tribunal. En tal caso, solicito que la SIC solicite una interpretación al Tribunal Andino. (Sobre la legitimación por activa de las oficinas de propiedad industrial como consultantes pueden consultarse: 105-IP-2014, 121-IP-2014, 242-IP-2015 etc).

Sumado a lo anterior, existen argumentos dentro del ordenamiento jurídico colombiano que van en absoluta armonía con el fragmento previamente citado, como lo es el caso de la Resolución 3676 de 2025, dónde en el artículo 1.1.14. evidencia que el sistema de propiedad industrial colombiano busca que intervengan varios tipos de personas naturales o jurídicas, dónde resaltamos el literal d.³ que expresa:

“Entidades sin ánimo de lucro inscritas en la Cámara de Comercio y cuyo objeto consista en el desarrollo de, investigación científica y tecnológica.”

Es aquí donde cobra aún más relevancia la participación de la Fundación IFarma en la presente oposición, puesto que como se dejó claro previamente, el objeto social de la Fundación está íntimamente relacionado puesto que es una persona jurídica con amplia trayectoria nacional e internacional en investigación en el campo de los medicamentos y varios campos de la Salud.

Por otro lado, otro fundamento relevante que reviste de legitimidad la oposición es el el Plan Nacional de Desarrollo, en la página 140, en el título 9 “Democratización del conocimiento: aprovechamiento de la propiedad intelectual y reconocimiento de los sabres tradicionales”⁴ dónde se menciona que en Colombia se buscará un equilibrio entre las necesidades e intereses de los titulares y usuarios de la propiedad intelectual, dónde también recobra una alta importancia la Fundación Ifarma a través de su objeto social y trayectoria, puesto que esta persona jurídica que se ha preocupado íntegramente sobre el equilibrio entre los intereses de los titulares, los usuarios de la propiedad intelectual y el fin social de la misma que no es más que todas las personas puedan gozar del desarrollo de la

3

<https://sedeelectronica.sic.gov.co/sites/default/files/normativa/RESOLUCION%203676%20DEL%2007%20DE%20FEBRERO%20DE%202025-MODIFICA%20TASAS%202025.pdf>

⁴ <https://colaboracion.dnp.gov.co/CDT/Prensa/Publicaciones/plan-nacional-de-desarrollo-2022-2026-colombia-potencia-mundial-de-la-vida.pdf>

tecnología que cumpla con todos los requisitos técnico legales para ser considerado como una creación patentable.

Por otro lado, en lo que se refiere a la lista de medicamentos esenciales de la OMS (EML-OMS), citada por el TJCAN, la siguiente lista está prevista para ser publicada en el 2025. Puesto que el dolutegravir, que al igual que el cabotegravir, es un inhibidor de la integrasa del VIH y ya se encuentra en la EML-OMS, es posible que cabotegravir llegue a ser incorporado. Otro factor que aporta en esta dirección es el hecho de que está surgiendo evidencia y ha tenido aprobaciones sanitarias relativamente recientes. Finalmente, puesto que el cabotegravir tiene una vida media es más apto para formulaciones de liberación prolongada, lo que representa una ventaja frente a las formulaciones orales de toma diaria.

Adicionalmente, autores como Natalia Lamprea⁵ profesora de la Universidad Externado y Oscar Lizarazo⁶ de la Universidad Nacional de Colombia, han indicado la facilidad para presentar oposiciones en otros países, en contraste con Colombia

“Este sistema de oposiciones deja a los ciudadanos colombianos en desventaja frente a la oportunidad que se tiene en el trámite de patentes en otras jurisdicciones, por ejemplo, ante la EPO cualquier persona puede presentar una oposición, en cualquier momento del trámite, sin costo alguno, se puede hacer en línea, e incluso, de manera anónima.”

En sentido similar, desde el DNP además de la protección de la innovación, en paralelo, se está impulsando el uso del dominio público:

Chalela Naffah, S., Blanco Cruz, L., Mejía Nieto, C., Carvajal, L.F. y Ferreira, W.A. 2025."Dominio público para el cierre de brechas tecnológicas y de innovación en Colombia." Revista La Propiedad Inmaterial. (Universidad Externado) 39 (feb. 2025), 245–271.DOI :<https://doi.org/10.18601/16571959.n39.09> .

Finalmente, documentos como el Marco Normativo para el Fomento del Desarrollo de Patentes Universitarias (Parlamento Andino, 2020) también reconocen la importancia del dominio público. Ciertamente las oposiciones son relevantes para preservar dicho dominio público.

⁵ LAMPREA BERMUDEZ Natalia, LIZARAZO CORTES Oscar Andres, BUITRAGO HURTADO Gustavo, "Propiedad industrial en el contexto universitario: el caso de la Universidad Nacional de Colombia" en el Libro: **CREAR Y PROTEGER Propiedad intelectual y transferencia de tecnología en la universidad**. En: Colombia ISBN: 978-958-783-301-0 Ed: Empresa Editorial Universidad Nacional De Colombia, v., p.13 - 72 1, diciembre 2017

⁶ Ibidem

MATERIA NO PATENTABLE

5. METODOS DE TRATAMIENTO

Las reivindicaciones 1 a 16 se refieren a métodos de tratamiento. Esta es materia no patentable en Colombia, la Comunidad Andina, de acuerdo con lo establecido en los artículos 15, 20, literal d, y 21 de la Decisión 486 de 2000, y la Guía Manual Patentes CAN de agosto 2022. Pese a la creatividad o habilidad de quienes redactan las reivindicaciones de las solicitudes de patentes.

En efecto, la reivindicación independiente No.1, de la versión del abril 11 de 2025 presentada en Colombia expresa:

Ibidem

“1. Un método para tratar la infección por VIH, el método caracterizado porque comprende: Un método para tratar la infección por VIH, el método caracterizado porque comprende: administrar a un humano que lo necesite una dosis de carga que comprende (i) una inyección intramuscular de cabotegravir o una sal farmacéuticamente aceptable del mismo y (ii) una inyección intramuscular de rilpivirina o una sal farmacéuticamente aceptable de la misma; y posteriormente, administrar una o más dosis de mantenimiento que comprenden (i) una inyección intramuscular de cabotegravir o una sal farmacéuticamente aceptable del mismo y (ii) una inyección intramuscular de rilpivirina o una sal farmacéuticamente aceptable de la misma; en donde el humano tiene de 2 años de edad a menos de 12 años de edad.” (negrilla subrayado fuera del texto original).” (Resaltado para la presente actuación)

La redacción de las reivindicaciones, junto con la interpretación literal del artículo 20, literal d) de la Decisión 486, demuestra de forma inequívoca que el uso de verbos como 'tratar' y/o 'administrar' corresponde claramente a un método de tratamiento.

En las reivindicaciones dependientes subsiguientes la solicitante se refiere al mismo método de tratamiento, donde a modo de ejemplo citamos algunos apartados como ejemplo que respaldan nuestra afirmación:

“2. El método de conformidad con la reivindicación 1, caracterizado porque el humano pesa de 10 kg a menos de 40 kg, preferentemente de 10 kg a 34.9 kg.

3. El método de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado porque el cabotegravir o una sal farmacéuticamente aceptable del mismo se administra como una inyección intramuscular de 50 mg a 600 mg.

4. El método de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado porque la una o más dosis de mantenimiento se administran una vez cada 4 semanas \pm 7 días o con menos frecuencia.” (Resaltado para la presente actuación)

11. Un método para tratar la infección por VIH, el método caracterizado porque Comprende: **administrar** a un humano que lo necesite una dosis de carga que comprende (i) una inyección intramuscular de cabotegravir o una sal farmacéuticamente aceptable del mismo y (ii) una inyección intramuscular de rilpivirina o una sal farmacéuticamente aceptable de la misma; (...).” (Resaltado para la presente actuación).

6. USOS Y SEGUNDOS USOS

Las reivindicaciones 12 a 16 de la solicitud de patente se refieren a usos. Para el presente caso, resulta pertinente traer a colación el sustento legal que impide que estos usos sean susceptibles de patente, como es el caso del artículo 14 y 21 de la Decisión 486 de 2000.

Respecto de los usos:

“Artículo 14.- Los Países Miembros otorgarán patentes para las invenciones, sean de **producto o de procedimiento,** en todos los campos de la tecnología, siempre que **sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.**” (Resaltado para la presente actuación)

Como identificamos en el anterior artículo, en un sentido literal de la norma, podemos evidenciar que las categorías admitidas o aceptadas son para productos o procedimiento, pero no los “usos”.

En el presente caso se evidencia que en la forma que está formulada la solicitud de patentes y sus reivindicaciones se está tratando de proteger un uso de unos compuestos (CAB+RIL), lo que, a la luz del artículo ya citado, no puede ser interpretado ni como un producto ni como un proceso.

Respecto de los segundos usos:

“Artículo 21.- **Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica,** de conformidad con el artículo 16 de la presente Decisión, **no serán objeto de nueva patente,** por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial.” (Resaltado para la presente actuación)

Para el caso de los segundos usos, la presente solicitud versa sobre el uso de principios activos ya conocidos (CAB, RIL), e incluso de una combinación conocida/divulgada (CAB+RIL), es decir ya está dentro del estado de la técnica tal como se evidencia en el punto 5 del presente escrito titulado “nivel inventivo”, divulgada y utilizada para el mismo fin en personas a partir de 12 años. La única diferencia de esta solicitud con el estado de la técnica es que es aplicado en niños de 2 a 12 años, por lo que estaríamos frente a un caso de un “segundo uso”, por lo que estamos frente una situación dónde se debe aplicar el artículo 21 de la Decisión citada previamente y no debe ser concedida la patente.

Respaldando las dos situaciones expuestas previamente, el Manual Andino para el examen de patentes primera edición del 12 de agosto de 2022, en el punto 4.6.9. expresa:

“4.6.9 Reivindicaciones caracterizadas por un uso.

*Las reivindicaciones que en el preámbulo se refieren a un producto o procedimiento, pero la parte característica describe únicamente el uso de dicho producto o procedimiento, no son objeto de patente debido a que están referidas a un uso, no patentable según la interpretación del Tribunal Andino en el **Proceso 89-AI-2000**, que no reconoce a los usos como materia patentable. De la misma manera, un producto o un procedimiento no será objeto de patente cuando dicho producto o procedimiento fuese conocido en el estado de la técnica y se le atribuyera un uso diferente al divulgado originalmente.*

*Cabe señalar que si el preámbulo de la reivindicación señala **“El uso de un determinado producto o procedimiento”** tampoco será objeto de patente, de acuerdo con la interpretación antes señalada (véase usos en el Apartado 7.4 del Capítulo III). Siendo así, en el caso de los segundos usos, ante este tipo de reivindicaciones caracterizadas por un uso diferente al conocido inicialmente, la oficina nacional competente debe notificar al solicitante que su invención no es aceptada porque los usos no son patentables de acuerdo con la jurisprudencia comunitaria andina interpretativa de la Decisión 486, y demostrar que el producto o procedimiento está comprendido en el estado de la técnica, por lo que cae dentro de la excepción del Artículo 21. Por lo tanto, se debe hacer el respectivo análisis de novedad, junto con la objeción relativa al uso.”* (Resaltado para la presente actuación).

En un mismo sentido, el Tribunal Andino de Justicia de la Comunidad Andina, dentro del proceso identificado con el número 260-IP-2017⁷, en los párrafos 5.1 a 5.4 aborda el tema

⁷ https://www.comunidadandina.org/DocOficialesFiles/Procesos/260_IP_2017.pdf

de la no patentabilidad de los segundos usos, haciendo referencia al artículo 21, previamente citado dónde hace referencia otros fallos anteriores como es el caso del proceso 85-IP-2009 dónde expresa en el punto 5.3. que la norma referenciada excluye la posibilidad del patentamiento de productos o procedimientos que ya tengan una patente concedida, así sea “*por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial*”. Y además especifica:

“El pretender obtener los beneficios que otorga la patente para un segundo uso de invenciones previamente patentadas, con el argumento de que es un uso distinto al originalmente reconocido por la patente inicial, no implica que se satisfaga el requisito esencial de novedad, toda vez que, al existir una patente previa del invento original, éste ya se encuentra en el estado de la técnica.”

(...) Al Tribunal le resulta claro, que sólo aquello que es nuevo puede ser protegido por una patente, principio incorporado al derecho comunitario con el objeto de incentivar la investigación; por lo que conceder protección del Estado a productos o procedimientos carentes de novedad, resultaría atentatorio tanto al propósito señalado como a la misma función social asignada al Derecho de Propiedad Industrial.”

(...) el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial, debe ser necesariamente entendido como la consagración en el artículo 21 de la Decisión 486, del principio de que no podrá reclamarse patente para usos distintos del invento o de la invención comprendidos y protegidos ya por la patente inicial o primigenia; regla prohibitiva para el otorgamiento de patentes de invención, que este Tribunal considera como parte de los requisitos establecidos por la referida Decisión. (negrilla y subrayado fuera del texto original).”

Adicionalmente, este no es el único apartado en que el Manual Andino para el examen de patentes se refiere a las reivindicaciones de uso. Al respecto el punto 7.4 también expresa que en el marco andino **las reivindicaciones de usos** y de segundos usos no son objeto de patente ya que se ha interpretado que estos no están comprendidos dentro de materia patentable conforme al artículo 17 previamente citado, dónde encontramos la sentencia 89-AI -2000 del TJCA.

7. NIVEL INVENTIVO.

Según la establecido en el artículo 16 de la Decisión 486 de 2000, recordamos el nivel inventivo como la circunstancia que, para una persona del oficio normalmente versada en

la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.

Este concepto ha sido reafirmado en múltiples ocasiones por distintas corporaciones como lo es el Consejo de Estado y el Tribunal Andino de Justicia. Al respecto el Tribunal de Cierre de la Jurisdicción Contenciosa Administrativa, en un fallo del 26 de enero de 2023, identificado con el radicado 1100103-24-000-2008-00089-00, demandante: BAYER HEALTHCARE AG, demandando: SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, señala:

“el requisito de nivel inventivo presupone que la invención represente un salto cualitativo en relación con la técnica existente y que, además de no ser obvia para una persona del oficio normalmente versada en la materia técnica, sea siempre el resultado de una actividad creativa del hombre, lo que no impide que se alcance la regla técnica propuesta utilizando procedimientos o métodos comunes o ya conocidos en el área técnica correspondiente, aunque tampoco debe constituir el resultado de derivaciones evidentes o elementales de lo ya existente para un experto medio en esa materia técnica.”

Una composición novedosa de AB donde A y B son conocidos de manera independiente, será inventiva si existe un efecto inesperado. Si el efecto se reduce a la suma de los efectos de A y B, no habrá nivel inventivo...”

Así las cosas, según el análisis realizado, las reivindicaciones 1 a 16 no tienen nivel inventivo. Lo anterior, según el documento “24.11.2023 (IB/373) International Preliminary Report on Patentability Chapter I”⁸ generado en el marco del procedimiento PCT.

Box No. V Reasoned statement under Rule 43bis.1[a][i] with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement			
1. Statement:			
Novelty (N)	Claims	1-16	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

FUENTE: OMPI-PatentScope. **Opinión escrita de la Administración encargada de la**

⁸ <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024056789>

búsqueda internacional. (WOSA: “Written Opinion of the International Searching Authority”)⁹

La fecha de prioridad de la solicitud de patente objeto de esta oposición es septiembre 16 de 2022, # de prioridad 63/407,425. En consecuencia, son relevantes los siguientes documentos del estado de la técnica publicados con anterioridad, como pruebas de la falta de altura inventiva:¹⁰

D	TITULOS ANTERIORIDADES.	FECHAS PUBLICACIÓN ANTERIORES A # PRIORIDAD (mes/Año)	
D1	Viiv Healthcare: "ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS", , 9 August 2021 (2021-08-09), XP055978246	08/2021	
D2	OVERTON EDGAR T ET AL: "Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study", THE LANCET, ELSEVIER, AMSTERDAM, NL, vol. 396, no. 10267, 9 December 2020 (2020-12-09), pages 1994-2005, XP086415462	12/2020	
D3	MURRAY MIRANDA ET AL: "Patient-Reported Outcomes in ATLAS and FLAIR Participants on Long-Acting Regimens of Cabotegravir and Rilpivirine Over 48 Weeks", AIDS AND BEHAVIOR, SPRINGER US, BOSTON, vol. 24, no. 12, 23 May 2020 (2020-05-23), pages 3533-3544, XP037295286	05/2020	
D4	THOUVILLE PAUL ET AL: "Long-acting antiretrovirals: a new era for the management and prevention of HIV infection", JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY, vol. 77, no. 2, 2 February 2022 (2022-02-02), pages 290-302, XP093027089	02/2020	PDF adjunto
D5	RAJOLI RAJITH K. R. ET AL: "In Silico Dose Prediction for Long-Acting Rilpivirine and Cabotegravir Administration to Children and Adolescents", CLINICAL PHARMACOKINETICS., vol. 57, no. 2, 24 May 2017 (2017-05-24), pages 255-266, XP093105015	05/2017	PDF Adjunto
D6	Anonymous: "U.S. FDA Approves CABENUVA (cabotegravir and rilpivirine) for Adolescents, Expanding the Indication of the First and Only Complete Long-Acting Injectable HIV Regimen",,, 29 March 2022 (2022-03-29), XP093105436	03/2022	PDF Adjunto

⁹ <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024056789>

¹⁰ <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024056789>

Respecto a los documentos señalados en el cuadro anterior, la Oficina de Patentes de Europa (EPA) señala en OMPI-PatentScope¹¹ **Opinión escrita de la Administración encargada de la búsqueda internacional**. (WOSA: “Written Opinion of the International Searching Authority”):

- “Varios documentos de la técnica anterior describen el tratamiento del VIH con cabotegravir intramuscular de acción prolongada y rilpivirina intramuscular de acción prolongada. D1-D4 incluso divulgan el mismo régimen de dosificación de las reivindicaciones independientes 1 y 11 actuales, es decir, la administración de una dosis de carga de cabotegravir intramuscular y rilpivirina intramuscular, seguida de dosis de mantenimiento de cabotegravir intramuscular y rilpivirina intramuscular, cada 4 u 8 semanas. La dosis inicial oral opcional de cabotegravir y rilpivirina antes de la dosis de carga, así como las cantidades iguales o superpuestas de los compuestos reivindicados, se describen en D1 y en los estudios descritos en D2-D4.
- La diferencia con respecto a las reivindicaciones actuales reside en que la combinación y el régimen de dosificación reivindicados deben administrarse a niños de entre 2 y menos de 12 años.
- La presente solicitud divulga un protocolo de un ensayo clínico que se llevará a cabo en el grupo de pacientes reivindicado. No se presentan resultados, y mucho menos sorprendentes o inesperados.
- El problema subyacente a la presente invención puede formularse como la provisión de un tratamiento adecuado para pacientes con VIH de entre 2 y menos de 12 años.
- Basándose en la eficacia, la farmacocinética y la farmacodinámica de un medicamento conocido para adultos, la búsqueda de una dosis y un régimen de dosificación adecuados para pacientes pediátricos se considera que entra dentro de las medidas de diseño comunes que un experto en la materia investigaría sin necesidad de un paso inventivo.
- Además, D5 ya divulga un modelo de predicción de dosis *in silico* para la misma combinación y tipo de formulación para el tratamiento de niños y adolescentes con VIH. Además, según D6, se ha aprobado una combinación de cabotegravir y rilpivirina inyectables de acción prolongada para niños de 12 años o más y con un peso mínimo de

¹¹ <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024056789>

35 kg. Por lo tanto, al menos para los niños en el rango superior reivindicado y con un peso similar, se aplicarían consideraciones similares.

- Por lo tanto, se considera que el objeto reivindicado es obvio con respecto al estado de la técnica citado y que la solicitud no aporta ninguna contribución al estado de la técnica." (Resaltado para la presente actuación)

Adicionalmente traemos a colación la tabla 2 de D4 que resume los principales ensayos clínicos realizados hasta la fecha de dicho estudio con cabotegravir/rilpivirina en personas con VIH o como profilaxis preexposición (PrEP).

Table 2.

Main clinical trials of LAI CAB/RPV for the treatment of PLWH and for PrEP

Trial	Phase	n	Arms	Results	Ref.
Treatment					
LATTE-2	IIb	286	LAI CAB (400 mg) + LAI RPV (600 mg) q4w LAI CAB (600 mg) + LAI RPV (900 mg) q8w CAB (30 mg) + ABC/3TC (600/300 mg) q24h	At Week 96, viral suppression: q4w: 87% (100 of 115 patients) q8w: 94% (108 of 115 patients) oral: 84% (47 of 56 patients)	41
FLAIR	III	566	LAI CAB (400 mg) + LAI RPV (600 mg) q4w DTG/ABC/3TC (50/600/300 mg) q24h	At Week 48, viral suppression: LAI: 93.6% (265 of 283 patients) oral: 93.3% (264 of 283 patients)	30
ATLAS	III	616	LAI CAB (400 mg) + LAI RPV (600 mg) q4w 2 NRTIs + 1 INSTI, NNRTI or boosted PI or unboosted ATV	At Week 48, viral suppression: LAI: 92.5% (285 of 308 patients) oral: 95.5% (294 of 308 patients)	31
ATLAS-2M	IIIb	1045	LAI CAB (400 mg) + LAI RPV (600 mg) q4w LAI CAB (600 mg) + LAI RPV (900 mg) q8w	At Week 48, viral suppression: q4w: 93% (489 of 523 patients) q8w: 94% (492 of 522 patients)	13
PrEP					
HPTN083 ^a	IIb/III	4566	LAI CAB (600 mg) q8w TDF/FTC (300/200 mg) q24h	LAI CAB: Incidence rate 0.41% (13 HIV infections) TDF/FTC: Incidence rate 1.22% (39 HIV infections)	42,43
HPTN084 ^a	III	3224	LAI CAB (600 mg) q8w TDF/FTC (300/200 mg) q24h	LAI CAB: Incidence rate 0.21% (4 HIV infections) TDF/FTC: Incidence rate 1.79% (34 HIV infections)	44,45

CAB, cabotegravir; RPV, rilpivirine; ABC, abacavir; 3TC, lamivudine; DTG, dolutegravir; ATV, atazanavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; n, number of participants assigned to randomization; q4w, every 4 weeks; q8w, every 8 weeks; q24h, once daily.

^a Ongoing studies.

D4 también informa que:

- “Hasta ahora, el cabotegravir y la rilpivirina han sido los fármacos más estudiados para el **tratamiento antirretroviral inyectable de larga duración (LAI-ART)**, tanto en monoterapia como en combinación, debido a su prolongado tiempo de vida media y su

alta potencia antirretroviral intrínseca. (Página 291). (Resaltado para la presente actuación).

- “En los estudios clínicos de fase III, la primera combinación dual LAI-ART de cabotegravir y rilpivirina se ha administrado tras un periodo preliminar de 4 semanas de tratamiento oral inicial (30 mg de cabotegravir más 25 mg de rilpivirina, una vez al día), con el fin de evaluar la tolerabilidad del fármaco, seguido de inyecciones intramusculares de cada fármaco en los músculos glúteos. Los regímenes mejor investigados hasta ahora consisten en inyecciones intramusculares de 2 o 3 ml, con intervalos de dosificación de 4 u 8 semanas, respectivamente.” (Página 293).
- “Los estudios FLAIR y ATLAS de fase III compararon el régimen de LAI cabotegravir/rilpivirina con los regímenes orales estándar de tres fármacos diarios. [30,31] Tras el periodo inicial oral, los participantes recibieron una dosis de carga inicial de LAI cabotegravir/rilpivirina IM de 600/900 mg, seguida de cabotegravir/rilpivirina LAI de 400/600 mg cada 4 semanas durante la fase de mantenimiento.” (Página 293).
- “Actualmente se están llevando a cabo estudios para investigar el cabotegravir/rilpivirina LAI en diversas situaciones y diferentes subpoblaciones. Por ejemplo, el estudio «Más opciones para niños y adolescentes» (MOCHA) tiene como objetivo establecer la dosis óptima y evaluar la seguridad, la tolerabilidad, la aceptabilidad y los perfiles farmacocinéticos del cabotegravir oral y de cabotegravir/rilpivirina LAI (solos o en combinación) en pacientes con supresión virológica de entre 12 y 18 años. Además, el ensayo de fase III LATITUDE, actualmente en curso, compara la eficacia, la seguridad y la durabilidad del cabotegravir/rilpivirina LAI administrado cada 4 semanas con un régimen estándar diario de tres fármacos en pacientes con antecedentes de adherencia subóptima al tratamiento oral y al control de su infección por VIH.[47]

Cabe destacar que, al igual que en el ensayo SOLAR en curso,[48] la decisión sobre el periodo de inicio oral queda ahora a la entera discreción de los pacientes participantes. De hecho, la necesidad real de la fase de inicio oral es actualmente objeto de debate.[49]” (Página 293)

En conclusión, de D4 evidencia lo siguiente:

- El régimen de inyecciones intramusculares de CAB+RIL cada 4 semanas fueron divulgados con anterioridad, incluyendo dosis inicial de carga de CAB/RIL 600/900 mg seguido de dosis de mantenimiento CAB/ RIL 400/600 mg.
- Que dichos estudios incluyen la administración por vía oral dosis iniciales de RIL + CAB (mencionado en reivindicaciones de solicitud de Colombia 7-10, 12). Incluso menciona que la necesidad/utilidad de la administración inicial oral está siendo debatida.
- Que existen estudios en curso que investigan el régimen en otras subpoblaciones, como por ejemplo en personas de entre 12 y 18 años (estudio MOCHA), **lo que sugiere el estudio del régimen en otras poblaciones, como niños.**

Al respecto podemos decir, como se mencionó atrás al citar el WOSA, que buscar una dosis y un régimen de administración adecuados para pacientes pediátricos es considerado una práctica de rutina para un experto en la materia y no involucra un paso inventivo.

Ahora, por parte de D5 y D6, como se mencionó atrás al citar el WOSA:

- El D5 divulga un modelo de predicción de dosis *in silico* para la misma combinación y tipo de formulación para el tratamiento de niños y adolescentes con VIH.
- Según el D6, la agencia sanitaria de EE. UU., la FDA, ha aprobado una combinación de cabotegravir inyectable de acción prolongada y rilpivirina para niños de 12 años o más con un peso de al menos 35 kg, basado en el ensayo MOCHA.

Ahora, por parte de D5 (Rajoli et al. 2017) es pertinente mencionar que es un artículo de investigación que simula posibles estrategias de dosificación para las formulaciones inyectables de acción prolongada existentes de cabotegravir y rilpivirina en niños y adolescentes (de 3 a 18 años), utilizando modelos farmacocinéticos. Los resultados indican que las dosis requeridas de CAB+RIL fueron proporcionales al peso, y que incluyeron dosis de carga intramuscular y la dosis de mantenimiento de cabotegravir entre 200 y 600 mg y entre 100 y 250 mg, respectivamente; y para rilpivirina, entre 250 y 550 mg y entre 150 y 500 mg, respectivamente, en distintos grupos de peso de niños con un rango de 15 a 70 kg. De modo importante, **D5 concluye que las predicciones del estudio pueden informar dosis de referencia para ensayos clínicos pediátricos para varias categorías de peso.**

De modo que el estado de la técnica comprende dosis de referencia para estudios pediátricos, reforzando la falta de actividad inventiva o ausencia de nivel inventivo en buscar una dosis y régimen adecuado de CAB+RIL intramuscular cada 4 semanas para niños de entre 2 y 12 años. Además, la solicitud únicamente proporciona un protocolo de ensayo

clínico para evaluar dicho régimen. No se presentan resultados, como lo informa también WOSA.

Finalmente, como referencia tenemos el número WO2019/016732 como estado de la técnica (Reivindicación 1: Un método para tratar el VIH que comprende la administración intramuscular una vez cada 4 semanas o con menor frecuencia de una combinación de cabotegravir o una sal farmacéuticamente aceptable del mismo y rilpivirina o una sal farmacéuticamente aceptable de la misma). Sin embargo, no dice nada diferente, no hay ningún salto cualitativo como lo menciona el Consejo de Estado en la Sentencia ya referenciada en la parte inicial del presente punto. Como consecuencia el examinador no tendría más opción que declarar la negación de la patente al no reunir íntegramente los tres requisitos de patentabilidad, especialmente el nivel inventivo aquí abordado respecto de las reivindicaciones 1 a 16.

Por todo lo anterior, las reivindicaciones no tienen altura inventiva. Adicionalmente, documentos de doctrina jurídica como los del Profesor Carlos M. Correa señalan:

*“Algunas solicitudes de patente reivindican invenciones que consisten en la dosis para la administración a pacientes de un producto existente, incluidas las dosis pediátricas. Aunque se redactan como reivindicaciones de producto, estas reivindicaciones tienen el mismo efecto que las reivindicaciones sobre métodos de tratamiento médico 40, ya que el objeto no es un producto o proceso, sino la forma en que un producto se utiliza terapéuticamente”.*¹²

En sentido similar, PNUD, UNDP-ONU: ***“Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective”***¹³

“Dosis: Las reivindicaciones sobre la dosis de un fármaco no cumplen con el requisito de aplicabilidad industrial. Deben considerarse un método de tratamiento médico, a pesar de su apariencia, por ejemplo, como una reivindicación de composición (o combinación).”

8. FALTA DE CLARIDAD. Artículo 30 DA 486/2000.

Las reivindicaciones no tienen suficiente claridad como indica WOSA-PCT:

“Aunque las reivindicaciones 13 a 16 se han redactado como reivindicaciones independientes separadas, parecen referirse efectivamente al mismo objeto y diferir entre sí únicamente en lo que respecta a la terminología utilizada para las características de dicho

¹² <https://ipaccessmeds.southcentre.int/wp-content/uploads/2019/07/ICTSD-WHO-WorkingPaper.pdf>

¹³ <https://www.undp.org/publications/guidelines-examination-patent-applications-relating-pharmaceuticals>

objeto. Por lo tanto, las reivindicaciones mencionadas carecen de concisión y, como tales, no cumplen los requisitos del artículo 6 del PCT.

Además, la reivindicación 11 comprende todas las características de la reivindicación 1 y, por lo tanto, no está formulada adecuadamente como una reivindicación dependiente de esta última (regla 6.4 del PCT)."

Esa falta de claridad implica que la solicitud de patente incumple la Decisión 486/2000 artículo 30 que establece de modo obligatorio:

*"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. **Deben ser claras y concisas y estar enteramente sustentadas por la descripción (...)**".*

9. INSUFICIENCIA DE LA DESCRIPCIÓN, ART 28 DA 486/2000.

Al enunciar un excesivamente amplio número de rangos de las formulaciones, la patente incumple lo establecido en el artículo 28

"Artículo 28.- La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información (...)

*e) **una descripción de la mejor manera** conocida por el solicitante **para ejecutar o llevar a la práctica la invención**, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y, (...)"*

10. OTROS ARGUMENTOS.

9.1 Evergreening. - Perennidad o Reverdecimiento de Patentes. Alargamiento de exclusividad.

Los solicitantes de la patente objeto de esta oposición ViiV y/o Janssen tienen más solicitudes de patente y patentes concedidas en Colombia. Algunas (al parecer) revelan moléculas iguales o similares. Sin perjuicio de un análisis más detallado.

Expediente No.	Título	Figura Característica	Fecha de presentación	Estado (s)	Titular
14085830 Fase nacional de la	COMPOSICIONES FARMACÉUTICAS QUE COMPRENDEN		26 Jul. 2012	Concedido hasta 2031) En febrero de 2015, Resolución 8099	VIIV HEALTHCARE COMPANY

Expediente No.	Título	Figura Característica	Fecha de presentación	Estado (s)	Titular
"familiar" PCT/US2011/022219 WO/2011/094150	DOLUTEGRAVIR Y RILPIVIRINA CON ACTIVIDAD ANTIVIRAL PARA VIH			Opositor Tito Noe Parra apoderado de Lafranco presentó recurso de reposición. En octubre de 2015 SIC confirmó concesión firmó la resolución el entonces superintendente Pablo Felipe Robledo	

FUENTE: Consulta en SIPI-SIC el 3107/2025.

Puede haber más solicitudes y patentes que no mencionen los nombres genéricos. Es decir, las DCI-Denominación Común Internacional, o los INN International Non Proprietary Name: Rilpivirina y/o Cabotegravir pero que materialmente incluyan una o las dos moléculas

De otro lado la SIC había negado (acertadamente) en 2012 y confirmado en 2013 la negación de otra patente de **Janssen** relacionada con Rilpivirina:

"CLORHIDRATO DE 4-[[4-[[4-(2-CIANOETENIL)-2,6-DIMETIL]AMINO]-2-PIRIMIDINIL]AMINO]BENZONITRILIO"

Ese título, o "nombre químico largo" en **formato o nomenclatura sistemática IUPAC** molécula o formula **corresponde a la Rilpivirina**, así en ese entonces no se mencionó el nombre genérico, DCI o INN.

Además, las patentes **07115501** (parental) y **07115501A** (divisional) ya revelan y protegen **Cabotegravir**. Además de Dolutegravir:

07115501 DERIVADO DE CARBAMOILPIRIDONA POLICÍCLICO QUE TIENE ACTIVIDAD INHIBIDORA DE LA INTEGRASA DEL VIH

07115501A DERIVADO DE CARBAMOILPIRIDONA POLICICLICO QUE TIENE ACTIVIDAD INHIBIDORA DE LA INTEGRASA DEL VIH

Título actualizado en la resolución de concesión: "DERIVADOS DE PIRIDO-PIRAZINA Y COMPOSICIONES QUE LOS CONTIENEN ÚTILES COMO INHIBIDORES DE LA INTEGRASA DEL VIH"

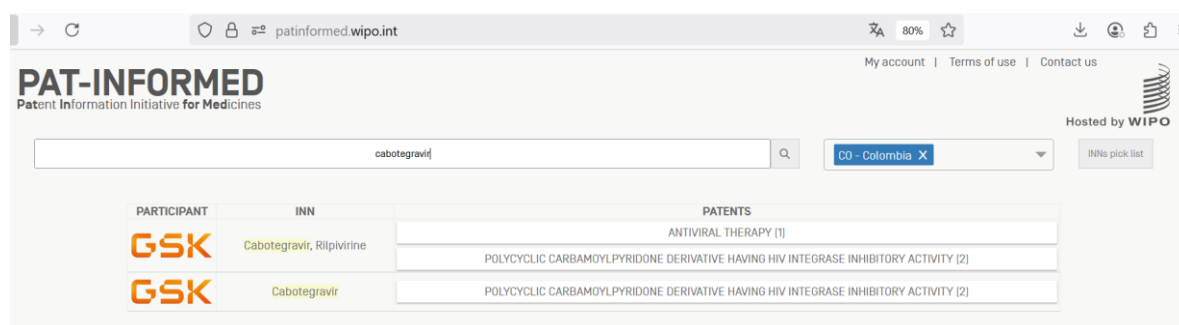
Una de esas patentes fue objeto de la licencia obligatoria sobre Dolutegravir emitida por la SIC y la Declaratoria de Interés Público emitida por Ministerio de Salud y Protección Social.

También hay más patentes que incluyen **Cabotegravir** en combinación o formulación con otros **antirretrovirales** como **Lenacapavir**:

- **15199357** COMPUESTOS TERAPÉUTICOS DE 2-FENILETIL-ACETAMIDA ADECUADOS CONTRA EL VIH.
- **NC2019/0001379**: COMPUESTOS DERIVADOS DE 1H-INDAZOL-7-IL)-6-(3-METIL-3-(METILSULFONIL)BUT-1-IL)-1-IL)PIRIDIN-2-IL)-2-(3,5-DIFLUOROFENIL)ETIL)-2 ((3BS,4AR)-5,5-DIFLUORO-3-(TRIFLUOROMETIL)-3B,4,4A,5-TETRAHIDRO-1H CICLOPROPA[3,4]CICLOPENTA[1,2-C]PIRAZOL-1-IL) ACETAMIDA **ÚTILES COMO ANTIRRETROVIRALES Y COMPOSICIONES QUE LOS COMPRENDEN.**

FUENTES: SIPI-SIC, SIC - Base de datos MedsPal¹⁴

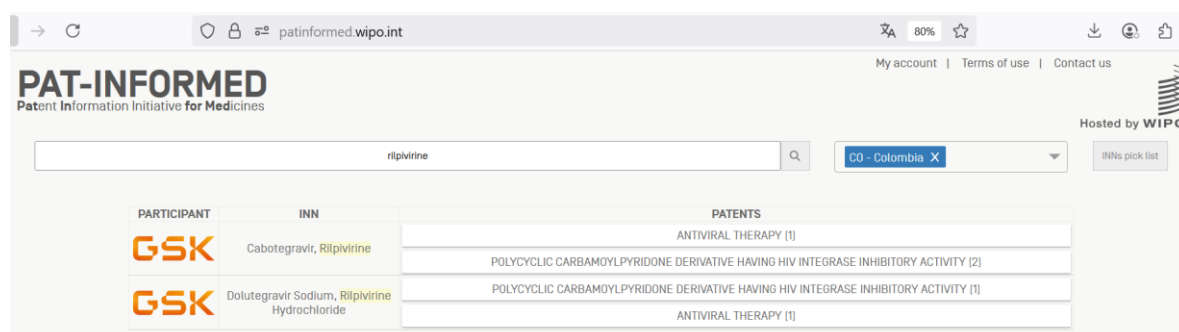
Algunas de estas patentes también se enuncian en la base de datos de OMPI e IFPMA “Pat-Informed”, pese que dicha base no es exhaustiva:



The screenshot shows the PAT-INFORMED website interface. The search bar contains 'cabotegravir'. The results table is as follows:

PARTICIPANT	INN	PATENTS
GSK	Cabotegravir, Rilpivirine	ANTIVIRAL THERAPY [1]
		POLYCYCLIC CARBAMOYL PYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY [2]
GSK	Cabotegravir	POLYCYCLIC CARBAMOYL PYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY [2]

FUENTE: <https://patinformed.wipo.int/>



The screenshot shows the PAT-INFORMED website interface. The search bar contains 'rilpivirine'. The results table is as follows:

PARTICIPANT	INN	PATENTS
GSK	Cabotegravir, Rilpivirine	ANTIVIRAL THERAPY [1]
		POLYCYCLIC CARBAMOYL PYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY [2]
GSK	Dolutegravir Sodium, Rilpivirine Hydrochloride	POLYCYCLIC CARBAMOYL PYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY [1]
		ANTIVIRAL THERAPY [1]

¹⁴ <https://www.medsPal.org/?Y291bnRyeT1Db2xvbWJpYSZrZXI3b3JkPWNhYm90ZWdyYXZpcg>

FUENTE: <https://patinformed.wipo.int/>

10. CONSIDERACIONES JURÍDICAS ADICIONALES.

A continuación, se hacen unas consideraciones jurídicas adicionales que deben entenderse de forma diferenciada y separada del análisis técnico de patentabilidad, especialmente del análisis de materia no patentable y de altura inventiva efectuado anteriormente, ese análisis de altura inventiva por sí solo es suficiente para desvirtuar la patentabilidad.

10.1. La solicitud de patente solicitada posiblemente solo alargaría indebidamente el tiempo protección sin cumplir los requisitos de patentabilidad.

El efecto práctico de esta concesión es alargar la protección unos años adicionales. Tal situación no solo va en contra de la normativa andina (Decisión Andina 486), sino que va en contra de la misión de la Superintendencia como Autoridad de Propiedad Industrial, pues es su deber velar porque solo se protejan las invenciones que cumplen los requisitos de patentabilidad. Como consecuencia de lo anterior, se generaría una situación monopólica en el mercado y se retrasaría la entrada de competidores al mercado, sin estimular la “innovación”, situación que -al parecer- estaría facilitando su Despacho de manera sistemática para un campo técnico tan sensible como es el farmacéutico, sin desconocer, posibles mejoras y esfuerzos positivos bajo la administración o gobierno actual. Por ejemplo, mayor número de requerimientos de fondo (arts 45), énfasis no solo en la agilidad, sino también en la calidad.

Es frecuente que la SIC no cite las patentes que concede en las búsquedas y en el estado de la técnica, pero dicha situación es cuestionable y hace que el estado de la técnica sea incompleto y, en consecuencia, el análisis de patentabilidad especialmente para determinar la novedad y altura inventiva resulte incompleto.

10.2. Argumentos contra la patentabilidad mediante patente sucesivas “secundarias”.

El eventual abuso del derecho a través de la “Perennización” de las patentes, extensión de la exclusividad, reverdecimiento o evergreening. El Panel o Grupo de Alto Nivel del secretario general de Las Naciones Unidas Sobre El Acceso a Los Medicamentos define este concepto en los siguientes términos:

“Perennización: Término utilizado para describir las estrategias de comercialización y concesión de patentes que tienen por objeto ampliar el período de protección que ofrece la patente o el período de vigencia de la exclusividad comercial, las cuales se consideran injustificables y, por tanto, abusivas. En algunos casos, por ejemplo, esta práctica podría implicar la presentación de solicitudes de patentes múltiples, a menudo consecutivas, para variantes o indicaciones mínimas e insignificantes del mismo compuesto”.

En sentido similar, las Guías de PNUD-ONU, UNDP-ONU dicen:

“Algunas solicitudes de patente reivindican, de forma independiente o como parte de una reivindicación más amplia, la dosis para administrar un fármaco en particular. **Las patentes sobre dosis constituyen otra forma de perpetuación**, que podría bloquear la comercialización de versiones genéricas cuando, por ejemplo, la dosis prescrita de un fármaco está incluida en el rango cubierto por la patente”.

“Un informe de la Oficina de Responsabilidad Gubernamental (Accountability Office de EE. UU. señaló:

*La práctica comúnmente conocida como producción de extensiones de línea, que consiste en derivar nuevos productos a partir de compuestos existentes, mediante **pequeños cambios en los productos existentes, como modificar la dosis de un medicamento...** Según los analistas, estos cambios suelen aplicarse a medicamentos de gran éxito poco antes del vencimiento de sus patentes. Algunos analistas también concluyeron que esta práctica redirige recursos que, de otro modo, podrían destinarse al desarrollo de medicamentos nuevos e innovadores” (Traducción libre). PNUD, UNDP-ONU: **“Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective”**¹⁵*

Es claro que las oposiciones deben basarse principalmente en argumentos técnico-científicos y jurídicos sobre los requisitos de patentabilidad: novedad, altura inventiva y aplicación industrial. Complementariamente en argumentos sobre la suficiencia de la descripción y la claridad.

Sin embargo, nada impide que se contextualice y se mencione el impacto de un determinado medicamento. No para que ese sea el fundamento de una eventual concesión parcial o negación, sino cuando menos para que la oficina de patentes realice un estudio profundo y diligente del estado de la técnica.

¹⁵ <https://www.undp.org/publications/guidelines-examination-patent-applications-relating-pharmaceuticals>

10.3. Impacto en el sistema de salud colombiano.

El Estado es el encargado de prestar el servicio de salud a todos los colombianos, en particular a aquellas personas con un estado de especial protección constitucional, “como quienes padecen enfermedades degenerativas, catastróficas y de alto costo” (T-261-17). Dentro de estos sujetos de especial protección se encuentran los pacientes diagnosticados con VIH, y en especial los pacientes menores de edad que padecen esta enfermedad.

Entendiendo el sistema de seguridad social en salud como uno en el que al Estado le corresponde organizar, dirigir y reglamentar la prestación de servicios de salud y saneamiento ambiental, y que la prestación de este servicio público puede hacerse en forma directa o por entidades privadas (C-1158-08), se debe tener en cuenta el impacto en el mismo, tanto en el acceso al medicamento por parte de los pacientes como el impacto en el sistema mismo.

La prestación del servicio por parte del Estado, aunado con su posición de garante frente a los derechos de los sujetos de especial protección conlleva obligaciones adicionales, como la obligación subsidiaria del Estado de asumir el costo de servicios de salud no incluidos en el POS o PBS cuando persona que los requiere no tiene capacidad económica (S. T-355/12, T-395/14, T-380/15), el suministro de tratamiento de alto costo sin cumplir periodo mínimo de cotización (T-797/01), el cubrimiento de medicamentos o tratamiento en casos en que existiendo ingresos no puede asumirse costo de los mismos (S. T-044/07), y el acceso a los servicios de salud que se requieran garantizado a las personas que padecen enfermedades catastróficas o de alto costo (S. T-760/08, T-520/12)

11. CONCLUSIÓN INICIAL. (Sin perjuicio de documento de sustento).

En consecuencia, con los argumentos presentados y los documentos aquí citados, es claro que la patente solicitada recae sobre materia NO patentable, métodos de tratamiento, carece de nivel inventivo, con base en los argumentos técnico-científicos y jurídicos específicos indicados a lo largo del documento. Es obvia a la luz del estado del arte conocido previamente.

12. ANEXOS. PRUEBAS. ANTERIORIDADES.

1. ISR, “Informe de Búsqueda Internacional” o “International Search Report, PatentScope, <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024056789>

2. WOSA: “Opinión Escrita de la Administración Encargada de la Búsqueda Internacional”, en este caso el examen la EPO, “Written Opinion of the International Searching OMPI, PatentScope, Authority”,
<https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2024056789>
3. Documentos D1 a D6.
4. Documento D4 en formato PDF.
5. Documento D5 en formato PDF.
6. Documento D6 en formato PDF.
7. Certificado de Existencia y Representación Legal de la Fundación Ifarma.
8. Poder para actuar otorgado por Juliana López, Representante Legal de la Fundación IFarma al Abogado Harold Humberto Silva Carvajal.
9. Constancia de pago de las tasas de tramitación de oposición.
10. Constancia de pago para sustentar la solicitud d prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.

13. NOTIFICACIONES:

Recibiré notificaciones en los correos: ifarma@ifarma.org, hsilva@ifarma.org y haroldhsilvac@gmail.com

Con el debido respeto suscribe:



Harold Humberto Silva Carvajal
C.C. No.1.022.433.355 de Bogotá
T.P. 391.454 del Consejo Superior de la Judicatura

Long-acting antiretrovirals: a new era for the management and prevention of HIV infection

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The long-acting antiretroviral cabotegravir and rilpivirine combination has just received FDA, EMA and Health Canada approval. This novel drug delivery approach is about to revolutionize the therapy of people living with HIV, decreasing the 365 daily pill burden to only six intramuscular injections per year. In addition, islatravir, a first-in-class nucleoside reverse transcriptase translocation inhibitor, is intended to be formulated as an implant with a dosing interval of 1 year or more. At present, long-acting antiretroviral therapies (LA-ARTs) are given at fixed standard doses, irrespectively of the patient's weight and BMI, and without consideration for host genetic and non-genetic factors likely influencing their systemic disposition. Despite a few remaining challenges related to administration (e.g. pain, dedicated medical procedure), the development and implementation of LA-ARTs can overcome long-term adherence issues by improving patients' privacy and reducing social stigma associated with the daily oral intake of anti-HIV treatments. Yet, the current 'one-size-fits-all' approach does not account for the recognized significant inter-individual variability in LA-ART pharmacokinetics. Therapeutic drug monitoring (TDM), an important tool for precision medicine, may provide physicians with valuable information on actual drug exposure in patients, contributing to improve their management in real life. The present review aims to update the current state of knowledge on these novel promising LA-ARTs and discusses their implications, particularly from a clinical pharmacokinetics perspective, for the future management and prevention of HIV infection, issues of ongoing importance in the absence of curative treatment or an effective vaccine.

Introduction

Since the introduction of highly active ART about 20 years ago, a succession of ameliorations, including simplification from complex regimens to single fixed-dose multidrug pills, have definitely improved both the efficacy and the tolerability of HIV infection management. In the absence of curative treatment or an effective vaccine, ART remains the mainstay of HIV treatment and prevention.

Current oral triple-drug treatments of HIV infection combine a potent HIV integrase strand transfer inhibitor (INSTI) (e.g. dolutegravir, bictegravir) or an NNRTI (e.g. rilpivirine, doravirine, etravirine) plus two NRTIs (e.g. tenofovir, emtricitabine, lamivudine). Lately, simplified dual-therapy combinations have revealed the same activity as conventional triple therapy.^{1–3} However, non-virological outcomes remain uncertain with dual therapy, and maintaining triple therapy has recently been advised by some authors since it is associated with a more favourable long-term anti-inflammatory profile.⁴ Non-boosted integrase inhibitor-based regimens are currently the preferred first-line treatment. They have been shown to

confer a high rate of viral suppression, a good tolerance and a high barrier to resistance.^{5,6}

Current antiretroviral regimens have, for the most part, achieved optimal antiretroviral efficacy and tolerability, transforming HIV infection from a deadly disease into a manageable chronic condition. Still, adherence to daily oral drug intake remains an issue, as it is the most important determinant for sustained viral suppression and prevention of emergence of drug-resistant viral strains. In fact, fewer than two thirds of patients maintain the frequently reported 90% adherence level associated with optimal viral suppression.⁷ Notably, with the improved pharmacokinetic (PK) profiles of the recent antiretrovirals, the threshold of adherence required to achieve viral suppression might now be lowered to 80%.^{8,9} Long-term adherence is hampered by several factors, including treatment fatigue for multidrug regimens that need to be taken indefinitely. Additional co-medications and drug-drug interactions (DDIs) bring further complexity, notably in the ageing population of people living with HIV (PLWH).^{10–12} A promising approach to overcome the adherence challenge and prevent drug

resistance is the development of long-acting formulations, which at present can ensure 2 month-long effective plasma concentrations.^{13,14} Such a dosing interval is likely to be prolonged in the near future with the development of novel antiretroviral agents. Long-acting antiretroviral therapy (LA-ART) will simultaneously improve patient privacy and reduce social stigmas associated with HIV. Eligible patients willing to start long-acting injectable ART (LAI-ART) are particularly interested (reportedly up to 70%)¹⁵ in the improved convenience, freedom, confidentiality and emotional benefits of not being constantly reminded of their HIV status through daily pill use. LAI-ART will raise an even higher rate of interest once the interval between injections has been further extended, thus decreasing the injection discomfort.¹⁶

For the prevention of HIV infection, pre-exposure prophylaxis (PrEP) by dual therapy with NRTIs, e.g. tenofovir disoproxil fumarate and emtricitabine or lamivudine, has demonstrated high efficacy in prospective trials.^{17,18} It has been recommended, among other prevention approaches, since 2015 by the WHO for populations with an HIV incidence above 3%. However, adherence to oral PrEP regimens is low in some populations^{17,19} and extended PrEP is needed in women because of the delay for the full protective effect in the vaginal tract. Detectable drug levels in blood are strongly correlated with the prophylactic effect (limit of quantification of 10 ng/mL in plasma, and $2.5 \text{ fmol}/2 \times 10^6$ cells for tenofovir diphosphate and $0.1 \text{ pmol}/2 \times 10^6$ cells for emtricitabine triphosphate in PBMCs).¹⁸ Indeed, there is an approximately 90% reduction in the risk of acquiring HIV-1 when drug levels in blood are detectable.¹⁹ As highly variable adherence to daily oral regimens profoundly affects the prophylactic effect, LAI-ART raises a strong interest in PrEP, in the absence of an effective vaccine against HIV.

During the past decades, blood concentration measurement has been increasingly invoked to optimize the therapeutic use of critical drugs through adjustment of concentration exposure via therapeutic drug monitoring (TDM). Candidate drugs for TDM have significant inter-subject PK variability, properly quantified by population PK studies and poorly predictable from individual patients' characteristics, along with limited within-subject PK variability over time. Their concentration–response and/or concentration–toxicity relationships must be consistent, with defined concentration ranges associated with optimal efficacy and minimal toxicity. TDM is current practice for some antibiotics, antiepileptics, immunosuppressants, antifungals and anti-HIV drugs.²⁰ Despite limited clinical validation, TDM of antiretrovirals is now commonly used in the case of drug interaction problems, virological failure, adverse drug reactions, special clinical conditions (pregnancy, paediatrics, liver failure, dialysis etc.)²¹ and for assessing short-term compliance. In the LA-ART era, where adherence will no longer be a confounding factor for inadequate clinical response, TDM might still benefit patients in clinical practice by preventing or correcting under- or overdosing (especially with respect to the dosage scheme), which increase the risk of potential treatment failure or toxicity, respectively.

The present narrative review aims to update the current state of knowledge regarding novel promising LA-ARTs, to discuss their implications for HIV management, and to focus on the clinical PK aspects, particularly on the suitability of a TDM service for optimizing ART blood exposure in patients. This article is divided into two sections covering antiretroviral agents that either have intrinsically favourable PK properties for LA-ART application, or whose half-life

($t_{1/2}$) has been considerably increased by pharmaceutical technology means.

Methods

For this review, we searched PubMed and Embase for publications and Clinicaltrials.gov for registered studies. We used the search terms 'long-acting antiretrovirals' or the names of the compounds presented, in combination with specific terms such as 'formulations' or 'pharmacokinetics'. The references of the identified articles were also examined and we selected those we considered relevant. In addition, we consulted, among others, reports of the Conference on Retroviruses and Opportunistic Infections (CROI) and the AIDS conference, as well as the pipeline of major HIV drug development companies. The compounds presented in the first part of the review are molecules that have reached Phase III clinical studies, or are already marketed and that are about to revolutionize the care of PLWH. On the other hand, promising formulation developments have been selected on the basis of their relevance for timely clinical implementation.

Molecules with suitable characteristics for LA-ART

Cabotegravir and rilpivirine

Cabotegravir is a potent INSTI, structurally similar to dolutegravir (Figure 1), with a high barrier to resistance and high antiviral potency.²² In individuals with HIV infection, trough concentrations (C_{\min}) under oral cabotegravir 30 mg once daily were roughly 25 times higher than the 90% protein-adjusted inhibitory concentration (PAIC_{90}) for HIV of 166 ng/mL.²³

Rilpivirine is a potent NNRTI, active against NNRTI-resistant HIV, with favourable allosteric binding due to its diarylpyrimidine structure, as shown in Figure 1.¹⁰ Oral rilpivirine 25 mg, marketed as EDURANT®, is prescribed in combination with emtricitabine and tenofovir alafenamide in treatment-naïve patients with a viral load below 100 000 copies/mL at baseline. The median EC_{50} of rilpivirine against HIV clinical isolates cultivated in PBMCs was 0.095 ng/mL, leading to a PAIC_{90} of 12 ng/mL.²⁴ Yet, this *in vitro* target value differs from *in vivo* levels indicated by clinical studies,²⁵ which concluded instead that a minimal plasma concentration of 50 ng/mL should be maintained to optimize the probability of therapeutic response.^{26,27}

Table 1 summarizes the differences in the PK parameters between oral and intramuscular (IM) cabotegravir and rilpivirine regimens.^{28–35}

So far, cabotegravir and rilpivirine have been the most extensively studied drugs for LAI-ART, both alone and in combination, due to their prolonged $t_{1/2}$ and their high intrinsic antiretroviral potency. Cabotegravir and rilpivirine have low aqueous solubility, allowing their formulation into, respectively, 200 or 300 mg/mL wet-milled suspension.^{36,37} This preparation produces pure nano-sized drug crystals stabilized by surfactants, a formulation suitable for IM depot injection.^{10,22,36} This nanosuspension technology increases the apparent $t_{1/2}$ of cabotegravir and rilpivirine, from 41 and 45 h to approximately 8.5 and 20.5 weeks, respectively, with the LAI formulation, although with substantial interindividual variability.³⁸ This variability in dose–exposure–response relationships could be addressed by TDM. In patients exhibiting substantially lower or higher C_{\min} , a personalized dosing schedule, shortening or extending the dosing intervals, could be implemented with

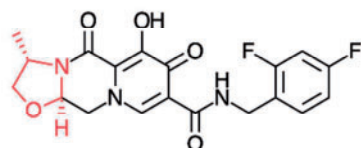
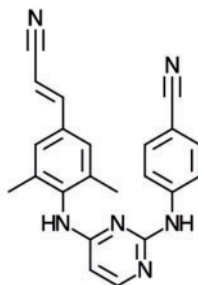
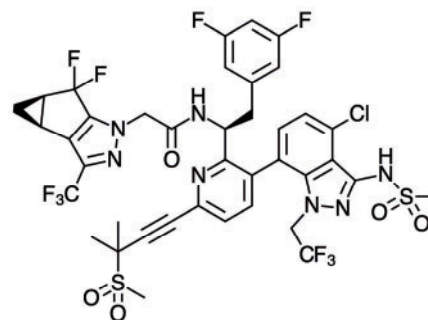
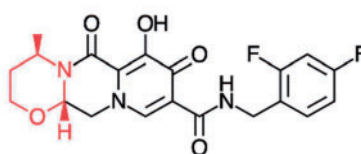
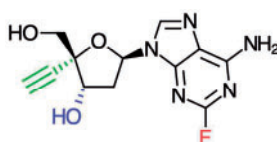
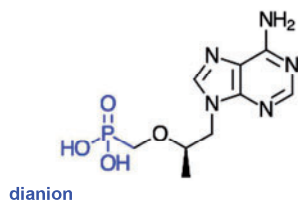
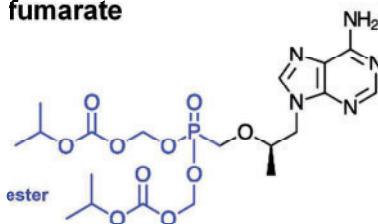
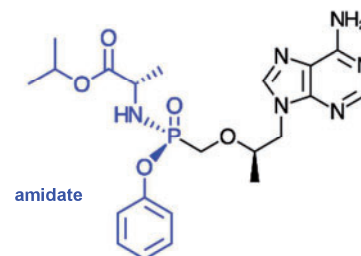
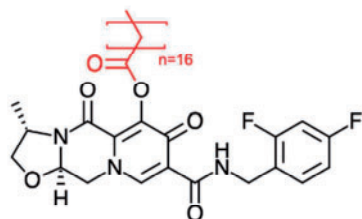
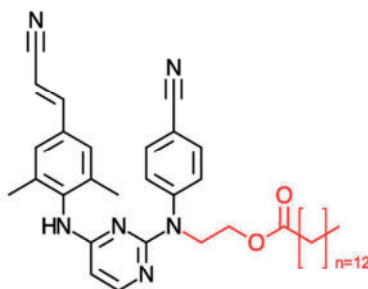
Cabotegravir**Rilpivirine****Lenacapavir****Dolutegravir****Islatravir****Tenofovir****Tenofovir disoproxil fumarate****Tenofovir alafenamide****Prodrugs of cabotegravir and rilpivirine in development****Prodrug of cabotegravir****Prodrug of rilpivirine**

Figure 1. Molecular structures of the compounds presented. The structural difference between cabotegravir and dolutegravir is highlighted in red. The chemical groups in colour for islatravir are discussed in the text. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

benefits in terms of efficacy or costs, respectively. Nanocrystals form a depot at the injection site, from which drug is slowly released. Since their particle size allows their physical filtration, nanoparticles are also drained into lymphatic vessels, where they

form secondary depots. They can also undergo phagocytosis by macrophages infiltrating the administration site, or incorporation into T lymphocytes. The lymphatic system then slowly releases the drug into the systemic circulation, contributing to the

Table 1. PK parameters of oral and IM cabotegravir and rilpivirine

CAB	C _{max} (µg/mL)	T _{max}	AUC _T (µg·h/mL)	C _{trough} (µg/mL)	t _{1/2}	V (L)	Substrate
Oral CAB 30 mg q24h	8.1 (7.9–8.2) ^a	3 h ^a	146 (143–149) ^a	4.7 (4.6–4.8) ^a	41 h ^a	12.3 ^{b,c}	UGT1A1 (UGT1A9) ^{b,e}
LA CAB 400 mg q4w	4.2 (4.1–4.3) ^a	7 d ^a	2461 (2413–2510) ^a	2.9 (2.9–3.0) ^a	5.6–11.5 w ^a		
LA CAB 600 mg q8w	4.0 ^b	7 d ^a	3764 ^b	1.6 ^b	5.6–11.5 w ^a		
RPV	C _{max} (ng/mL)	T _{max}	AUC _T (ng·h/mL)	C _{trough} (ng/mL)	t _{1/2}	V (L)	Substrate
Oral RPV 25 mg q24h	204 ± 76 ^{b,d}	4–5 h ²⁸	2589 ± 869 ^{b, d}	67 ± 30 ^{b, d}	45–50 h ^b	152 ^b	CYP3A (CYP2C19) ^{b,e}
LA RPV 600 mg q4w	116 (113–119) ^a	3–4 d ^a	65 603 (63 756–67 503) ^a	82.2 (79.9–84.6) ^a	13–28 w ^a	132 ^b	
LA RPV 900 mg q8w	133 ^b	3–4 d ^a	127 031 ^b	65.6 ^b	13–28 w ^a		

CAB, cabotegravir; RPV, rilpivirine; C_{max}, maximum concentration; T_{max}, time to achieve C_{max}; AUC_T, AUC to trough concentration; t_{1/2}, terminal half-life; q24h, once daily; q4w, every 4 weeks; q8w, every 8 weeks; d, days; w, weeks; UGT, uridine 5'-diphospho-glucuronosyltransferase; CYP, cytochrome P450.

^aGeometric mean (95% CI) obtained from the official product monograph.²⁹ The values presented are based on individual *a posteriori* estimates for subjects in the FLAIR³⁰ and ATLAS³¹ studies from separate population PK analysis models generated for cabotegravir and rilpivirine.

^bThese parameters were obtained from the HIV Drug Interactions fact sheets of the University of Liverpool.^{32–35}

^cFollowing oral administration.

^dn = 12, healthy volunteers.

^eIn brackets, minor or potential contribution.

long-acting antiretroviral effect.³⁹ Measurable plasma cabotegravir concentrations have been reported in individuals up to 1 year after a single injection.^{22,40} Thus, such observed long t_{1/2} results from a combination of both the suitable intrinsic properties of the molecules and their nanoformulation development.

Table 2 summarizes the main clinical trials carried out to date with LAI cabotegravir/rilpivirine in PLWH^{13,30,31,41} and with LAI cabotegravir for PrEP.^{42–45}

In Phase III clinical studies, the first dual LAI-ART combination of cabotegravir and rilpivirine has been given after a preliminary 4 week oral lead-in period (cabotegravir 30 mg plus rilpivirine 25 mg, once daily), to assess drug tolerability, followed by IM injections of each drug into the gluteal muscles. The regimens best investigated so far consist of 2 or 3 mL IM injections, at 4 or 8 week dosing intervals, respectively.

This combination was studied in the landmark LATTE-2 trial,⁴¹ which compared the dosing regimens of LAI cabotegravir/rilpivirine 400/600 mg (two 2 mL injections) every 4 weeks, or LAI cabotegravir/rilpivirine 600/900 mg (two 3 mL injections) every 8 weeks, with an oral three-drug regimen of cabotegravir/lamivudine/abacavir. At Week 96, viral suppression was maintained in 84% of patients receiving oral treatment, 87% of patients in the 4 week group and 94% of patients in the 8 week group. In the 8 week group, mean cabotegravir and rilpivirine C_{min} were nine and five times, respectively, above the PAIC₉₀ against WT HIV.

The FLAIR and ATLAS Phase III studies compared the LAI cabotegravir/rilpivirine regimen with standard daily three-drug oral regimens.^{30,31} After the oral lead-in period, the participants received an initial loading dose of IM LAI cabotegravir/rilpivirine 600/900 mg, followed by LAI cabotegravir/rilpivirine 400/600 mg every 4 weeks through the maintenance phase. At Week 48, the FLAIR trial concluded that viral suppression was maintained in 93.6% of patients receiving the LAI therapy and in 93.3% of patients on oral triple therapy. The ATLAS study showed, for its part, that viral suppression was maintained in 92.5% of patients receiving the

injections and in 95.5% of patients on oral therapy. Efficacy and safety of the long-acting therapy in these trials were similar and confirmed that the 4 week LAI cabotegravir/rilpivirine regimen was non-inferior to standard daily three-drug oral regimens.

The subsequent ATLAS-2M study, which specifically compared the 4 week regimen and the 8 week regimen, reaffirmed that the LAI cabotegravir/rilpivirine 8 week regimen was highly effective and non-inferior to the 4 week injection regimen.¹³ Viral suppression was maintained in 94% and 93% of patients in the 8 and 4 week regimens, respectively. The efficacy and safety of the LAI cabotegravir/rilpivirine 8 week regimen also appears to be supported by the ongoing Phase III POLAR study,⁴⁶ which has included 100 treatment-naïve PLWH, who had remained virologically suppressed to less than 50 copies/mL on daily oral cabotegravir plus rilpivirine in the Phase IIb LATTE trial.²³

Ongoing studies are now investigating LAI cabotegravir/rilpivirine in various situations and different subpopulations. For instance, the 'More Options for Children and Adolescents' (MOCHA) study aims to establish the optimal dosing and assess the safety, tolerability, acceptability and PK profiles of oral cabotegravir and LAI cabotegravir/rilpivirine (alone or in combination) in virologically suppressed patients aged between 12 and 18 years. In addition, the ongoing LATITUDE Phase III trial is comparing the efficacy, safety and durability of LAI cabotegravir/rilpivirine administered every 4 weeks to a standard daily three-drug regimen in patients with a history of suboptimal adherence to oral treatment and control of their HIV infection.⁴⁷

Of note, such as in the ongoing SOLAR trial,⁴⁸ the decision regarding the oral lead-in period is now at the sole discretion of participating patients. Indeed, the actual necessity of the oral lead-in phase is currently debated.⁴⁹

Lastly, one study examined the PK of cabotegravir and the neonatal outcomes in three women who confirmed pregnancy during clinical trials.⁵⁰ Rilpivirine concentrations were not assessed. The rate of prolonged terminal decline (or 'PK tail', discussed later)

Table 2. Main clinical trials of LAI CAB/RPV for the treatment of PLWH and for PrEP

Trial	Phase	n	Arms	Results	Ref.
Treatment					
LATTE-2	I Ib	286	LAI CAB (400 mg) + LAI RPV (600 mg) q4w LAI CAB (600 mg) + LAI RPV (900 mg) q8w CAB (30 mg) + ABC/3TC (600/300 mg) q24h	At Week 96, viral suppression: q4w: 87% (100 of 115 patients) q8w: 94% (108 of 115 patients) oral: 84% (47 of 56 patients)	41
FLAIR	III	566	LAI CAB (400 mg) + LAI RPV (600 mg) q4w DTG/ABC/3TC (50/600/300 mg) q24h	At Week 48, viral suppression: LAI: 93.6% (265 of 283 patients) oral: 93.3% (264 of 283 patients)	30
ATLAS	III	616	LAI CAB (400 mg) + LAI RPV (600 mg) q4w 2 NRTIs + 1 INSTI, NNRTI or boosted PI or unboosted ATV	At Week 48, viral suppression: LAI: 92.5% (285 of 308 patients) oral: 95.5% (294 of 308 patients)	31
ATLAS-2M	IIIb	1045	LAI CAB (400 mg) + LAI RPV (600 mg) q4w LAI CAB (600 mg) + LAI RPV (900 mg) q8w	At Week 48, viral suppression: q4w: 93% (489 of 523 patients) q8w: 94% (492 of 522 patients)	13
PrEP					
HPTN083 ^a	I Ib/III	4566	LAI CAB (600 mg) q8w TDF/FTC (300/200 mg) q24h	LAI CAB: Incidence rate 0.41% (13 HIV infections) TDF/FTC: Incidence rate 1.22% (39 HIV infections)	42,43
HPTN084 ^a	III	3224	LAI CAB (600 mg) q8w TDF/FTC (300/200 mg) q24h	LAI CAB: Incidence rate 0.21% (4 HIV infections) TDF/FTC: Incidence rate 1.79% (34 HIV infections)	44,45

CAB, cabotegravir; RPV, rilpivirine; ABC, abacavir; 3TC, lamivudine; DTG, dolutegravir; ATV, atazanavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; n, number of participants assigned to randomization; q4w, every 4 weeks; q8w, every 8 weeks; q24h, once daily.

^aOngoing studies.

of cabotegravir concentration after treatment discontinuation was found to be in the expected range for non-pregnant women, and no adverse effects on maternal and neonatal health were reported. After stopping treatment, all women started a standard daily oral regimen and maintained undetectable viral load during 52 weeks of follow-up. Further trials remain necessary to better inform the use of cabotegravir and rilpivirine in pregnancy.

The LAI formulations of cabotegravir and rilpivirine have also been studied for PrEP. Yet, LAI rilpivirine as a single PrEP agent appears to be of questionable relevance because of a low barrier to resistance,^{51,52} and storage and transportation constraints (e.g. cold chain required). Alternatively, LAI cabotegravir 800 mg injected every 12 weeks for PrEP has been studied in healthy men at high risk of HIV infection (ECLAIR study).⁵³ Lower than expected cabotegravir plasma levels in this study led to revised LAI cabotegravir dosages, subsequently evaluated in the HIV Prevention Trials Network (HPTN). The ongoing HPTN 083 study is being conducted in 4566 HIV-uninfected MSM and transgender women. The blinded comparison was prematurely stopped in May 2020 because it had already met its specified pre-study objectives, showing that cabotegravir injected every 8 weeks was highly effective and clinically superior to daily oral tenofovir disoproxil fumarate/emtricitabine for PrEP.⁴² Based on these results, in November 2020 the FDA granted the breakthrough therapy designation for the single agent LAI cabotegravir as PrEP. However, despite these impressive results, the HPTN 083 trial raised some

concerns.⁵⁴ It has been suggested that cabotegravir may delay the detection of HIV infection in people starting PrEP because it rapidly suppresses the viral load to undetectable levels. In addition, 'breakthrough' infections despite adequate plasma levels were reported in four participants. Multiple hypotheses should therefore be addressed in further investigations, including how cabotegravir concentrations vary between various body compartments (e.g. diffusion into rectal, vaginal and penile mucosal tissues) and whether higher C_{min} should be targeted in some individuals. In the absence of biomarkers for PrEP, TDM could be advised in specific cases for ascertaining trough levels at the start of prophylaxis or in case of comorbidities or co-medications that could affect exposure to cabotegravir and hence would impair the protection against HIV infection. Moreover, one participant who was found retrospectively to be HIV positive at baseline developed cabotegravir resistance mutations during PrEP.

In the ongoing HPTN 084 study, LAI cabotegravir is being compared with daily oral tenofovir disoproxil fumarate/emtricitabine in 3224 women, aged 18–45 years, at risk of HIV infection in sub-Saharan Africa. LAI cabotegravir was found to be significantly more effective than oral PrEP in preventing HIV acquisition among cisgender women.^{44,55} LAI cabotegravir is planned to be administered also to adolescent girls within the framework of the ancillary study HPTN 084/01 (safety, tolerability and acceptability of LA cabotegravir for the prevention of HIV among adolescents).⁵⁶

From a regulatory perspective, the Health Canada authority was the first to approve the LAI cabotegravir/rilpivirine combination in March 2020 under the brand name CABENUVA[®], which is marketed as a co-pack with two separate injectable medicines. It is indicated, after an oral lead-in period, as a complete regimen for the maintenance treatment of HIV-1 infection in adults, replacing a current oral ART regimen ensuring virological suppression (HIV-1 RNA less than 50 copies/mL).²⁹ The EMA has recently approved LAI cabotegravir/rilpivirine under the name VOCABRIA[®] (cabotegravir injection and tablets), REKAMBYS[®] (rilpivirine injection) and EDURANT[®] (rilpivirine tablets). The FDA initially raised some concerns about the treatment's manufacturing process (albeit not related to safety), which were addressed by the manufacturers, allowing approval of the LAI cabotegravir/rilpivirine combination CABENUVA[®] on 21 January 2021.

Islatravir

Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor (Figure 1) with multiple mechanisms of action. The unusual 4'-ethynyl group (Figure 1, in green) blocks primer translocation and causes chain termination during viral RNA transcription. The 3'-hydroxy group (Figure 1, in blue) contributes to the high binding affinity for the reverse transcriptase. The 2-fluoro group (Figure 1, in red) protects islatravir from metabolism by hampering its deamination by adenosine deaminase, and this contributes to its long $t_{1/2}$.^{57,58}

In humans, islatravir is phosphorylated intracellularly into the active metabolite islatravir triphosphate. The plasma $t_{1/2}$ of islatravir after oral administration is 50–60 h, while the intracellular $t_{1/2}$ of islatravir triphosphate is 130–210 h. At steady state, intracellular concentrations of islatravir triphosphate in PBMCs were 1000 times higher than concomitant islatravir levels measured in plasma.⁵⁷ Islatravir has been given orally at dosages of 10, 30 and 100 mg weekly, with good viral responses and tolerance. Notably, in a Phase Ib study,⁵⁸ a single dose of 0.5 mg was found to significantly suppress plasma HIV-1 RNA for at least 7 days. With higher doses, an extended period of viral suppression could be achieved, opening the way for possible regimens with longer dosing intervals. Moreover, islatravir in combination with the NNRTI doravirine 100 mg per day appeared to work at least as well as the three-drug regimen of doravirine/tenofovir disoproxil fumarate/lamivudine, such as described in a double-blind randomized dose-ranging Phase IIb trial.⁵⁹ After 96 weeks, the highest response was observed in the arm of patients receiving 0.75 mg islatravir, with 90.0% having an undetectable viral load (i.e. HIV RNA less than 50 copies/mL), compared with 80.6% in the control group. This optimal daily dosing regimen of doravirine/islatravir 100/0.75 mg is now being tested in an ongoing Phase III comprehensive clinical development programme among various PLWH populations.^{60,61}

Islatravir was also shown to have a particular potency against resistant HIV variants⁵⁸ and, to date, no resistance to islatravir has been observed in PLWH treated by islatravir.⁵⁷ Consequently, islatravir is currently being evaluated in a Phase IIa study as a monthly oral PrEP.⁶²

Based on the technology successfully used for implantable contraceptives, islatravir has been formulated as a non-degradable subcutaneous implant that slowly releases drug from a biodegradable polylactic co-glycolic acid matrix. The $t_{1/2}$ described for

implants of approximately 100 days might make it amenable to LA administration with dosing intervals of 1 year or more.^{57,63} Indeed, the results of a Phase I study with radiopaque islatravir-eluting implants seems to support sufficient drug release for HIV prophylaxis for at least 1 year.⁶⁴ Islatravir implants are also currently being investigated in combination with other LA drugs for HIV treatment.⁶⁵

Lenacapavir

Lenacapavir (GS-6207) (Figure 1) is a first-in-class capsid inhibitor, which interferes with multiple capsid-dependent functions essential for viral replication, namely capsid assembly and disassembly, as well as nuclear transport and virus production.⁶⁶ Lenacapavir exhibits antiviral activity at picomolar levels (mean EC_{50} of 0.05 ng/mL) *in vitro*. After a single dose of 100 mg or more, plasma concentrations at 12 weeks remained above the reported 95% protein-adjusted effective concentration ($PAEC_{95}$) of 3.87 ng/mL. Moreover, it showed high synergy and no cross-resistance with currently approved antiretroviral drugs.^{66,67}

The ongoing CAPELLA Phase II/III trial will assess the safety and efficacy of oral lenacapavir in PLWH with multiresistant viral strains, when administered as an add-on to a failing regimen.⁶⁸ Preliminary results presented at CROI 2021 showed that lenacapavir was safe and well tolerated, and led to a rapid and clinically relevant decline in viral load.⁶⁹ Those results support its use in treatment and prevention of HIV. In addition, the manufacturer announced that a single 900 mg dose (3×1 mL or 2×1.5 mL injection), formulated as sustained-delivery subcutaneous injection, yielded therapeutic plasma concentration coverage for at least 6 months.⁷⁰ Lenacapavir has therefore the potential to be administered every 6 months by subcutaneous injections.⁴⁷

Notably, the manufacturers of islatravir and lenacapavir have recently announced a joint venture for the clinical evaluation of a combination of these two long-acting drugs.^{71,72} This collaboration is likely to accelerate the development of a highly promising dual formulation.

Antibody-based strategies

Ibalizumab is a humanized IgG4 antibody that binds to the extracellular CD4 domain and prevents HIV entry through allosteric inhibition. It was the first monoclonal antibody approved by the FDA, specifically in combination with other antiretrovirals, for patients failing to respond to treatment due to multiresistance.^{5,73} Ibalizumab is injected intravenously (IV) as a single loading dose of 2000 mg, followed by maintenance doses of 800 mg injected IV every 2 weeks.^{73,74}

Before entering into Phase III, ibalizumab received an orphan drug status from the FDA and then a breakthrough therapy status.⁷⁵ Subsequently, the single-arm open-label Phase III TMB-301 trial found that ibalizumab combined with an optimized background regimen significantly reduced viral load and increased CD4 count.⁷⁶ Like other monoclonal antibodies targeting cell surface molecules, ibalizumab exhibits non-linear PK. This is probably due to dose-dependent receptor-mediated saturable elimination.⁷⁷

Compared with other LAI-ART, ibalizumab has the disadvantage of requiring a shorter administration interval. Moreover, if a

maintenance dose is missed by 3 days or more, a loading dose has to be readministered, leading to potential discomfort for the patients.⁷⁴ Despite a shorter administration schedule compared with other LAI-ARTs, ibalizumab represents a novel opportunity for heavily treatment-experienced adults with multiresistant HIV infection.

Leronlimab is a humanized IgG4 directed towards CCR5 and can therefore only be given to individuals infected with CCR5-tropic HIV, which represents the vast majority of patients. Leronlimab seems to have a synergistic effect with the CCR5 antagonist maraviroc, but also to be active against maraviroc-resistant strains.^{73,74}

Unlike ibalizumab, leronlimab is administered by subcutaneous injection every week. It has demonstrated efficacy in maintaining viral suppression in virologically suppressed patients as monotherapy, and can be effective as well in treatment-experienced patients with MDR HIV in combination with other ART. Currently being studied in Phase IIb/III studies, it has received fast-track orphan drug status from the FDA.^{73,74}

It should be noted that, like all therapeutic proteins, ibalizumab and leronlimab have the potential to trigger immunogenicity but, to our knowledge, no cases have yet been reported.

LA-ART agents based on novel pharmaceutical formulations

Cabotegravir and rilpivirine development

One limitation that may hamper wide acceptance of LAI cabotegravir/rilpivirine is the rather high volume of the two extended-release suspensions that, at present, need to be slowly injected IM, associated with significant pain at the injection site frequently being reported. Injecting larger volumes of the current formulation as an attempt to extend the dosing interval is likely to result in unacceptable pain and to decrease patient acceptance. This may be overcome by using more potent formulations with improved physicochemical and pharmaceutical properties, which would decrease injection-related problems and allow faster injection.⁷⁸ In this regard, a novel formulation of cabotegravir, referred to as long-acting slow-release (LASER) ART, was developed by esterification of cabotegravir with stearic acid, an aliphatic fatty acid, for producing a prodrug (see Figure 1) encapsulated into a poloxamer nanoformulation, which shows improved lipophilicity, hydrophobicity, cellular entry and retention. This inactive prodrug is slowly hydrolysed by esterases in physiological conditions to yield cabotegravir. This nanoparticle formulation of a crystal prodrug could thus improve the drug delivery profile in PLWH, and therefore reduce injection-related problems. The evaluation of this formulation was shown to provide a year-long PK profile, opening the path to applications that could be considered as 'chemical vaccines' against HIV.^{79–81} Similarly, for rilpivirine, a formulation as an *N*-acyloxyalkyl prodrug (see Figure 1) was developed to slow down the release of the active moiety and to achieve a longer $t_{1/2}$. Prodrug bioconversion seems to proceed via enzymatic cleavage of the methylene ester by esterases into an *N*-hydroxymethyl rilpivirine, which in turn is hydrolysed into the active compound. More generally, alteration of physicochemical and PK properties through prodrug modifications—particularly those enhancing lipophilicity—can improve tissue distribution, cellular uptake and retention, notably in macrophages. After a single IM injection in mice, this

novel rilpivirine prodrug formulation maintained concentrations above the PAIC₉₀ for 25 weeks in plasma and in secondary tissue deposition.⁸²

However, as both of these prodrugs depend on esterase activity for yielding their active form, inter-individual differences in enzymatic activity could influence the active drug levels and hence the therapeutic outcomes. The clinical consequences of genetic variations of esterases, which would affect their enzymatic activity, are unclear at present,⁸³ but deserve investigation in future studies.

Secondly, the particle size of nanocarriers seems also to play an important role in the distribution of LA formulations, notably through the lymphatic system. Currently marketed LAI cabotegravir and LAI rilpivirine formulations have an average particle size of 200 nm.^{10,22} Reduction in particle size below 100 nm could potentially increase the uptake by the lymphatic system, resulting in improved circulation time.^{39,84}

Implant formulations

Tenofovir alafenamide is a prodrug of tenofovir, an NRTI, and one of the antiretroviral agents most widely used at present. Tenofovir alafenamide is 10 times more potent than tenofovir disoproxil fumarate and has the valuable advantage of being directly taken up into cells to be converted intracellularly to the parent drug (tenofovir) and then to the active intracellular diphosphate. Systemic toxicity is therefore reduced with tenofovir alafenamide, compared with tenofovir disoproxil fumarate, because it produces much lower tenofovir levels in plasma, the latter being associated with kidney tubular damage and, in the long term, with bone demineralization.^{5,85} The three chemical forms of tenofovir are shown in Figure 1.

Preliminary new formulations of tenofovir alafenamide have frequently been associated with local toxicity problems and further developmental efforts are therefore still necessary before clinical implementation. Recently, a promising subdermal implant that releases tenofovir alafenamide for at least 6 months of HIV protection was developed. This implant appeared safe and well tolerated in mice and sheep. Given its favourable PK and tolerability profile, it seems promising for the future development of new LA technologies.⁸⁶ Other examples of implants of tenofovir alafenamide^{87–89} are presented in Table 3.

Dolutegravir-based regimens are one of the preferred first-line and second-line treatments, associating dolutegravir with two NRTIs.^{5,90} Therefore, different models of implants have been developed for dolutegravir to overcome the lack of adherence associated with daily oral pill intake. An ultra-long-acting removable drug delivery system could deliver dolutegravir for up to 9 months. Following subcutaneous drug injection, the implant solidifies *in vivo* within 48 h, and its subsequent biodegradation results in sustained drug release.⁹¹ This breakthrough formulation allows modulation of the kinetics of drug release through careful adjustment of polymer lactic/glycolic acid ratios and molecular weights. In addition, multiple drugs could be included, and possibly refilled *in situ*.^{92,93} Lastly, it does not need surgical removal after complete drug release.

Overall, the possibility of rapid surgical removal of such implants from patients would exempt patients from an oral lead-in period for tolerability assessment.

Table 3. Types of implants of tenofovir alafenamide (TAF) for long-acting therapy currently under investigation

Types of implant	Drug release properties
A subcutaneous silicone implant delivers TAF from orthogonal channels coated with polyvinyl alcohol.	It provides measurable plasma concentrations of TAF over more than 6 weeks and delivers TAF at near constant rate for up to 40 days after implantation. ⁸⁷
A reservoir-style implant with an extruded tube of a biodegradable polymer [poly (ϵ -caprolactone)] membrane.	It can deliver TAF with sustained zero-order release kinetics. After subcutaneous injection, the biological fluid from the environment can enter and solubilize TAF, which is then passively transported across the membrane and released from the implant. ⁸⁸
A subcutaneous implant formed with pressed TAF pellets and extruded polyurethane tubing.	This modular implant is tunable to adjust the rate and duration of TAF release through adjustment of geometry and membrane composition. ⁸⁹

Microarray patches

Microarray patch (MAP) technologies, also referred to as microneedle patches, have been explored in a proof-of-concept trial for the use of LA rilpivirine to facilitate intradermal administration.⁹⁴ Nanoparticles could be delivered into the systemic circulation by slow dissolution (approximately 25 min) and absorption through the skin. Concentration maintenance at four times the PAIC₉₀ for 28 days was reported in rats.⁹⁵

Overall, MAPs could expand access and adherence to HIV treatment. In particular, in low-resource settings where the number of trained medical staff is limited, potential self-administration could be of great interest.^{94,96}

Dapivirine vaginal ring

Dapivirine, an NNRTI formulated as a monthly vaginal ring, was recently approved by the EMA for HIV prevention in women living in high HIV-burden settings. The ring is intended for adult women as a complementary approach to reduce the risk of HIV infection during vaginal sex. It should be used in addition to safer sex practices when women cannot use or do not have access to oral PrEP.⁹⁷

According to a systematic review of two Phase III trials (RING study⁹⁸ and ASPIRE study⁹⁹), a beneficial 29% reduction in HIV risk has been demonstrated with the intravaginal dapivirine ring (relative risk of 0.71; 95% CI 0.57–0.89).¹⁰⁰ Despite appearing to be less effective than oral PrEP, the vaginal ring represents an alternative for women who are unable to take oral PrEP according to the recommendations. Moreover, current developments are underway to include both contraception and HIV prevention in a single intravaginal ring.⁹⁷

Challenges for the development of LA-ART formulations

Despite their promises, neither the approved LAI cabotegravir/rilpivirine combination, nor further LA-ARTs to come are fully devoid of limitations. The existence of the so-called ‘PK tail’ after treatment cessation is of particular concern.^{53,101} During this prolonged terminal decay, ART plasma concentrations are declining to reach non-suppressive levels below PAEC₉₅, leading to a risk of viral replication rebound together with selection of drug-resistant variants.¹⁰¹ It is therefore currently recommended to initiate daily oral ART as soon as the LA-ART discontinuation is considered, so as to maintain therapeutic plasma levels throughout the PK tail period.⁸⁵ However, according to the interim results of the HPTN 083 study, no resistance has yet emerged in people with low cabotegravir levels during this decline.⁵⁴ On the other hand, it has been claimed that the overall DDI risk would be smaller for LAI-ARTs than for oral ARTs, due to the lower importance of intestinal absorption, liver first-pass, metabolism and transport processes.^{102,103} However, DDIs affecting drug clearance might still occur. Drug transporters (e.g. ABCC1, ABCC4, ABCC5, OATP2B1 etc.) and metabolizing enzymes (CYP450s, UGTs) are expressed in skeletal muscles and subcutaneous adipose tissue, and some of them have shown functional activity.⁸⁴ The vulnerability of LAI-ART to DDIs constitutes therefore a relevant issue warranting further investigations.

Globally, treatment constraints and stigma are recognized as definite hurdles against optimal adherence to HIV therapy. LAI-ART represents therefore a promising opportunity to overcome such barriers by improving patient privacy and reducing the psychological and social burden associated with the daily intake of anti-HIV pills. Yet, such a novel mode of ART administration will certainly imply organizational constraints, including infrastructures for parenteral administration and thorough selection of patients suitable for such therapy, not to mention discomfort due to injections.^{40,104,105} However, there are good chances that current and next-generation LA-ARTs will ultimately benefit a large number of PLWH.

The first-generation injectable formulation of LAI cabotegravir/rilpivirine is temperature sensitive and requires a cold chain at 2°C–8°C throughout the drug shipment and storage, which probably makes it less suitable for countries with limited access to refrigeration. Thus, the second wave of LAI-ARTs will need to remain stable at the temperatures and moisture conditions of tropical resource-limited settings.

Further formulation efforts are also appropriate to alleviate the injection-induced pain, possibly using removable microneedle patches. Less harsh and painful modes of administration would be better accepted, particularly by children and adolescents.¹⁰⁶ This would facilitate optimization of the dosing regimen to the target patient population at special risk of virological failure.¹⁰⁷

Moreover, only potent antiretroviral drugs are likely candidates for implant formulation because the quantity that they can accommodate is small. Drug candidates must therefore demonstrate inhibition of viral replication at conveniently low concentrations.^{63,92} Yet, implant formulations seem so far to provide more

predictable and constant drug release than LAI formulations. In the case of adverse events, DDI occurrence or treatment discontinuation, the implant may be surgically removed, while LAI cessation inevitably results in a sustained period of subtherapeutic concentrations. Indeed, once the implant is removed, the drug concentration decreases rapidly, as does the associated effect. The PK tail problem, as observed for LAI-ART, may thus not be a concern for implants. Obviously, this is not the case with molecules having a long $t_{1/2}$, because the drug in circulation after implant removal could remain at significant levels for a considerable period. In addition, multiple implants with different dosages would be necessary to allow for dose escalation in clinical dose-finding and safety studies.⁹¹ When starting a treatment, multiple dosages would probably be necessary in order to assess tolerance. Depending on the manufacturing cost of these products, their implementation could then be largely hindered.

Furthermore, in the case of non-biodegradable polymers, the insertion and removal of the implant need surgical intervention by trained personnel. Nevertheless, the widespread use and general acceptance of contraceptive implants in low-income countries indicate that antiretroviral implants could be appropriate worldwide.⁶³ One possible improvement might be to make them refillable, so that implantation and removal do not need to be repeated.¹⁰⁸ For instance, a transcutaneously reloadable drug-eluting implant using nanochannels was shown to release tenofovir alafenamide and emtricitabine over an extended period of more than 2 months.¹⁰⁹

On the other hand, even if biodegradable polymer implants may *a priori* appear more attractive in the case of adverse events, they can be removed only early after injection; surgical removal weeks or months after implantation will probably fail because of implant dispersion.⁹¹

Ultimately, the acceptability of these new technologies will be key to their implementation in clinical practice. As with contraceptive implants, multiple barriers will arise, such as patient worries and misconceptions, access to the treatment and the price of these new products.^{110,111} In fact, these new technologies may be more readily accepted by people who are already familiar with them (whether through injections or implants) as part of contraception or disease treatment.¹¹⁰ In this context, long-release implants would potentially be the most acceptable for PLWH, as they would require fewer clinic visits and invasive procedures.

Formulations for the co-administration of LA-ART and a contraceptive are currently being developed in Phase I studies. These combined technologies address multiple sexual and health needs for women, particularly in sub-Saharan Africa. Other drugs that prevent sexually transmitted infections could also be combined.¹¹² Vaginal rings containing dapivirine with levonorgestrel,¹¹³ and tenofovir with levonorgestrel,^{114,115} are being studied. In addition, cabotegravir could also be injected every 8 weeks for PrEP, aligned with appointments for LA contraceptive injections. As previously mentioned, an implant of islatravir is currently under development for PrEP and could potentially be administered with a hormonal contraceptive in the same device.

Finally, LA oral treatment may ultimately become the best way to improve HIV management for the majority of PLWH, as there would be no inconveniences associated with an invasive procedure, little or no infrastructure requirements and no additional investments on the part of patients. The combination of the highly

promising LA drugs lenacapavir and islatravir will probably represent a turning point in the management and prevention of HIV. Indeed, given the intrinsic characteristics and formulation possibilities of both these molecules, it is likely that this combination would allow for less frequent administration than, for example, the current LAI cabotegravir/rilpivirine.

Research gaps

It is noteworthy that LAI-ART is expected to make treatment adherence no longer represent a confounding factor for insufficient clinical response, as drugs will be administered parenterally under direct medical supervision. Nevertheless, in specific instances such as DDIs, issues at the injection site or special pathophysiological conditions, the monitoring of ART plasma levels will remain an important component of optimal patient follow-up in the LA-ART era. As prescription of LAI-ART represents a novel therapeutic paradigm, infectious diseases specialists may wish to obtain information on whether their patients are exposed to appropriate antiretroviral drug levels over the whole IM dosing intervals, with regard to not only efficacy but also tolerability and long-term safety. The potential impact of DDIs and pharmacogenetic traits might deserve further attention.

At present, LAI cabotegravir and LAI rilpivirine are marketed at standard dosage for all patients, while highly variable situations may occur in the real world. Marked alterations of LA-ART exposure can be postulated and might be simply unknown. We are notably concerned by the initiation of treatments for coincidental or inaugural diseases with definite risk of DDIs (TB, HCV infection or cancer etc.) in underweight or obese patients and, should it occur, in the case of pregnancy. The influence of physiological changes during pregnancy on ART exposure in women receiving LA-ART is unknown: alterations in the protein binding and volume of distribution of these new drugs could indeed lead to changes in PK and possibly to insufficient HIV coverage or adverse fetal events. Monitoring of pregnancy outcomes will require open-label extension studies. Further issues may add to the complexity of the management of PLWH on LA-ART, particularly in the ageing population who develop age-related physiological changes and frequently comorbidities. Polypharmacy is common among elderly PLWH and may cause DDIs that could affect their quality of life. The acceptability and actual benefits of LAI-ART in this population deserve thorough investigation. LA oral drugs to come might be revealed as more promising in older PLWH.

Similarly to implantable contraception exposure, where decreased etonorgestrel levels were reported in higher body weight individuals,¹¹⁶ BMI and gender have been identified in clinical trials to affect absorption rate⁵¹ and overall exposure to LAI-ART.^{51,117} A high BMI seems indeed to lead to a slower absorption rate and lower plasma concentrations of LAI-ART,^{22,52,117} and may be associated, among other baseline factors, with an increased risk of virological failure.¹¹⁸ Independently, longer periods with undetectable ART plasma concentrations were also observed in patients with higher BMI.¹⁰¹ This issue has been addressed in injection guideline recommendations, whereby longer needles are required for patients with a BMI of 30 or greater.¹⁰¹ Yet, BMI does not distinguish between adipose and muscle tissue, and therefore does not provide information on the distribution of body fat.^{22,117} Muscle density, accumulated scar tissue after

prolonged therapy, physical activity, as well as ambient temperature, may have an impact on the PK exposure after LAI administration.⁸⁴ In addition, unforeseen local problems at the injection site might also have important consequences on drug absorption.

Finally, precision medicine strategies should take into account the all-too-often neglected dimension of variability in dose–exposure–response relationships. In fact, it is likely that TDM, despite non-negligible costs, will be needed at least in selected subgroups of patients to assess the concentration exposure resulting from a given dosing regimen.

To this end, concentration monitoring of the LA-ARTs, namely LAI cabotegravir/rilpivirine in the first instance, is currently being initiated within the framework of the Swiss HIV Cohort Study (SHCS).¹¹⁹ It aims to verify whether standard dosage ensures appropriate antiretroviral plasma exposure in various types of real-life patients receiving LA-ART. It will bring indications on the potential suitability of altering the LA-ART dosing schedule, through shortening or extending dosing intervals, in certain patients exhibiting, respectively, lower or higher C_{min} .

Conclusions

Injectable-based formulations of molecules with intrinsic high potency and long $t_{1/2}$, such as cabotegravir and rilpivirine, are on their way to being implemented worldwide. The LAI cabotegravir/rilpivirine formulation can ensure 2 month-long effective plasma concentrations and thus could have a major impact on HIV management in the coming years. This dosing interval is due to be further extended in the near future, with the development of novel antiretroviral agents. Nevertheless, potential issues related to the long PK profile will need to be further characterized, to ensure the safe and effective use of this treatment in all patients. Alternatively, implant development represents another promising approach to improve HIV treatment and prevention. As for contraceptives, this implant approach should be rather well accepted. However, further developments remain necessary to make the use of these technologies definitely amenable to patients. Lastly, LA oral drugs or implants to come may appear best suited to implementation in elderly PLWH or any other subpopulation that may be refractory to relatively invasive treatments.

In the growing movement of precision medicine, further research efforts might improve the prescription of LA-ARTs, with regard to not only efficacy but also tolerability, long-term safety, overcoming of DDIs and possibly pharmacogenetic traits, together with patients' choice and best convenience. In this regard, TDM is at the forefront of this trend to personalize treatment, and even prophylaxis, to best meet the needs of the patient. LA-ARTs will transform not only the treatment of HIV infection, but also its prevention. Yet, these approaches have so far been tested in the strict framework of clinical trials, which do not account for the complex real-world situation of many PLWH. The implementation and deployment of such revolutionary approaches for the treatment and prevention of HIV infection need, at present, to be accompanied by close follow-up of patients on LA-ART. This includes the monitoring of viral suppression and CD4 count, and also the measurement of antiretroviral drug levels in plasma—and possibly in body tissues and cellular compartments. Further studies are thus warranted for maximizing the remarkable therapeutic and prophylactic potential of LA-ARTs against HIV infection in the real-life situation.

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In Silico Dose Prediction for Long-Acting Rilpivirine and Cabotegravir Administration to Children and Adolescents

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Abstract

Background and Objectives Long-acting injectable antiretrovirals represent a pharmacological alternative to oral formulations and an innovative clinical option to address adherence and reduce drug costs. Clinical studies in children and adolescents are characterised by ethical and logistic barriers complicating the identification of dose optimisation. Physiologically-based pharmacokinetic modelling represents a valuable tool to inform dose finding prior to clinical trials. The objective of this study was to simulate potential dosing strategies for existing long-acting injectable depot formulations of cabotegravir and rilpivirine in children and adolescents (aged 3–18 years) using physiologically-based pharmacokinetic modelling.

Methods Whole-body physiologically-based pharmacokinetic models were developed to represent the anatomical, physiological and molecular processes and age-related changes in children and adolescents through allometric equations. Models were validated for long-acting injectable intramuscular cabotegravir and rilpivirine in adults. Subsequently, the anatomy and physiology of children and adolescents were validated against available literature. The optimal doses of monthly administration of cabotegravir and rilpivirine were identified in children and adolescents, to achieve trough concentrations over the target concentrations derived in a recent efficacy trial of the same formulations.

Results Pharmacokinetic data generated through the physiologically-based pharmacokinetic simulations were similar to observed clinical data in adults. Optimal doses of long-acting injectable antiretrovirals cabotegravir and rilpivirine were predicted using the release rate observed for existing clinical formulations, for different weight groups of children and adolescents. The intramuscular loading dose and maintenance dose of cabotegravir ranged from 200 to 600 mg and from 100 to 250 mg, respectively, and for rilpivirine it ranged from 250 to 550 mg and from 150 to 500 mg, respectively, across various weight groups of children ranging from 15 to 70 kg.

Conclusions The reported findings represent a rational platform for the identification of suitable dosing strategies and can inform prospective clinical investigation of long-acting injectable formulations in children and adolescents.

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Key Points

Mathematical models defining anatomical, physiological and molecular processes were constructed to simulate drug pharmacokinetics in children and adolescents.

Two clinically available long-acting formulations of cabotegravir and rilpivirine were used to report minimum doses needed in paediatric individuals relative to their weight.

Evaluation of a mathematical model to identify minimum doses in children and adolescents represents an innovative method to inform dosing strategies in various types of populations over a range of therapeutic areas.

1 Introduction

Human immunodeficiency virus (HIV) is one of the leading causes of death that is treated as a global priority. Initiation of highly active antiretroviral therapy has saved millions of lives in the past decade [1]. However, adherence to antiretroviral therapy continues to be one of the major issues hindering treatment efficacy and suboptimal adherence can vary considerably in patients from 50 to 70% in the clinical setting [2]. Currently available formulations necessitate lifelong daily dosing and poor adherence has been attributed to numerous factors including pill fatigue, side effects and a range of socioeconomic considerations associated with different populations [3]. Problems can be particularly exacerbated in specific sub-populations of patients such as paediatric patients, where drug administration is additionally influenced by the caregiver, the family or the social environment [4].

Long-acting injectable (LAI) formulations have the potential of solving the adherence issues related to oral (PO) formulations, reducing the amount of antiretroviral (ARV) used for the therapy and consequently the cost of therapy. The use of LAI formulations in paediatric patients has already been hypothesised in different disease areas and the use of LAI antipsychotics has been recently described in adolescents [5–7].

Two LAI ARV formulations have recently been developed and several others are currently under investigation [1]. Rilpivirine and cabotegravir, owing to their long half-lives and potency, have been selected for monthly and quarterly long-acting administration, respectively [1, 8]. Clinical studies investigating the combination of cabotegravir and rilpivirine LAI formulations are currently

ongoing to assess their safety and efficacy in adults [9]. Recent clinical trials (LATTE and LATTE-2) conducted in HIV-infected adults show that the cabotegravir and rilpivirine combination is safe and efficacious, which provides similar antiviral activity to efavirenz plus the nucleoside reverse transcriptase inhibitors tenofovir and emtricitabine [10]. The combination of rilpivirine and cabotegravir has the potential of being the first long-acting antiretroviral regimen that will not require a daily PO dose of any companion drugs, representing a pivotal achievement in the antiretroviral pharmacology. However, the identification of safe and effective dosing strategies for paediatric patients is complicated by multiple factors. Differences in anatomical and physiological characteristics of children and adolescents compared with adults have a relevant effect on the absorption, distribution, metabolism and excretion processes and are not correctly captured through traditional allometric scaling approaches [11]. Additionally, logistic and ethical challenges in designing dose finding/optimisation studies have limited medical guidance [12].

Physiologically-based pharmacokinetic (PBPK) modelling represents a valuable tool to optimise doses prior to clinical trials in paediatric patients, thus minimising the time and cost invested in optimising doses. Physiologically based pharmacokinetic modelling is the mathematical description of anatomical, physiological and molecular processes defining pharmacokinetics. Compared with techniques usually used to select paediatric doses of adult formulations [13–16], PBPK modelling is a bottom-up approach integrating *in vitro* data, such as apparent intestinal permeability, intrinsic clearance and protein binding, in a mathematical description of absorption, distribution, metabolism and excretion to predict *in vivo* pharmacokinetics [17].

Previous studies identified trough concentrations of 1.2 µg/mL and 17 ng/mL for cabotegravir and rilpivirine, respectively, need to be achieved to warrant efficacy [18, 19]. No toxicity limited concentrations have been reported previously [1]. Therefore, the aim of this study was to simulate the pharmacokinetics and inform optimal doses of LAI intramuscular (IM) formulations of cabotegravir and rilpivirine in 95% of children and adolescents aged 3–18 years through PBPK modelling for HIV treatment.

2 Methods

The PBPK models were constructed using Simbiology® Version 4.3.1, a product of Matlab® Version 8.2 (MathWorks, Natick, MA, USA). Instant and uniform distribution of drugs into tissues, no reabsorption of the drug from the large intestine and a blood-flow limited model [20]

were assumed. A previously published adult IM PBPK model was used in this study [21]. The pharmacokinetics of LAI IM cabotegravir and rilpivirine were simulated and validated in adult PBPK models and later optimised for different weight categories of children (aged 3–12 years) and adolescents (aged 12–18 years). Children and adolescents between the ages of 3 and 18 years were divided into World Health Organization weight groups [22] and 100 virtual individuals were generated in each weight category.

2.1 Anatomy

Adult PBPK models were defined by key characteristics such as age and weight of the individuals. These defining characteristic values were further used for the computation of organ and tissue volumes, as well as blood flow rates through allometric equations described by Bosgra et al. [23]. The anatomy and physiology of children and adolescents were obtained from various literature sources, validated against available clinical data prior to dose optimisation [23–33]. To improve the confidence of the constructed paediatric PBPK models, validation against intravenous lorazepam and intramuscular ceforanide as reference drugs was also conducted [34]. The various equations used for the construction of paediatric PBPK models and validations across different ages are available in the Electronic Supplementary Material.

2.2 Simulation of Absorption, Distribution, Metabolism and Excretion Processes

Drug diffusion from the IM compartment was assumed to obey first-order rate kinetics and the equation was obtained from Tegenge et al. [35]. The release rate of cabotegravir was obtained from the literature [36] and for rilpivirine, was derived using 48-week clinical data from LATTE-2, a recent phase II efficacy trial of these two formulations used in combination [19]. The intrinsic clearance values derived from in vitro data were obtained from the literature [37] and extrapolated to systemic clearance [38]. The distribution of the drug to different organs and tissues was simulated using previously published equations [21].

2.3 Model Validation

The physicochemical properties of cabotegravir and rilpivirine used in the model are presented in Table 1. The validation of the drug properties against clinical data was conducted in 100 virtual adults for a 800-mg quarterly dose of cabotegravir (from weeks 12–28) and for a subsequent monthly dose of 900 mg of rilpivirine (after the initial dose of 1200 mg) [1]. The release rate of rilpivirine was identified from the clinical data using the PBPK model [1]. The

Table 1 Physicochemical properties and in vitro and population pharmacokinetic data of antiretrovirals

	Cabotegravir	Rilpivirine
Molecular weight	427	366
Log $P_{o:w}$	1.04 [64]	4.32 [65]
Protein binding (%)	99.30 [54]	99.70 [65]
pK_a	10.04 [64]	3.26 [65]
R	0.441 [66]	0.67 [65]
Polar surface area	99.2	
Hydrogen bond donors	2	
Caco-2 permeability (cm/s)		12×10^{-6} [65]
CYP3A4 CL_{int} ($\mu\text{L}/\text{min}/\text{pmol}$)		2.04 [65]
UGT1A1 CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$)	4.5 [37]	
UGT1A9 CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$)	2.2 [37]	
Release rate (h^{-1})	4.5×10^{-4} [36]	9×10^{-4} [1]

CL_{int} intrinsic clearance, CYP cytochrome P450, $\text{Log } P_{o:w}$ partition coefficient between octanol and water, pK_a logarithmic value of the dissociation constant, R blood-to-plasma drug ratio, UGT uridine diphosphate glucuronosyltransferase

release rate was also validated against the LATTE-2 pharmacokinetic curve of cabotegravir and rilpivirine. The cabotegravir release rate was assumed to be $4.54 \times 10^{-4} \text{ h}^{-1}$ as in LATTE-2 (or prior adult studies); however, there was a decrease in the release rate of rilpivirine from 9×10^{-4} to $5 \times 10^{-4} \text{ h}^{-1}$, because the rilpivirine formulation included in LATTE-2 was different from a previous investigation and [19] with a slower release rate [1]. A schematic of the LATTE-2 dosing regimen implemented in this study is shown in Fig. 1.

2.4 Dose Prediction

After the validation of the physicochemical parameters, the anatomy and physiology were modified to describe children and adolescents using appropriate allometric equations obtained from the literature, as described in the Electronic Supplementary Material [12, 23, 25–28, 39]. Following the IM injection, dose optimisation in healthy paediatric individuals was conducted such that at least 95 out of the 100 virtual individuals had a mean trough concentration (C_{trough}) over the target trough concentrations for the required duration. Based on the LATTE-2 study, a target C_{trough} of $1.35 \mu\text{g}/\text{mL}$ was used as the minimum target trough concentration for cabotegravir dose predictions following a 10-mg PO dose, and $70 \text{ ng}/\text{mL}$ was used as the average concentration for rilpivirine following a 25-mg dose [19]. A PO dosing regimen for 4 weeks (steady state) followed by a loading dose and eleven maintenance doses for a 4-weekly IM administration of rilpivirine and cabotegravir were simulated, for a total period of 52 weeks.

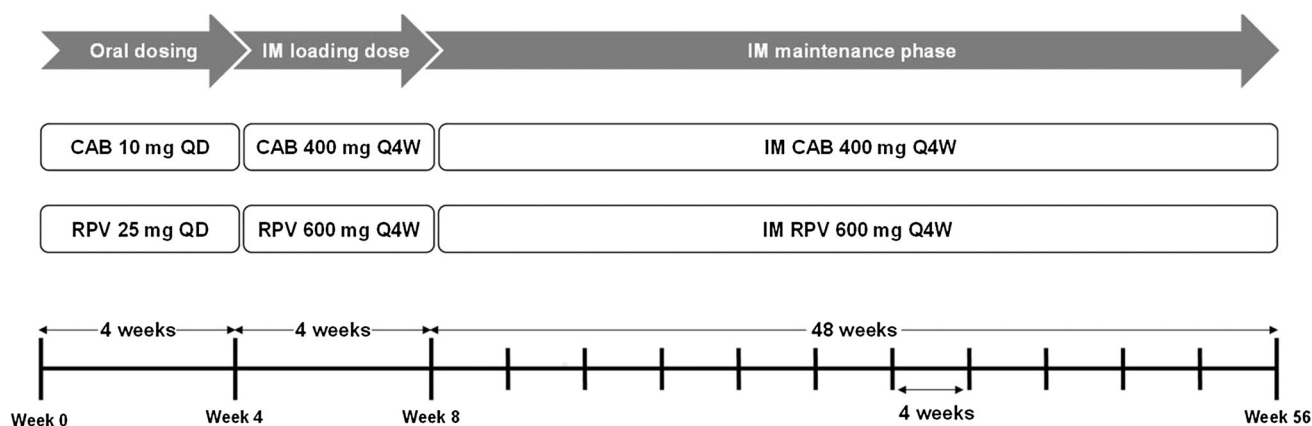


Fig. 1 Validation of adult physiologically-based pharmacokinetic model using the LATTE-2 dosing regimen. Oral dosing regimen was followed for 4 weeks, followed by a single 4-weekly intramuscular

(IM) dose and 11 4-weekly intramuscular maintenance doses. CAB cabotegravir, *QD* once daily, *Q4W* 4-weekly dose, *RPV* rilpivirine

2.5 Sensitivity Analysis

A differential sensitivity analysis was performed to identify the key parameters that impact the pharmacokinetic profiles of LA formulations [40]. Analysis was performed for the loading dose and the first maintenance dose of the cabotegravir and rilpivirine LAI IM formulation in adults. Sensitivity was analysed using the provided inbuilt feature of Simbiology at user-defined values without normalisation in the computation. Six parameters (blood-to-plasma ratio, cardiac output, plasma clearance, liver weight, fraction unbound and release rate) were analysed against drug plasma concentrations. Each parameter was varied by 20% from its mean value and 100 simulations were conducted while keeping the rest of the parameters constant. The sensitivity coefficient (ϕ_i) indicates the change of plasma concentration values (Y) with respect to a unit change in a parameter (X) as shown in Eq. (1) [40]:

$$\phi_i = \frac{\% \Delta Y}{\% \Delta X}. \quad (1)$$

3 Results

The structure and equation of the current PBPK model are based on a previous publication and modified to represent antiretroviral distribution in paediatric and adolescent individuals [21]. The anatomy and physiology of children and adolescents were also validated against the literature and the results are presented in the Electronic Supplementary Material. Physiologically-based pharmacokinetic models were initially qualified by validation against available clinical data for both cabotegravir and rilpivirine in adults to ensure that the selected drug properties were appropriate. The mean simulated pharmacokinetic parameters for maximum plasma concentration (C_{max}), C_{trough} and area under the plasma concentration–time curve (AUC) were compared against available clinical data for the LA formulations for both drugs used in adults (cabotegravir, second IM dose of 800 mg and rilpivirine 900 mg after the initial dose of 1200 mg) [shown in Table 2; Fig. 2]. A stringent qualification of accuracy was applied whereby PBPK models were considered validated only if the mean value was within 0.5-fold from the clinical

Table 2 Validation of cabotegravir and rilpivirine after the second intramuscular dose in adults: clinical [1] vs. simulated pharmacokinetic data

Drug	Dose (mg)	AUC		C_{max}		C_{trough}	
		Clinical	Predicted	Clinical	Predicted	Clinical	Predicted
Cabotegravir ^a	800 mg quarterly	4467 (52)	5166 (23)	3.3 (59)	3.5 (21)	1.1 (140)	1.2 (24)
Rilpivirine ^b	900 mg monthly	74,420 (35)	84,270 (44)	168 (37)	157 (42)	79.1 (44)	72.1 (45)

Values are represented as geometric mean

AUC area under the plasma concentration–time curve, C_{max} maximum plasma concentration, C_{trough} trough plasma concentration, % CV coefficient of variation expressed as a percentage

^a For cabotegravir, C_{max} and C_{trough} are $\mu\text{g/mL}$ and AUC is $\mu\text{g} \times \text{h/mL}$ at day 84

^b For rilpivirine, C_{max} and C_{trough} are ng/mL and AUC is $\text{ng} \times \text{h/mL}$ at day 28

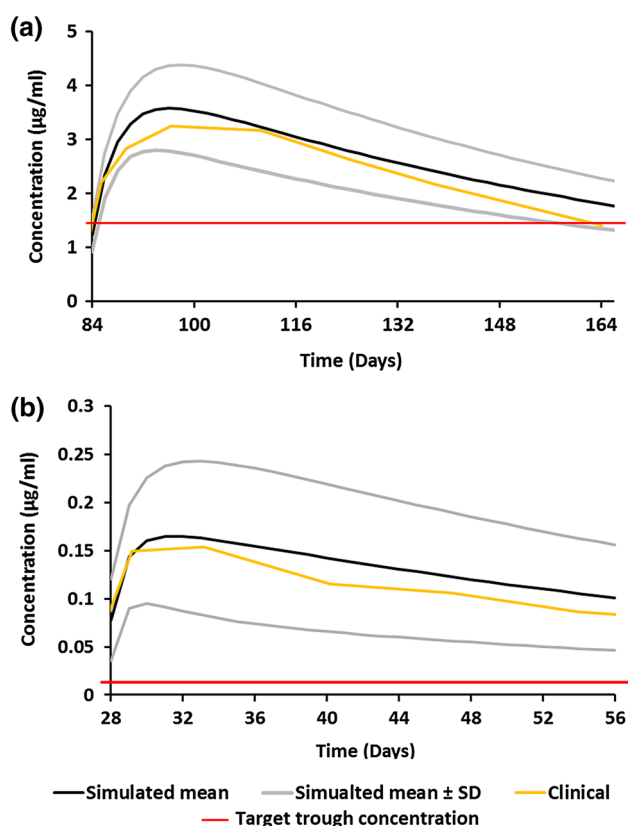


Fig. 2 Validation of the physiologically-based pharmacokinetic model parameters against clinical data for the second intramuscular administration in adults. **a** Cabotegravir (800 mg followed by 800 mg quarterly). **b** Rilpivirine (1200 mg followed by 900 mg monthly) [1]. *SD* standard deviation

value, rather than the conventional two-fold agreement limits [41].

The formulation characteristics were maintained equal to the adult formulation for the simulations in children and adolescents, assuming a similar release rate of the drugs from the formulations, and the use of the same formulations in adults, children and adolescents. Intramuscular doses were optimised to have a pharmacokinetic profile with the concentration exceeding the 10 mg PO C_{trough} for cabotegravir over the duration of treatment and an average concentration over the C_{trough} of 25 mg PO rilpivirine for the first 12 IM doses (Fig. 3). For rilpivirine, it was also ensured that the concentrations were always above the 90% protein-binding-adjusted inhibitory concentration (PAIC_{90}) value of 12.1 ng/mL [18] subsequent to the loading dose. A summary of predicted doses for both cabotegravir and rilpivirine for different weight categories is shown in Table 3.

3.1 Cabotegravir

The validation for 800 mg of IM cabotegravir resulted in mean predicted AUC, C_{max} and C_{trough} values that were

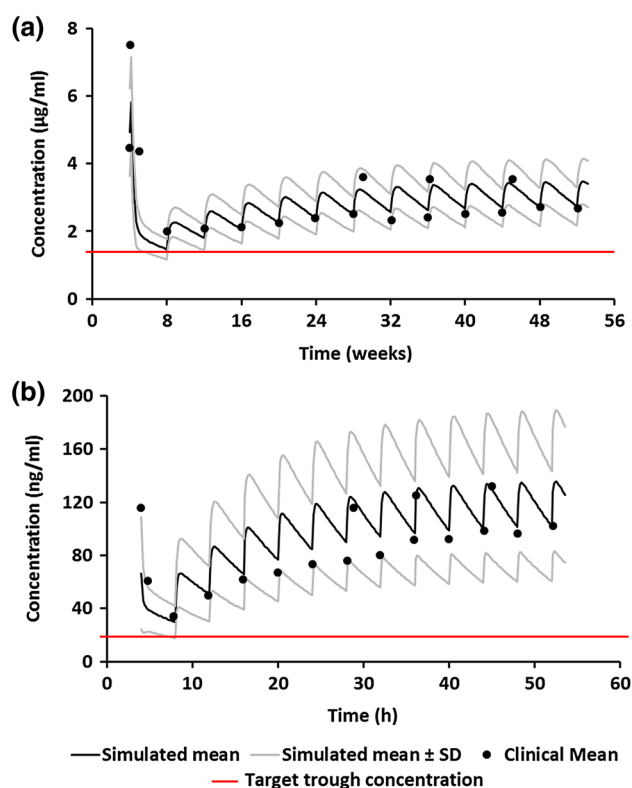


Fig. 3 Validation of the release rate against clinical data from the 48-week LATTE-2 study in adults. **a** cabotegravir and **b** rilpivirine [19]. The target trough concentration is 1.35 µg/mL for cabotegravir and 12 ng/mL for rilpivirine. *SD* standard deviation

+15.6, +6.1 and +9.1% compared with clinical values, respectively [1]. A target trough concentration of 1.35 µg/mL (10 mg PO C_{trough}) was chosen from the literature [1]. The doses for different weight groups were informed such that at least 95 out of the 100 virtual individuals had a C_{trough} value over the target trough concentration for a duration of 48 weeks (Fig. 4). The daily PO dose administered for a period of 4 weeks was 10 mg for weights ranging between 14 and 50 kg and 20 mg for weights between 50 and 70 kg. For IM cabotegravir, the loading dose ranged between 200 and 600 mg and maintenance doses between 100 and 250 mg for the simulated plasma C_{trough} to stay over the 10 mg PO C_{trough} as described in Table 3.

3.2 Rilpivirine

The simulated mean AUC, C_{max} and C_{trough} values were +13.2, -6.5 and -8.8%, compared with the clinical data [1]. After the validation of the rilpivirine PBPK model, the first-order kinetic release rate was identified to be $9 \times 10^{-4} \text{ h}^{-1}$ [1]. The validation was then performed to find the optimal release rate for rilpivirine pharmacokinetics from the LATTE-2 study. Because of the

Table 3 Prediction of the dose (in mg) for cabotegravir and rilpivirine for different weight categories of children and adolescents with an initial 4 weeks of the oral (PO) dose followed by an intramuscular loading dose and 11 maintenance doses lasting 4 weeks each

Weight (kg)	Rilpivirine (mg)			Cabotegravir (mg)		
	Oral	Loading dose	Maintenance dose	Oral	Loading dose	Maintenance dose
14–19.9	25	250	150	10	200	100
20–24.9		250	200		250	100
25–29.9		250	200		250	100
30–34.9		300	250		350	150
35–39.9		350	300		350	150
40–44.9		400	300		400	150
45–49.9		450	350		450	150
50–54.9		450	400	20	450	200
55–59.9		500	400		500	200
60–64.9		500	450		550	200
65–69.9		550	500		600	250
Target concentration in ng/mL (achieved by a PO dose in mg) [references]	70 (25 mg PO C_{trough}) [19]			1370 (10 mg PO C_{trough}) [19]		

C_{trough} trough concentration

reformulation of rilpivirine, the optimal release rate was observed to be $5 \times 10^{-4} \text{ h}^{-1}$. The optimal doses were informed for different weight categories such that the average drug C_{trough} plasma concentrations of 48 weeks remained over 70 ng/mL (25 mg PO C_{trough}) [19]. A fixed daily PO dose of 25 mg was administered for 4 weeks prior to IM doses. The loading dose ranged from 250 to 550 mg and the maintenance doses from 200 to 500 mg across weight groups from 15- to 70-kg individuals. The optimal doses ensured plasma concentrations over the PAIC₉₀ value and average IM concentrations over 25 mg PO C_{trough} for at least 95 out of 100 individuals (Fig. 5).

3.3 Sensitivity Analysis

Figure 6 shows the mean differential sensitivity analysis plot of 100 runs for six chosen parameters with respect to time. The analysis was performed for two successive (loading and maintenance) monthly IM doses of cabotegravir and rilpivirine in adults.

For cabotegravir, the analysis indicated that the plasma concentration is sensitive to only two of the six factors and a higher influence was observed in the first days following administration. Cardiac output and systemic clearance of the drug had higher sensitivity towards the variation in plasma concentrations. Protein binding, release rate, liver weight and blood-to-plasma ratio were negligibly sensitive. This indicates that physiological factors and the UGT content in the liver had a higher potential to influence the simulated pharmacokinetics. Sensitivity against cardiac output was negative for most of the duration, indicating an increased effect against plasma concentration even when

the value changes by $\pm 20\%$ from the mean. Sensitivity against systemic clearance had a similar trend to cardiac output but with lower intensity. During the initial days after the administration of the maintenance dose, both these factors showed a positive relationship against plasma concentration, indicating a lower effect.

For rilpivirine, the change in plasma concentration was not sensitive when cardiac output, liver weight and release rate varied $\pm 20\%$ from the mean. Blood-to-plasma ratio had a higher positive effect immediately after dosing, implying a lower influence on plasma concentration. Blood-to-plasma ratio and systemic clearance showed a positive relationship over the entire dosing period, indicating a decreased effect against plasma concentration. Protein binding fluctuated between positive and negative; however, the variation is minimal, signifying minimal or no effect on plasma concentration.

4 Discussion

Optimal treatment adherence is essential for the effective inhibition of viral replication and to mitigate development of resistance to ARVs. Although PO formulations have been demonstrated to result in therapeutic concentrations, sub-optimal adherence in patients who are receiving PO daily dosing for treatment and prevention have been described [2, 42–45]. Alternative administration strategies could support higher adherence, reducing the frequency of administration and addressing pill fatigue. More specifically, formulations allowing a monthly or quarterly administration could address the adherence issue, thus

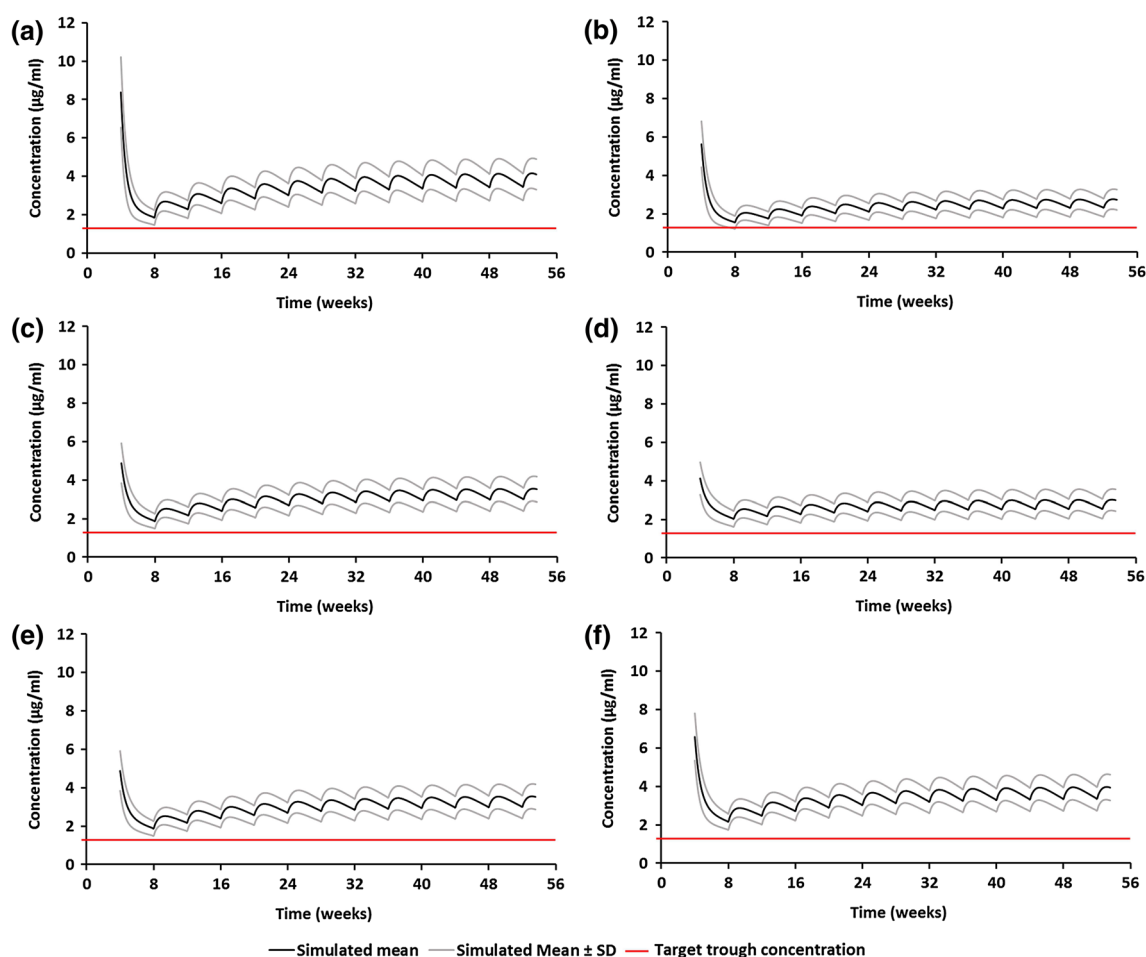


Fig. 4 Plasma concentrations of cabotegravir loading and maintenance doses from weeks 4–52 for different weight categories of children and adolescents. **a** 14–19.9 kg, **b** 25–29.9 kg, **c** 35–39.9 kg, **d** 45–49.9 kg, **e** 55–59.9 kg and **f** 65–69.9 kg. The mean plasma

concentrations are over the target trough concentrations of 1.37 µg/mL. Concentration data were derived from optimized dosing strategies calculated for each weight band, as described in Sect. 3. SD standard deviation

decreasing the risk of drug resistance. Antiretrovirals with high potency and favourable pharmacokinetics are essential for the development of the LAI strategy. The recent development of novel formulations of cabotegravir and rilpivirine constitutes a remarkable step towards the definition of LAI strategies, providing innovative pharmacological tools for adults [1]. Dose optimisation in special populations of patients such as children and adolescents is complex owing to their unique physiological and anatomical characteristics compared with adults. Traditionally, clinical trials have not been frequently conducted in these patient populations because of ethical and logistical considerations [46]. However, recent regulations promote clinical studies in paediatric patients to evaluate safety and efficacy prior to therapy [47, 48]. The present study focuses on the identification of dosing strategies of cabotegravir and rilpivirine in children and adolescents using computational pharmacokinetic modelling for HIV treatment.

Various PBPK models have been developed for adults, and recently, this modelling technique has also been used for a variety of special populations including children and adolescents [32, 49]. Drug distribution can be simulated in special populations of patients through the integration of age-related anatomical and physiological changes into the mathematical PBPK framework. Physiologically-based pharmacokinetic modelling has been recently used for the prediction of midazolam and theophylline in neonates, infants and children [12]. In two other studies, the relationship between adult and paediatric clearance rates was established using the cytochrome P450 ontogeny for six compounds and then simulations were performed for five different drugs at different age groups [50, 51]. An oseltamivir PBPK model was used to predict the pharmacokinetics in neonates and infants with influenza [52] and a disease-specific model was also recently developed in children with and without liver cirrhosis [53].

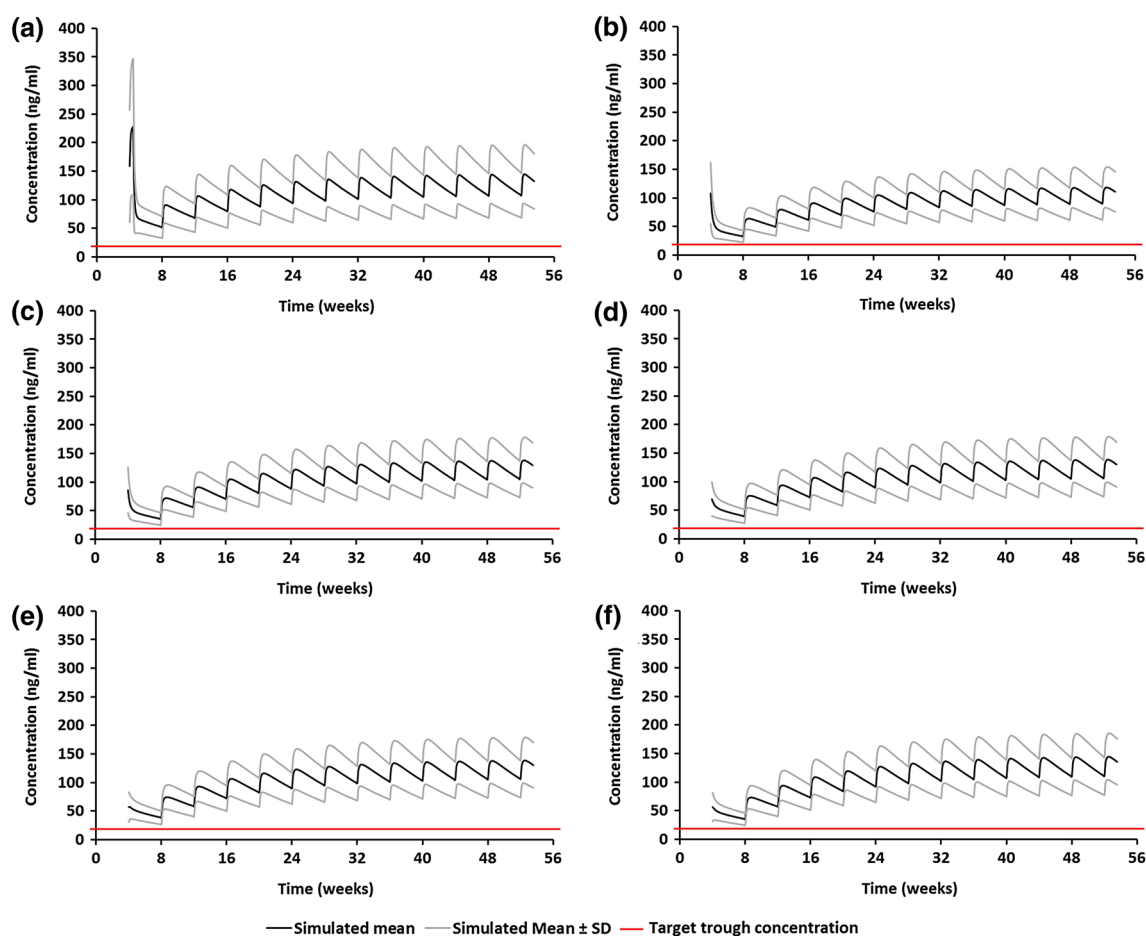


Fig. 5 Plasma concentrations of rilpivirine loading and maintenance doses from weeks 4–52 for different weight categories of children and adolescents. **a** 14–19.9 kg, **b** 25–29.9 kg, **c** 35–39.9 kg, **d** 45–49.9 kg, **e** 55–59.9 kg and **f** 65–69.9 kg. The mean plasma

concentrations are over the target trough concentrations of 17 ng/mL. Concentration data were derived from optimized dosing strategies calculated for each weight band, as described in Sect. 3. *SD* standard deviation

Both cabotegravir and rilpivirine are characterised by long-half lives and physicochemical properties that are compatible with nanoformulations for LAIs, representing attractive options for continuous therapy [1, 54]. Using physicochemical properties and in vitro data, the pharmacokinetics of cabotegravir and rilpivirine in adults was validated against available clinical data. The model validation was conducted at the second dose of the LAI ARVs to have a mathematical representation of the pharmacokinetics at steady state. Low accuracy and precision were observed in the ÉCLAIR study where the simulated C_{trough} value of cabotegravir was 1.35 $\mu\text{g/mL}$ compared with the observed value, which was less than 0.66 $\mu\text{g/mL}$ ($4 \times \text{PAIC}_{90}$) [55]. Hence, stringent guidelines were applied for the validation process where $\pm 50\%$ deviation from the mean clinical values was considered acceptable instead of the conventional two-fold deviation [41]. The pharmacokinetic parameters AUC, C_{max} and C_{trough} simulated through the PBPK approach were in agreement with the

clinical data and, therefore, our PBPK model was considered robust for predicting the LAI IM doses in children and adolescents. In the simulation of LAI pharmacokinetics in children, the release rates of the LAI formulations were maintained equal to the validation in adults, to facilitate bridging to a paediatric simulation. Although the physiology of the muscular tissues is different between adults and children, this could potentially support the use of the existing formulations in paediatric clinical studies with no further reformulation [56]. However additional studies are required because there is a possibility that smaller doses with less injection volume could decrease the total surface area and strain in the muscle, thereby altering the pharmacokinetic profile. The doses were optimised such that cabotegravir and rilpivirine concentrations were over the target trough concentrations (described in Sect. 2) for the duration of the dose. Although PAIC_{90} values indicate a trough concentration to suppress the virus in vitro, this does not translate into effective therapeutic activity in vivo [57].

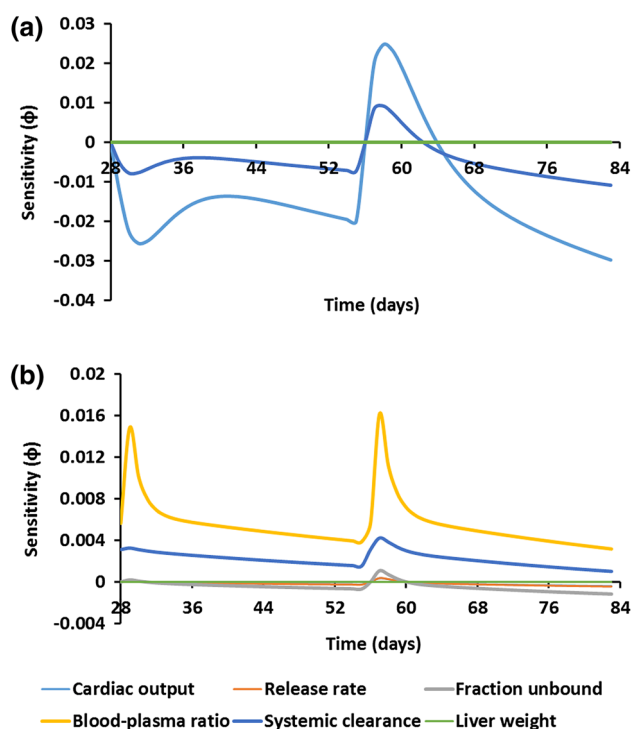


Fig. 6 Differential sensitivity analysis of plasma concentration against key parameters (blood-plasma ratio, cardiac output, fraction unbound, liver weight, release rate and systemic clearance) in adults for the 4-weekly intramuscular loading dose and the first maintenance dose. **a** cabotegravir and **b** rilpivirine

Therefore, the dose optimisation was conducted considering LATTE-2 study target trough concentrations.

The required dose was proportional to the weight of the individual, which indicates increases in the volume of distribution and systemic clearance in adolescents. As the weight of the individual increased from 15 to 70 kg, the required dose of cabotegravir tripled in an individual weighing 70 kg compared with a 15-kg individual, whereas the dose needed was just over double in the case of rilpivirine. Fluctuation in maximum and trough plasma concentration of cabotegravir is $>2 \mu\text{g/mL}$ compared with rilpivirine ($<100 \text{ ng/mL}$). Additionally, cabotegravir is more sensitive to variations in clearance and cardiac output compared with rilpivirine (as shown in Fig. 6) and because of these physiological variations across weight groups, a higher dose is required in the case of cabotegravir for adolescents compared with children. This indicates that doses cannot be linearly extrapolated based on weight and a deeper understanding of important mechanistic processes influencing the pharmacokinetics in children and adolescents is required. The loading doses are higher compared with the maintenance doses as the extra dose is essential to maintain drug plasma concentrations over the $C_{\text{trough}}/\text{PAIC}_{90}$ values. Because the maintenance dose for cabotegravir is low compared with rilpivirine, they could be more

suitable for a less frequent (bimonthly or quarterly) administration.

Long-acting injectable formulations may improve the problems faced with low adherence of therapies in children and adolescents. The identification of optimal doses in healthy paediatric individuals should be given priority as most of the doses for prescribed drugs are simply scaled from adult doses with varying success. However, pain involved during the administration of IM injections has the potential to refrain children from preferring this route and opting for PO dosing regimens. Chloramphenicol dose scaling from adults in neonates and infants reached toxic concentrations, which led to a higher mortality rate, an example of where the developmental pharmacology of paediatric patients was ignored [58]. The mortality rate was high in neonates affected with kernicterus who were administered penicillin/sulfoxazole than with oxytetracycline in another case [59]. In both these cases, an immature glucuronidation system led to the accumulation of the drug, resulting in high plasma concentrations and conclusively demonstrating that the physiological processes of the child cannot always be accounted for by scaling adult doses [59, 60].

Although the simulated doses for children and adolescents could represent a valuable guideline for drug safety and efficacy clinical studies, the applied modelling strategies have some limitations. Numerous barriers can complicate the implementation of dosing recommendations for special populations. Because anatomical and physiological changes in children follow a non-linear trend, pharmacokinetic and pharmacodynamic investigations need to be conducted to evaluate the safety, efficacy and tolerability profiles in children and the current modelling approach can support a rational identification of suitable dosing strategies [61]. Especially in infants and neonates aged younger than 3 years, the ontogeny of cytochrome P450 expression in the liver and wide variation in organ weights and volumes could lead to low accuracy in model prediction and hence this study focuses on children aged older than 3 years. Some anatomical and physiological features and the associated complex biological processes have not been simulated owing to a paucity of relevant data [35]. Absence of information on drug transporters at the injection site could alter the absorption, distribution and metabolic processes, which could not be captured in the current PBPK model. Evidence suggests that cabotegravir undergoes enterohepatic recirculation; however, quantitative evaluation of this physiological process is absent and hence could not be incorporated in the PBPK model [62]. Recent investigation with a paliperidone LAI micro-suspension revealed formation of a granuloma as a result of macrophage accumulation surrounding the site of injection. This phenomenon further controlled drug release from the depot

and evidence also showed drug uptake and release from macrophages [63]. The extent of the occurrence of this phenomenon and the size of the depot could alter the release rates and thereby drug pharmacokinetics, which was not accounted for in this study. Physiological and metabolic variation of muscle composition in children compared with adults was not accounted for during the dose optimisation process [56]. Low clinical C_{\max} compared with the simulated pharmacokinetic curve (Fig. 2) could be owing to the fraction of drug distributed through the lymphatic circulation. Additionally, the potential adverse effects considering the differences in the anatomy and physiology of children compared with adults, prolonged exposure and the inability to discontinue therapy once administered are important factors to be assessed before drug administration [3].

Long-acting injectable therapy has attracted considerable attention in various therapeutic areas, including chronic HIV infection. For example, the National Institutes of Health recently provided support to set up a worldwide team involving researchers from academia and the pharmaceutical industry to facilitate the development of LAI formulations for HIV. This Long-Acting/Extended Release Antiretroviral Resource Program (LEAP; <http://www.longactinghiv.org>) includes a PBPK modelling service to facilitate the design of long-acting formulations for HIV and related infectious diseases. This type of support may improve the efficiency of the selection of formulations, doses and dose intervals for paediatric and other special populations.

5 Conclusion

Physiologically-based pharmacokinetic models were successfully validated for both cabotegravir and rilpivirine LAI formulations against available clinical data in adults. A novel PBPK model for the prediction of pharmacokinetics in children and adolescent was developed to simulate dose selection in this vulnerable group. Dosing strategies for cabotegravir and rilpivirine were estimated in different weight groups of children and adolescents considering two efficacy target trough concentrations. From this modelling study, the predicted paediatric dosing of cabotegravir and rilpivirine differs for each weight category and scaling adult doses could have led to plasma concentrations either below the $PAIC_{90}$ /Minimum Effective Concentration value or above a safe level. Different dosing fractions compared with adult dosages for cabotegravir and rilpivirine indicate that drug-specific physicochemical parameters and absorption, distribution, metabolism and excretion characteristics play a key role in controlling the pharmacokinetics. Physiologically-based pharmacokinetic predictions

from this study could potentially inform reference doses required to conduct paediatric clinical trials for various weight categories.

Author Contributions RKRR performed the physiologically based pharmacokinetic modelling. RKRR and MS wrote the manuscript. DJB, SR, CFM, CF and AO reviewed the manuscript.

Compliance with Ethical Standards

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Conflict of interest David J. Back receives consulting or advisor fees from Abbvie, Boehringer Ingelheim, Gilead, Janssen, Merck and ViiV. He also receives research funding from Abbvie, Boehringer Ingelheim, BMS, Gilead, Janssen, Merck and ViiV. Steve Rannard receives funding from ViiV and AstraZeneca and has many human immunodeficiency virus nanomedicine patents. Charles Flexner receives consulting or advisor fees from Abbvie, Boehringer Ingelheim, Bristol Myers-Squibb, Gilead and GlaxoSmithKline, Merck and ViiV. Andrew Owen receives research funding from Merck, ViiV Healthcare, Janssen, Pfizer and AstraZeneca, consultancy from Merck and Norgine and is a co-inventor of patents relating to human immunodeficiency virus nanomedicines. Marco Siccardi receives research funding from ViiV and Janssen. Rajith K. R. Rajoli and Caren Freel Meyers have no conflicts of interest to declare.

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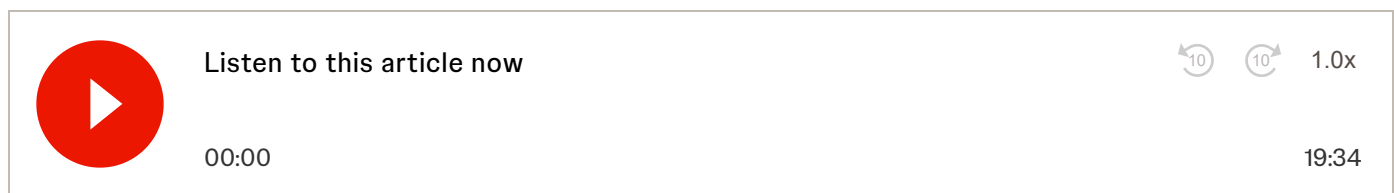
Innovative Medicine

U.S. FDA Approves CABENUVA (cabotegravir and rilpivirine) for Adolescents, Expanding the Indication of the First and Only Complete Long-Acting Injectable HIV Regimen

CABENUVA offers virologically suppressed adolescents 12 years of age or older living with HIV-1 an injectable treatment option with as few as six dosing days per year

March 29, 2022

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TITUSVILLE, N.J., March 29, 2022 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced the U.S. Food and Drug Administration (FDA) has approved CABENUVA (cabotegravir and rilpivirine) for the treatment of HIV-1 in virologically suppressed adolescents (HIV-1 RNA less than 50 copies per milliliter [c/mL]) who are 12 years of age or older, weigh at least 35 kg and are on a stable antiretroviral regimen, with no history of treatment failure, nor known or suspected resistance to either cabotegravir or rilpivirine.^{1,2} Co-developed as part of a collaboration with ViiV Healthcare, CABENUVA is the first and only complete long-acting HIV-1 treatment

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a single-dose vial, a product of Janssen Sciences Ireland Unlimited Company, one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

“HIV remains one of the most significant challenges in global health, and as part of our decades-long commitment to fighting HIV, Janssen is working tirelessly to advance innovative new treatment options for young people living with HIV,” said James Merson, Ph.D., Global Therapeutic Area Head, Infectious Diseases, Janssen Research & Development, LLC. “With this milestone, we’re continuing to redefine how HIV can be managed so that even more people, including adolescents, can benefit from long-acting injectable therapies.”

The expanded indication for CABENUVA is supported by studies in adults and by data from the Week 16 interim analysis of the ongoing More Options for Children and Adolescents (MOCHA) study from ViiV Healthcare’s collaboration with the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT). The efficacy of CABENUVA in adolescents is extrapolated from adults with support from pharmacokinetic analyses showing similar drug exposure. The safety profile in adolescents with the addition of either oral cabotegravir followed by injectable cabotegravir (n=8) or oral rilpivirine (n=15) followed by injectable rilpivirine (n=13) was consistent with the safety profile established with cabotegravir plus rilpivirine in adults.

Based on data from the Week 16 analysis of the MOCHA study in 23 adolescents, adverse reactions were reported in 61% of patients receiving either cabotegravir or rilpivirine in addition to their current antiretroviral treatment. The majority of these individuals (86%) had a Grade 1 or Grade 2 adverse reaction. The adverse reactions reported by more than one patient (regardless of severity) were injection site pain (n=13) and insomnia (n=2). Two patients had Grade 3 adverse reactions of hypersensitivity (n=1) and insomnia (n=1). The Grade 3 adverse reaction of drug hypersensitivity led to discontinuation of rilpivirine during oral lead-in. Sixty-two percent of patients who received at least one injection of cabotegravir or rilpivirine reported at least one injection site reaction. All injection site reactions were Grade 1 or Grade 2.¹

“We’re proud of our longstanding efforts to address the needs of young people living with HIV,” said Candice Long, President, Infectious Diseases & Vaccines, Janssen Therapeutics, a Division of Janssen Products, LP. “By advancing new treatment options to meet the unique needs of adolescents living with HIV, we can help build a future where young people are not defined or limited by their diagnosis.”

The U.S. Centers for Disease Control and Prevention **reported** that people aged 13-24 accounted for 21% of all new HIV diagnoses in the U.S. and dependent areas in 2018.³ Adhering to treatment regimens can be difficult for children and adolescents, who may skip HIV medicine doses to hide

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In **January 2021**, the FDA approved CABENUVA to be administered every month to adults living with HIV-1. In **February 2022**, the FDA approved an expanded label for CABENUVA to be administered every two months to adults living with HIV-1. The FDA approved a label update in **March 2022** that made the oral lead-in period optional for adults living with HIV-1 who planned to begin the injectable treatment regimen. The oral lead-in period is also optional for adolescent patients.

The once-monthly and every-two-months version of cabotegravir and rilpivirine injectable treatment has been approved for adults by the European Commission, Health Canada, the Australia Therapeutic Goods Administration, and the Swiss Agency for Therapeutic Products. Regulatory reviews continue with additional submissions planned throughout 2022.

Johnson & Johnson's Commitment to HIV

Johnson & Johnson has been committed to the fight against HIV for decades, playing a central role in bringing nine therapeutics to people living with HIV, and continuing to drive innovation in HIV prevention and care. Johnson & Johnson also works with vulnerable communities on the frontlines of the HIV epidemic through initiatives such as **Positively Fearless**, **DREAMS Thina Abantu Abasha**, the **MenStar Coalition** and the **New Horizons Collaborative**.

To learn more, visit [jnj.com/hiv](https://www.jnj.com/hiv)

About CABENUVA (cabotegravir and rilpivirine)

CABENUVA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents who are 12 years of age or older and weighing at least 35 kg to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than <50 copies per /mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

The complete regimen combines the integrase strand transfer inhibitor (INSTI) cabotegravir, developed by ViiV Healthcare, with rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) developed by Janssen. Rilpivirine is approved in the U.S. as a 25 mg tablet taken once a day to treat HIV-1 in combination with other antiretroviral agents in antiretroviral treatment-naïve patients 12 years of age and older and weighing at least 35 kg with a viral load $\leq 100,000$ HIV RNA c/mL.

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MOCHA ([NCT03497676](#)) is a Phase 1/2, multi-center, open-label, non-comparative study of oral cabotegravir or rilpivirine and long-acting cabotegravir or rilpivirine in virologically suppressed adolescents living with HIV-1 who are 12 to less than 18 years old. The study is designed to confirm the dose and evaluate the safety, tolerability, acceptability, and pharmacokinetics of cabotegravir and rilpivirine in adolescents living with HIV. Caregivers of adolescent participants in the United States are also enrolled to take part in a single in-depth qualitative interview to contribute to the evaluation of tolerability and acceptability of long-acting therapy, with **favorable feedback overall**.⁴ The study is being conducted at research centers in Botswana, South Africa, Thailand, Uganda and the United States.

Important Safety Information for CABENUVA (cabotegravir 200 mg/mL; rilpivirine 300 mg/mL) extended-release injectable suspensions

CABENUVA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents who are 12 years of age or older and weighing at least 35 kg to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than <50 copies per /mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

CONTRAINDICATIONS

- Do not use CABENUVA in patients with previous hypersensitivity reaction to cabotegravir or rilpivirine
- Do not use CABENUVA in patients receiving carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, systemic dexamethasone (>1 dose), and St John's wort

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions:

- Hypersensitivity reactions, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported during postmarketing experience with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries

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Post-Injection Reactions:

- Serious post-injection reactions (reported in less than 1% of subjects) were reported within minutes after the injection of rilpivirine, including dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest). These events may have been associated with inadvertent (partial) intravenous administration and began to resolve within a few minutes after the injection
- Carefully follow the Instructions for Use when preparing and administering CABENUVA. The suspensions should be injected slowly via intramuscular injection and avoid accidental intravenous administration. Observe patients briefly (approximately 10 minutes) after the injection. If a post-injection reaction occurs, monitor and treat as clinically indicated

Hepatotoxicity:

- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine with or without known pre-existing hepatic disease or identifiable risk factors
- Patients with underlying liver disease or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations
- Monitoring of liver chemistries is recommended and treatment with CABENUVA should be discontinued if hepatotoxicity is suspected

Depressive Disorders:

- Depressive disorders (including depressed mood, depression, major depression, mood altered, mood swings, dysphoria, negative thoughts, suicidal ideation or attempt) have been reported with CABENUVA or the individual products
- Promptly evaluate patients with depressive symptoms

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:

- The concomitant use of CABENUVA and other drugs may result in known or potentially significant drug interactions (see Contraindications and Drug Interactions)
- Rilpivirine doses 3 and 12 times higher than the recommended oral dosage can prolong the QTc interval
- CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes

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- To minimize the potential risk of developing viral resistance, it is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injection doses of CABENUVA when dosed monthly and no later than 2 months after the final injections of CABENUVA when dosed every 2 months. If virologic failure is suspected, switch the patient to an alternative regimen as soon as possible

ADVERSE REACTIONS

- The most common adverse reactions (incidence $\geq 2\%$, all grades) with CABENUVA were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash
- The safety of CABENUVA in adolescents is expected to be similar to adults

DRUG INTERACTIONS

- Refer to the applicable full Prescribing Information for important drug interactions with CABENUVA, VOCABRIA, or EDURANT
- Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended
- Drugs that are strong inducers of UGT1A1 or 1A9 are expected to decrease the plasma concentrations of cabotegravir. Drugs that induce or inhibit CYP3A may affect the plasma concentrations of rilpivirine
- CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There are insufficient human data on the use of CABENUVA during pregnancy to adequately assess a drug-associated risk for birth defects and miscarriage. Discuss the benefit-risk of using CABENUVA during pregnancy and conception and consider that cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CABENUVA. An Antiretroviral Pregnancy Registry has been established
- **Lactation:** The CDC recommends that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Breastfeeding is also not recommended due to the potential for developing viral resistance in HIV-positive infants, adverse reactions in a breastfed infant, and detectable cabotegravir and

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At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

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To learn more about Janssen's commitment to the prevention and treatment of HIV, please visit jnj.com/HIV.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding rilpivirine and development of potential preventive and treatment regimens for HIV. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Sciences Ireland Unlimited Company, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 2, 2022, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other filings with the Securities and

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CON FUNDAMENTO EN LAS INSCRIPCIONES EFECTUADAS EN EL REGISTRO DE ENTIDADES SIN ÁNIMO DE LUCRO, LA CÁMARA DE COMERCIO CERTIFICA:

NOMBRE, IDENTIFICACIÓN Y DOMICILIO

Razón social: FUNDACION IFARMA
Nit: 830091891 6, Regimen Comun
Domicilio principal: Bogotá D.C.

INSCRIPCIÓN

Inscripción No. S0015611
Fecha de Inscripción: 11 de septiembre de 2001
Último año renovado: 2025
Fecha de renovación: 8 de abril de 2025
Grupo NIIF: Grupo III.

UBICACIÓN

Dirección del domicilio principal: Cra.15 No.32-70 Piso 1
Municipio: Bogotá D.C.
Correo electrónico: ifarma@ifarma.org
Teléfono comercial 1: 2454757
Teléfono comercial 2: 3158780717
Teléfono comercial 3: No reportó.

Dirección para notificación judicial: Cra.13 No.32-51 Torre Iii
Ofc.1115
Municipio: Bogotá D.C.
Correo electrónico de notificación: ifarma@ifarma.org
Teléfono para notificación 1: 3381490
Teléfono para notificación 2: 3231472
Teléfono para notificación 3: No reportó.

La Entidad NO autorizó para recibir notificaciones personales a través de correo electrónico, de conformidad con lo establecido en los artículos 291 del Código General del Proceso y 67 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo.

CERTIFICADO DE EXISTENCIA Y REPRESENTACIÓN LEGAL**Fecha Expedición: 24 de mayo de 2025 Hora: 12:55:16**

Recibo No. AA25929175

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CONSTITUCIÓN

Por Acta del 30 de agosto de 2001 de Asamblea de Asociados, inscrito en esta Cámara de Comercio el 11 de septiembre de 2001, con el No. 00043760 del Libro I de las entidades sin ánimo de lucro, se constituyó la persona jurídica de naturaleza Fundación denominada FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SISTEMAS DE SALUD.

ENTIDAD QUE EJERCE INSPECCIÓN, VIGILANCIA Y CONTROL

Entidad que ejerce la función de inspección, vigilancia y control:
ALCALDIA MAYOR DE BOGOTA

REFORMAS ESPECIALES

Por Acta No. 0000002 del 15 de marzo de 2002 de Asamblea de Asociados, inscrito en esta Cámara de Comercio el 1 de abril de 2002, con el No. 00048042 del Libro I de las entidades sin ánimo de lucro, la entidad cambió su denominación o razón social de FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SISTEMAS DE SALUD a FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SITEMAS DE SALUD SIGLA FUNDACION IFARMA.

Por Acta No. 002 del 12 de noviembre de 2009 de Asamblea de Fundadores, inscrito en esta Cámara de Comercio el 18 de enero de 2010, con el No. 00165923 del Libro I de las entidades sin ánimo de lucro, la entidad cambió su denominación o razón social de FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SITEMAS DE SALUD SIGLA FUNDACION IFARMA a FUNDACION IFARMA.

TÉRMINO DE DURACIÓN

La Entidad no se encuentra disuelta y su duración es indefinida.

OBJETO SOCIAL

CERTIFICADO DE EXISTENCIA Y REPRESENTACIÓN LEGAL**Fecha Expedición: 24 de mayo de 2025 Hora: 12:55:16**

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Contribuir al crecimiento social y económico de Colombia y de otros países, a través del trabajo especializado en la investigación, el mejoramiento y el desarrollo de los aspectos relativos a la formulación y ejecución de políticas, la administración, la gestión y el uso adecuado de los medicamentos en particular y la salud y la seguridad social en general. La fundación, para cumplir con su objeto social, utilizará el conocimiento, la experiencia y la experticia de profesionales nacionales e internacionales ampliamente acreditados. Buscará recopilar las experiencias existentes nacional e internacionalmente en los temas de su objeto social. La fundación igualmente buscará actuar como un soporte del sistema de seguridad social en salud y de la prestación de servicios de salud, especialmente pero no exclusivamente, en los temas relativos a la oferta suficiente y competitiva de los recursos terapéuticos que la población requiere. Ello sin incluir en su objeto social la prestación de servicios de salud. Igualmente fomentará el debate, el análisis y la investigación en todos los temas relativos a su objeto, con el propósito de generar e innovar líneas de acción y desarrollo, para lo cual buscará y promoverá la acción conjunta con los organismos nacionales e internacionales que tienen similares objetivos. La fundación utilizará los medios que estime convenientes para comunicar y difundir el conocimiento generado por su accionar. La fundación podrá desarrollar planes, proyectos y programas de investigación, asistencia técnica, asesoría y consultoría, e innovación tecnológica en los campos de la salud, la seguridad social y el desarrollo social. Igualmente podrá editar, producir y comercializar libros, impresos y otras publicaciones, así como producir, editar y comercializar servicios informativos. Facultades: para cumplir con su objeto social y precautelar su patrimonio, la fundación podrá celebrar, en los términos de la ley, todos los actos y contratos que estén directamente relacionados con el objeto antes indicado y los que tengan como finalidad ejercer los derechos o cumplir con las obligaciones que legal o convencionalmente se deriven de la existencia y actividad de la fundación, así entre otros actos y contratos podrá adquirir, enajenar y gravar toda clase de bienes muebles o inmuebles, tangibles e intangibles, girar, aceptar, endosar, otorgar, garantizar y negociar toda clase de títulos valores, celebrar el contrato de mutuo, designar apoderadosos judiciales y extrajudiciales; participará en la creación o en la administración de otras entidades relacionadas con el objeto social, podrá igualmente, asociarse, realizar uniones temporales o alianzas

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estratégicas con otra u otras entidades con o Sin Ánimo de Lucro para el logro de objetivos comunes; representar en el país o en el exterior a otras entidades con similar objeto social. En su accionar en otros países se regirá por las leyes de los mismos.

PATRIMONIO

\$ 79.333.263,00

REPRESENTACIÓN LEGAL

La representación legal de la fundación estará a cargo del Director. El Representante Legal suplente cumplirá las funciones de suplir las ausencias temporales o definitivas del Director y reemplazarlo cuando se necesario con las mismas responsabilidades y facultades.

FACULTADES Y LIMITACIONES DEL REPRESENTANTE LEGAL

El Director de la fundación tendrá las siguientes funciones: 1. Dirigir la fundación de conformidad con las decisiones del consejo directivo y con los presentes estatutos. 2. Representar a la fundación en todos los actos y operaciones que celebre con terceros, tanto judicial como extrajudicialmente, por si o por conducto de apoderado. 3. Cumplir y hacer cumplir los estatutos, reglamentos, acuerdos y decisiones del consejo directivo. 4. Designar al personal de la fundación, celebrar los contratos del caso y decidir sobre promociones, sanciones, retiros y reemplazos a que haya lugar y coordinar la actividad de los distintos empleados y dependencias de la fundación. 5. Ejecutar los negocios de la fundación; velar por los bienes de la misma, por sus operaciones técnicas, sus estados financieros y documentos; suscribir los actos y contratos de la fundación sin restricción alguna en los montos de estos siempre que no estén en contradicción al objeto social de la misma, ni afecten sus bienes y bajo las condiciones establecidos por los estatutos, reglamentos y por el consejo directivo. Firmar los estados financieros. 6. Vigilar el recaudo e inversión de los recursos de la fundación, y la correcta disposición de sus bienes. 7. Presentar anualmente al consejo directivo el informe sobre el desarrollo de las actividades de la fundación y sus estados financieros. 8. Coordinar

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las acciones necesarias para el cumplimiento de los objetivos de la fundación y llevar la vocería oficial de la fundación en público y ante los medios de comunicación. 9. Las demás que le señalen los estatutos y la ley y las que, siendo compatibles con su cargo, le asigne el consejo directivo.

NOMBRAMIENTOS**REPRESENTANTES LEGALES**

Por Acta No. 002 del 8 de septiembre de 2022, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 10 de octubre de 2022 con el No. 00357962 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Directora	Juliana Lopez Mendez	C.C. No. 1019039896

Por Acta No. 02-2018 del 31 de octubre de 2018, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 12 de febrero de 2019 con el No. 00313035 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Representante	Nubia Esperanza	C.C. No. 52056935
Legal Suplente	Sanchez Hernandez	

ÓRGANO DE ADMINISTRACIÓN**ÓRGANO DE ADMINISTRACIÓN**

Por Acta No. 002 del 8 de septiembre de 2022, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 10 de octubre de 2022 con el No. 00357963 del Libro I de las entidades sin ánimo de lucro, se designó a:

PRINCIPALES

CARGO	NOMBRE	IDENTIFICACIÓN
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CERTIFICADO DE EXISTENCIA Y REPRESENTACIÓN LEGAL

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Miembro Luz Stella Vargas De C.C. No. 24323756
Consejo Ocampo
Directivo

Miembro Maria Veronica P.P. No. 1711438984
Consejo Espinosa Serrano
Directivo

Miembro Carlos Eduardo Duran P.P. No. 502204134
Consejo Salinas
Directivo

REVISORES FISCALES

Por Acta No. 0000001 del 12 de agosto de 2008, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 20 de octubre de 2008 con el No. 00144330 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Revisor Fiscal Principal	Sandra Liliana Castrillon Riascos	C.C. No. 52516934 T.P. No. 110470-T

Por Acta del 30 de agosto de 2001, de Asamblea de Asociados, inscrita en esta Cámara de Comercio el 11 de septiembre de 2001 con el No. 00043760 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Revisor Fiscal Suplente	Edelberto De Jesus Rendon Valencia	C.C. No. 10243476

REFORMAS DE ESTATUTOS

Los estatutos de la Entidad han sido reformados así:

DOCUMENTO	INSCRIPCIÓN
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Acta No. 0000002 del 15 de marzo de 2002 de la Asamblea de Asociados	00048042 del 1 de abril de 2002 del Libro I de las entidades sin ánimo de lucro
Acta No. 0000002 del 15 de diciembre de 2007 de la Consejo de Fundadores	00132980 del 26 de marzo de 2008 del Libro I de las entidades sin ánimo de lucro
Acta No. 002 del 12 de noviembre de 2009 de la Asamblea de Fundadores	00165923 del 18 de enero de 2010 del Libro I de las entidades sin ánimo de lucro
Acta No. 002 del 11 de diciembre de 2012 de la Consejo de Fundadores	00218986 del 10 de enero de 2013 del Libro I de las entidades sin ánimo de lucro
Acta No. 002 del 27 de septiembre de 2016 de la Consejo de Fundadores	00291466 del 24 de mayo de 2017 del Libro I de las entidades sin ánimo de lucro

RECURSOS CONTRA LOS ACTOS DE INSCRIPCIÓN

De conformidad con lo establecido en el Código de Procedimiento Administrativo y de lo Contencioso Administrativo y la Ley 962 de 2005, los actos administrativos de registro, quedan en firme dentro de los diez (10) días hábiles siguientes a la fecha de inscripción, siempre que no sean objeto de recursos. Para estos efectos, se informa que para la Cámara de Comercio de Bogotá, los sábados NO son días hábiles.

Una vez interpuestos los recursos, los actos administrativos recurridos quedan en efecto suspensivo, hasta tanto los mismos sean resueltos, conforme lo prevé el artículo 79 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo.

A la fecha y hora de expedición de este certificado, NO se encuentra en curso ningún recurso.

CLASIFICACIÓN DE ACTIVIDADES ECONÓMICAS - CIIU

Actividad principal Código CIIU: 8699

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TAMAÑO EMPRESARIAL

De conformidad con lo previsto en el artículo 2.2.1.13.2.1 del Decreto 1074 de 2015 y la Resolución 2225 de 2019 del DANE el tamaño de la empresa es Microempresa

Lo anterior de acuerdo a la información reportada por el matriculado o inscrito en el formulario RUES:

Ingresos por actividad ordinaria \$ 62.753.116

Actividad económica por la que percibió mayores ingresos en el período - CIIU : 8699

INFORMACIÓN COMPLEMENTARIA

Que, los datos del empresario y/o el establecimiento de comercio han sido puestos a disposición de la Policía Nacional a través de la consulta a la base de datos del RUES.

El suscrito secretario de la Cámara de Comercio de Bogotá, en el ejercicio de la facultad conferida por los artículos 43 y 144 del Decreto número 2150 de 1995.

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la mencionada entidad.

El registro ante las Cámaras de Comercio no constituye aprobación de estatutos. (Decreto 2150 de 1995 y Decreto 427 de 1996).

La persona jurídica de que trata este certificado se encuentra sujeta a la inspección, vigilancia y control de las autoridades que ejercen esta función, por lo tanto deberá presentar ante la autoridad correspondiente, el certificado de registro respectivo, expedido por la Cámara de Comercio, dentro de los 10 días hábiles siguientes a la fecha de inscripción, más el término de la distancia cuando el domicilio de la persona jurídica sin ánimo de lucro que se registra es diferente al de la Cámara de Comercio que le corresponde. En el

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caso de reformas estatutarias además se allegara copia de los estatutos.

Toda autorización, permiso, licencia o reconocimiento de carácter oficial, se tramitará con posterioridad a la inscripción de las personas jurídicas sin ánimo de lucro en la respectiva Cámara de Comercio.

El presente certificado no constituye permiso de funcionamiento en ningún caso.

Este certificado refleja la situación jurídica registral de la entidad sin ánimo de lucro, a la fecha y hora de su expedición.

Este certificado fue generado electrónicamente con firma digital y cuenta con plena validez jurídica conforme a la Ley 527 de 1999.

Firma mecánica de conformidad con el Decreto 2150 de 1995 y la autorización impartida por la Superintendencia de Industria y Comercio, mediante el oficio del 18 de noviembre de 1996.



MARIO FERNANDO AVILA CRISTANCHO



harold silva <haroldhsilvac@gmail.com>

Otorgamiento poder para oposición ante la SIC (CAB+RIP) Abogado Harold Humberto Silva Carvajal

Juliana Lopez <jlopezm@ifarma.org>

4 de agosto de 2025, 12:57 p.m.

Para: harold silva <haroldhsilvac@gmail.com>, Fundacion Ifarma <ifarma@ifarma.org>

Bogotá D.C, agosto de 2025

Honorable Despacho

Superintendencia de Industria y Comercio

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

E. S. D.

REFERENCIA:	EXPEDIENTE NACIONAL NC2025/0004675
TITULO:	Patente PCT "MÉTODO PARA TRATAR VIH CON CABOTEGRAVIR Y RILPIVIRINA EN PACIENTES PEDIÁTRICOS" PCT/EP2023/075264 -WO/2024/056789.
SOLICITANTE(S)	JANSSEN SCIENCES IRELAND UNLIMITED COMPANY. - VIIV HEALTHCARE UK
DE PATENTE:	(NO.3) LIMITED
OPOSITOR:	FUNDACIÓN IFARMA
ACTUACIÓN:	OTORGAMIENTO PODER ESPECIAL

JULIANA LÓPEZ MÉNDEZ identificada con la cédula de ciudadanía No 1.019.039.896 de Bogotá y domiciliada en la ciudad de Bogotá en calidad de representante legal de la **FUNDACIÓN IFARMA** identificada con el NIT **830.091.891-6**, , con domicilio en Bogotá, todo lo cual acredito en el certificado de existencia y representación legal, respetuosamente mediante el presente escrito, **CONFIERO PODER ESPECIAL, AMPLIO Y SUFICIENTE** a **HAROLD HUMBERTO SILVA CARVAJAL**, mayor de edad, domiciliado en la ciudad de Bogotá, abogado en ejercicio, identificado con cédula de ciudadanía No. 1.022.433.355 de Bogotá y portador de la tarjeta profesional No. 391.454 del Consejo Superior de la Judicatura, con dirección electrónica de notificación haroldhsilvac@gmail.com como abogado, para que de conformidad con los trámites legales Nacionales y andinos vigentes, en nombre y representación de la Fundación indicada: intervenga con el fin de presentar oposición a la solicitud de patente identificada con el expediente NC2025/0004675, titulada "MÉTODO PARA TRATAR VIH CON CABOTEGRAVIR Y RILPIVIRINA EN PACIENTES PEDIÁTRICOS" PCT/EP2023/075264 -WO/2024/056789.

El apoderado queda expresamente facultado para recibir, radicar, desistir, sustituir, transigir, conciliar, renunciar, reasumir, recibir y entregar dineros, solicitar y aportar pruebas, formular tachas, interponer y sustentar recursos, excepciones, presentar memoriales, así como para realizar todas las gestiones que consideren convenientes para el cabal desempeño de sus funciones durante la duración del presente mandato.

El presente poder se otorga en los términos y con las formalidades establecidas en el Artículo 5 del Decreto 806 de 2020 y Ley 2213 de 2022, y se remite a través del correo electrónico de ifarma@ifarma.org o; al correo electrónico registrado en el Registro Nacional de Abogados: haroldhsilvac@gmail.com.

Del Honorable Magistrado

Atentamente,

JULIANA LÓPEZ MÉNDEZ

C.C. No. 1.019.039.896 de Bogotá

Representante Legal

--



Juliana López Méndez TS, Epidemióloga

Directora

Fundación IFARMA

<https://www.ifarma.org/>

Juliana López Méndez SW, Epidemiologist

Director

IFARMA Foundation

Aviso legal: El contenido de este mensaje y los archivos adjuntos son confidenciales y de uso exclusivo de la Fundación IFARMA. Se encuentran dirigidos sólo para el uso del destinatario al cual van enviados. La reproducción, lectura y/o copia se encuentran prohibidas a cualquier persona diferente a este y puede ser ilegal. Si usted lo ha recibido por error, infórmenos y elimínelo de su correo. Los Datos Personales serán tratados conforme a la Ley 1581 de 2012 y a nuestra Política de Datos Personales. Las opiniones, informaciones, conclusiones y cualquier otro tipo de dato contenido en este correo electrónico, no relacionados con la actividad de la Fundación, se entenderá como personales y de ninguna manera son avaladas por la Fundación.

2 archivos adjuntos



poder oposicion cab+rip.pdf

284K



CERL - IFARMA (1).pdf

158K



harold silva <haroldhsilvac@gmail.com>

Otorgamiento poder para oposición ante la SIC (CAB+RIP) Abogado Harold Humberto Silva Carvajal

harold silva <haroldhsilvac@gmail.com>
Para: Juliana Lopez <jlopezm@ifarma.org>
CC: Fundacion Ifarma <ifarma@ifarma.org>

4 de agosto de 2025, 12:58 p.m.

Buenas tardes

Acuso de recibido y acepto el poder especial para las tareas indicadas.

Gracias

[Texto citado oculto]

--

Harold Humberto Silva Carvajal
C.C. No. 1.022.433.355
T.P. No. 391454 del C.S. de la J.

Bogotá D.C, agosto de 2025

Honorable Despacho
Superintendencia de Industria y Comercio
Delegatura de Propiedad Industrial
División de Nuevas Creaciones
E. S. D.

REFERENCIA: EXPEDIENTE NACIONAL NC2025/0004675
TITULO: Patente PCT "MÉTODO PARA TRATAR VIH CON CABOTEGRAVIR Y RILPIVIRINA EN PACIENTES PEDIÁTRICOS" PCT/EP2023/075264 -WO/2024/056789.
SOLICITANTE(S) JANSSEN SCIENCES IRELAND UNLIMITED COMPANY. - VIIV HEALTHCARE UK
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OPOSITOR: FUNDACIÓN IFARMA
ACTUACIÓN: OTORGAMIENTO PODER ESPECIAL

JULIANA LÓPEZ MÉNDEZ identificada con la cédula de ciudadanía No 1.019.039.896 de Bogotá y domiciliada en la ciudad de Bogotá en calidad de representante legal de la **FUNDACIÓN IFARMA** identificada con el NIT **830.091.891-6**, , con domicilio en Bogotá, todo lo cual acredito en el certificado de existencia y representación legal, respetuosamente mediante el presente escrito, **CONFIERO PODER ESPECIAL, AMPLIO Y SUFICIENTE** a **HAROLD HUMBERTO SILVA CARVAJAL**, mayor de edad, domiciliado en la ciudad de Bogotá, abogado en ejercicio, identificado con cédula de ciudadanía No. 1.022.433.355 de Bogotá y portador de la tarjeta profesional No. 391.454 del Consejo Superior de la Judicatura, con dirección electrónica de notificación haroldhsilvac@gmail.com como abogado, para que de conformidad con los trámites legales Nacionales y andinos vigentes, en nombre y representación de la Fundación indicada: intervenga con el fin de presentar oposición a la solicitud de patente identificada con el expediente NC2025/0004675, titulada "MÉTODO PARA TRATAR VIH CON CABOTEGRAVIR Y RILPIVIRINA EN PACIENTES PEDIÁTRICOS" PCT/EP2023/075264 -WO/2024/056789.

El apoderado queda expresamente facultado para recibir, radicar, desistir, sustituir, transigir, conciliar, renunciar, reasumir, recibir y entregar dineros, solicitar y aportar pruebas, formular tachas, interponer y sustentar recursos, excepciones, presentar memoriales, así como para realizar todas las gestiones que consideren convenientes para el cabal desempeño de sus funciones durante la duración del presente mandato.

El presente poder se otorga en los términos y con las formalidades establecidas en el Artículo 5 del Decreto 806 de 2020 y Ley 2213 de 2022, y se remite a través del correo electrónico de ifarma@ifarma.org o; al correo electrónico registrado en el Registro Nacional de Abogados: haroldhsilvac@gmail.com.

Del Honorable Magistrado

Atentamente,



JULIANA LÓPEZ MÉNDEZ
C.C. No. 1.019.039.896 de Bogotá
Representante Legal

Acepto,



Harold Humberto Silva Carvajal
C.C. No.1.022.433.355 de Bogotá
T.P. 391.454 del Consejo Superior de la Judicatura

CERTIFICADO DE EXISTENCIA Y REPRESENTACIÓN LEGAL

Fecha Expedición: 24 de mayo de 2025 Hora: 12:55:16

Recibo No. AA25929175

Valor: \$ 11,600

CÓDIGO DE VERIFICACIÓN A25929175D1778

Verifique el contenido y confiabilidad de este certificado, ingresando a www.ccb.org.co/certificados/electronicos y digite el respectivo código, para que visualice la imagen generada al momento de su expedición. La verificación se puede realizar de manera ilimitada, durante 60 días calendario contados a partir de la fecha de su expedición.

CON FUNDAMENTO EN LAS INSCRIPCIONES EFECTUADAS EN EL REGISTRO DE ENTIDADES SIN ÁNIMO DE LUCRO, LA CÁMARA DE COMERCIO CERTIFICA:

NOMBRE, IDENTIFICACIÓN Y DOMICILIO

Razón social: FUNDACION IFARMA
Nit: 830091891 6, Regimen Comun
Domicilio principal: Bogotá D.C.

INSCRIPCIÓN

Inscripción No. S0015611
Fecha de Inscripción: 11 de septiembre de 2001
Último año renovado: 2025
Fecha de renovación: 8 de abril de 2025
Grupo NIIF: Grupo III.

UBICACIÓN

Dirección del domicilio principal: Cra.15 No.32-70 Piso 1
Municipio: Bogotá D.C.
Correo electrónico: ifarma@ifarma.org
Teléfono comercial 1: 2454757
Teléfono comercial 2: 3158780717
Teléfono comercial 3: No reportó.

Dirección para notificación judicial: Cra.13 No.32-51 Torre Iii
Ofc.1115
Municipio: Bogotá D.C.
Correo electrónico de notificación: ifarma@ifarma.org
Teléfono para notificación 1: 3381490
Teléfono para notificación 2: 3231472
Teléfono para notificación 3: No reportó.

La Entidad NO autorizó para recibir notificaciones personales a través de correo electrónico, de conformidad con lo establecido en los artículos 291 del Código General del Proceso y 67 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo.

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CONSTITUCIÓN

Por Acta del 30 de agosto de 2001 de Asamblea de Asociados, inscrito en esta Cámara de Comercio el 11 de septiembre de 2001, con el No. 00043760 del Libro I de las entidades sin ánimo de lucro, se constituyó la persona jurídica de naturaleza Fundación denominada FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SISTEMAS DE SALUD.

ENTIDAD QUE EJERCE INSPECCIÓN, VIGILANCIA Y CONTROL

Entidad que ejerce la función de inspección, vigilancia y control:
ALCALDIA MAYOR DE BOGOTA

REFORMAS ESPECIALES

Por Acta No. 0000002 del 15 de marzo de 2002 de Asamblea de Asociados, inscrito en esta Cámara de Comercio el 1 de abril de 2002, con el No. 00048042 del Libro I de las entidades sin ánimo de lucro, la entidad cambió su denominación o razón social de FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SISTEMAS DE SALUD a FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SITEMAS DE SALUD SIGLA FUNDACION IFARMA.

Por Acta No. 002 del 12 de noviembre de 2009 de Asamblea de Fundadores, inscrito en esta Cámara de Comercio el 18 de enero de 2010, con el No. 00165923 del Libro I de las entidades sin ánimo de lucro, la entidad cambió su denominación o razón social de FUNDACION INSTITUTO PARA LA INVESTIGACION DEL MEDICAMENTO EN LOS SITEMAS DE SALUD SIGLA FUNDACION IFARMA a FUNDACION IFARMA.

TÉRMINO DE DURACIÓN

La Entidad no se encuentra disuelta y su duración es indefinida.

OBJETO SOCIAL

CERTIFICADO DE EXISTENCIA Y REPRESENTACIÓN LEGAL**Fecha Expedición: 24 de mayo de 2025 Hora: 12:55:16**

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Contribuir al crecimiento social y económico de Colombia y de otros países, a través del trabajo especializado en la investigación, el mejoramiento y el desarrollo de los aspectos relativos a la formulación y ejecución de políticas, la administración, la gestión y el uso adecuado de los medicamentos en particular y la salud y la seguridad social en general. La fundación, para cumplir con su objeto social, utilizará el conocimiento, la experiencia y la experticia de profesionales nacionales e internacionales ampliamente acreditados. Buscará recopilar las experiencias existentes nacional e internacionalmente en los temas de su objeto social. La fundación igualmente buscará actuar como un soporte del sistema de seguridad social en salud y de la prestación de servicios de salud, especialmente pero no exclusivamente, en los temas relativos a la oferta suficiente y competitiva de los recursos terapéuticos que la población requiere. Ello sin incluir en su objeto social la prestación de servicios de salud. Igualmente fomentará el debate, el análisis y la investigación en todos los temas relativos a su objeto, con el propósito de generar e innovar líneas de acción y desarrollo, para lo cual buscará y promoverá la acción conjunta con los organismos nacionales e internacionales que tienen similares objetivos. La fundación utilizará los medios que estime convenientes para comunicar y difundir el conocimiento generado por su accionar. La fundación podrá desarrollar planes, proyectos y programas de investigación, asistencia técnica, asesoría y consultoría, e innovación tecnológica en los campos de la salud, la seguridad social y el desarrollo social. Igualmente podrá editar, producir y comercializar libros, impresos y otras publicaciones, así como producir, editar y comercializar servicios informativos. Facultades: para cumplir con su objeto social y precautelar su patrimonio, la fundación podrá celebrar, en los términos de la ley, todos los actos y contratos que estén directamente relacionados con el objeto antes indicado y los que tengan como finalidad ejercer los derechos o cumplir con las obligaciones que legal o convencionalmente se deriven de la existencia y actividad de la fundación, así entre otros actos y contratos podrá adquirir, enajenar y gravar toda clase de bienes muebles o inmuebles, tangibles e intangibles, girar, aceptar, endosar, otorgar, garantizar y negociar toda clase de títulos valores, celebrar el contrato de mutuo, designar apoderadosos judiciales y extrajudiciales; participará en la creación o en la administración de otras entidades relacionadas con el objeto social, podrá igualmente, asociarse, realizar uniones temporales o alianzas

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estratégicas con otra u otras entidades con o Sin Ánimo de Lucro para el logro de objetivos comunes; representar en el país o en el exterior a otras entidades con similar objeto social. En su accionar en otros países se regirá por las leyes de los mismos.

PATRIMONIO

\$ 79.333.263,00

REPRESENTACIÓN LEGAL

La representación legal de la fundación estará a cargo del Director. El Representante Legal suplente cumplirá las funciones de suplir las ausencias temporales o definitivas del Director y reemplazarlo cuando se necesario con las mismas responsabilidades y facultades.

FACULTADES Y LIMITACIONES DEL REPRESENTANTE LEGAL

El Director de la fundación tendrá las siguientes funciones: 1. Dirigir la fundación de conformidad con las decisiones del consejo directivo y con los presentes estatutos. 2. Representar a la fundación en todos los actos y operaciones que celebre con terceros, tanto judicial como extrajudicialmente, por si o por conducto de apoderado. 3. Cumplir y hacer cumplir los estatutos, reglamentos, acuerdos y decisiones del consejo directivo. 4. Designar al personal de la fundación, celebrar los contratos del caso y decidir sobre promociones, sanciones, retiros y reemplazos a que haya lugar y coordinar la actividad de los distintos empleados y dependencias de la fundación. 5. Ejecutar los negocios de la fundación; velar por los bienes de la misma, por sus operaciones técnicas, sus estados financieros y documentos; suscribir los actos y contratos de la fundación sin restricción alguna en los montos de estos siempre que no estén en contradicción al objeto social de la misma, ni afecten sus bienes y bajo las condiciones establecidos por los estatutos, reglamentos y por el consejo directivo. Firmar los estados financieros. 6. Vigilar el recaudo e inversión de los recursos de la fundación, y la correcta disposición de sus bienes. 7. Presentar anualmente al consejo directivo el informe sobre el desarrollo de las actividades de la fundación y sus estados financieros. 8. Coordinar

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las acciones necesarias para el cumplimiento de los objetivos de la fundación y llevar la vocería oficial de la fundación en público y ante los medios de comunicación. 9. Las demás que le señalen los estatutos y la ley y las que, siendo compatibles con su cargo, le asigne el consejo directivo.

NOMBRAMIENTOS**REPRESENTANTES LEGALES**

Por Acta No. 002 del 8 de septiembre de 2022, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 10 de octubre de 2022 con el No. 00357962 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Directora	Juliana Lopez Mendez	C.C. No. 1019039896

Por Acta No. 02-2018 del 31 de octubre de 2018, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 12 de febrero de 2019 con el No. 00313035 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Representante	Nubia Esperanza	C.C. No. 52056935
Legal Suplente	Sanchez Hernandez	

ÓRGANO DE ADMINISTRACIÓN**ÓRGANO DE ADMINISTRACIÓN**

Por Acta No. 002 del 8 de septiembre de 2022, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 10 de octubre de 2022 con el No. 00357963 del Libro I de las entidades sin ánimo de lucro, se designó a:

PRINCIPALES

CARGO	NOMBRE	IDENTIFICACIÓN
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Miembro	Luz Stella Vargas De	C.C. No. 24323756
Consejo	Ocampo	
Directivo		

Miembro	Maria Veronica	P.P. No. 1711438984
Consejo	Espinosa Serrano	
Directivo		

Miembro	Carlos Eduardo Duran	P.P. No. 502204134
Consejo	Salinas	
Directivo		

REVISORES FISCALES

Por Acta No. 0000001 del 12 de agosto de 2008, de Consejo de Fundadores, inscrita en esta Cámara de Comercio el 20 de octubre de 2008 con el No. 00144330 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Revisor Fiscal Principal	Sandra Liliana Castrillon Riascos	C.C. No. 52516934 T.P. No. 110470-T

Por Acta del 30 de agosto de 2001, de Asamblea de Asociados, inscrita en esta Cámara de Comercio el 11 de septiembre de 2001 con el No. 00043760 del Libro I de las entidades sin ánimo de lucro, se designó a:

CARGO	NOMBRE	IDENTIFICACIÓN
Revisor Fiscal Suplente	Edelberto De Jesus Rendon Valencia	C.C. No. 10243476

REFORMAS DE ESTATUTOS

Los estatutos de la Entidad han sido reformados así:

DOCUMENTO	INSCRIPCIÓN
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Acta No. 0000002 del 15 de marzo de 2002 de la Asamblea de Asociados	00048042 del 1 de abril de 2002 del Libro I de las entidades sin ánimo de lucro
Acta No. 0000002 del 15 de diciembre de 2007 de la Consejo de Fundadores	00132980 del 26 de marzo de 2008 del Libro I de las entidades sin ánimo de lucro
Acta No. 002 del 12 de noviembre de 2009 de la Asamblea de Fundadores	00165923 del 18 de enero de 2010 del Libro I de las entidades sin ánimo de lucro
Acta No. 002 del 11 de diciembre de 2012 de la Consejo de Fundadores	00218986 del 10 de enero de 2013 del Libro I de las entidades sin ánimo de lucro
Acta No. 002 del 27 de septiembre de 2016 de la Consejo de Fundadores	00291466 del 24 de mayo de 2017 del Libro I de las entidades sin ánimo de lucro

RECURSOS CONTRA LOS ACTOS DE INSCRIPCIÓN

De conformidad con lo establecido en el Código de Procedimiento Administrativo y de lo Contencioso Administrativo y la Ley 962 de 2005, los actos administrativos de registro, quedan en firme dentro de los diez (10) días hábiles siguientes a la fecha de inscripción, siempre que no sean objeto de recursos. Para estos efectos, se informa que para la Cámara de Comercio de Bogotá, los sábados NO son días hábiles.

Una vez interpuestos los recursos, los actos administrativos recurridos quedan en efecto suspensivo, hasta tanto los mismos sean resueltos, conforme lo prevé el artículo 79 del Código de Procedimiento Administrativo y de lo Contencioso Administrativo.

A la fecha y hora de expedición de este certificado, NO se encuentra en curso ningún recurso.

CLASIFICACIÓN DE ACTIVIDADES ECONÓMICAS - CIIU

Actividad principal Código CIIU: 8699

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TAMAÑO EMPRESARIAL

De conformidad con lo previsto en el artículo 2.2.1.13.2.1 del Decreto 1074 de 2015 y la Resolución 2225 de 2019 del DANE el tamaño de la empresa es Microempresa

Lo anterior de acuerdo a la información reportada por el matriculado o inscrito en el formulario RUES:

Ingresos por actividad ordinaria \$ 62.753.116

Actividad económica por la que percibió mayores ingresos en el período - CIIU : 8699

INFORMACIÓN COMPLEMENTARIA

Que, los datos del empresario y/o el establecimiento de comercio han sido puestos a disposición de la Policía Nacional a través de la consulta a la base de datos del RUES.

El suscrito secretario de la Cámara de Comercio de Bogotá, en el ejercicio de la facultad conferida por los artículos 43 y 144 del Decreto número 2150 de 1995.

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la mencionada entidad.

El registro ante las Cámaras de Comercio no constituye aprobación de estatutos. (Decreto 2150 de 1995 y Decreto 427 de 1996).

La persona jurídica de que trata este certificado se encuentra sujeta a la inspección, vigilancia y control de las autoridades que ejercen esta función, por lo tanto deberá presentar ante la autoridad correspondiente, el certificado de registro respectivo, expedido por la Cámara de Comercio, dentro de los 10 días hábiles siguientes a la fecha de inscripción, más el término de la distancia cuando el domicilio de la persona jurídica sin ánimo de lucro que se registra es diferente al de la Cámara de Comercio que le corresponde. En el

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caso de reformas estatutarias además se allegara copia de los estatutos.

Toda autorización, permiso, licencia o reconocimiento de carácter oficial, se tramitará con posterioridad a la inscripción de las personas jurídicas sin ánimo de lucro en la respectiva Cámara de Comercio.

El presente certificado no constituye permiso de funcionamiento en ningún caso.

Este certificado refleja la situación jurídica registral de la entidad sin ánimo de lucro, a la fecha y hora de su expedición.

Este certificado fue generado electrónicamente con firma digital y cuenta con plena validez jurídica conforme a la Ley 527 de 1999.

Firma mecánica de conformidad con el Decreto 2150 de 1995 y la autorización impartida por la Superintendencia de Industria y Comercio, mediante el oficio del 18 de noviembre de 1996.



MARIO FERNANDO AVILA CRISTANCHO

COMPROBANTE

NIT	Medio de Pago	No. Transacción	No. Autorización/CUS	Fecha y Hora
8001760892	BANCO AV VILLAS	137386821	1678054063	04/08/2025 06:15:38-p.m.

Razón Social: **SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

Usuario Pagador: **1019039896**

Descripción del Pago: **SIPI**

Dirección IP: **190.27.107.189**

Total Pagado **\$ 777,000.00**

Descripción	Cantidad	Valor Pagado	Valor Servicio
SIPI	1	\$ 777,000.00	COP\$ 777,000.00

NIT	Medio de Pago	No. Transacción	No. Autorización/CUS	Fecha y Hora
8001760892	BANCO AV VILLAS	137386821	1678054063	04/08/2025 06:15:38-p.m.

Número Id del Pagador

1019039896

Identificador de Pago

3696524

Nombre y Apellidos Pagador

JULIANA LOPEZ MENDEZ

Tipo de Documento Empresa R

NI

Numero de Factura

1321964

Tipo de Documento Pagador

CC

Numero Id Empresa R

930091891

Nombre Empresa R

FUNDACION IFARMA