

Report of the Medicines Patent Pool Expert Advisory Group on the Proposed Licence Agreement between MPP and ViiV Healthcare company (ViiV) on cabotegravir

Introduction

The Expert Advisory Group (**EAG**) of the Medicines Patent Pool (**MPP**) submits the following report to the Governance Board of the Medicines Patent Pool (**Board**) on the proposed Licence Agreement between MPP and ViiV for cabotegravir for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 (the **Agreement**).

This report reflects the outcome of consultations with the EAG on 15 July 2022, chaired by Peter Beyer and joined by EAG members Deus Mubangizid, Gugu Mahlangu, Jan Gheuens, Jennifer Cohn, Jordan Jarvis, Valérie Paris, and Zeba Aziz. The EAG was joined by two members of the Scientific Advisory Panel, Wim Vandeveldel and François Venter¹. Some members, Ellen 't Hoen and Fatima Suleman, who were not able to attend the meeting sent input via correspondence before the meeting that was taken into account when drafting this report. Further, one member of the EAG recused himself from the consultations due to a potential conflict of interest. A recording of the EAG discussions was made available to members who could not attend.

Background, Overview of the Proposed Agreement

(a) Background to the negotiations

Since 2018, MPP has identified cabotegravir Long-Acting (**CAB-LA**) for HIV pre-exposure prophylaxis (**PrEP**) as a priority for in-licensing. In 2020, two large-scale efficacy trials found that CAB-LA for PrEP provided high levels of protection among people at risk of HIV-1 and was superior to oral PrEP (discussed below). On 20 December 2021, ViiV received FDA approval for CAB-LA for use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1.

Initially in 2018, ViiV was not open for licensing as it assumed that generic manufacturing would not lead to lower prices. ViiV's assessment was based on the assumption that a generic manufacturer would develop a like-to-like version of ViiV's CAB-LA for PrEP product. However, more recent and extensive assessments by MPP concluded that a bioequivalent version of ViiV's CAB-LA for PrEP product could be developed by a generic manufacturer at a lower cost.

On 27 May 2022, MPP and ViiV formally entered into negotiations to agree terms and execute a voluntary licence as quickly as possible to help enable at-scale access to low-cost generic CAB-LA (including cabotegravir oral tablets) for PrEP in the developing world.

(b) Desirability of CAB-LA for PrEP

CAB-LA is a long-acting injectable drug for PrEP. It is the first and only long-acting PrEP option that has been approved by the US FDA for use in at-risk adults and adolescents weighing at least 35 kilograms for PrEP to reduce the risk of sexually acquired HIV-1. MPP informed the EAG that CAB-LA for PrEP is of medical significance due to its clinical profile and formulation, which is more effective in preventing HIV-1 acquisition compared to oral PrEP options.

¹ François Venter declared that his unit does investigator-driven clinical trials that address cabotegravir as treatment (in combination with rilpivirine), and has grants under evaluation - implementation studies involving CAB as PrEP. He declared that he is not doing any registration/commercial studies for ViiV, for any drug, but that ViiV have provided study drug (dolutegravir) for another study he heads (ADVANCE), and provided past grant support to the study. He further declared that he sits on ViiV's advisory boards. The Chair of the EAG concluded that these declarations would not preclude him from participating in the assessment.

The MPP reported that the clinical data shows that CAB-LA for PrEP is 89% more effective than daily oral PrEP (tenofovir/emtricitabine) and is generally well tolerated with a good safety profile. Cabotegravir oral tablets may be administered for approximately one month prior to the initiation of CAB-LA for PrEP, for example, to assess the tolerability of the medicine (noting that the US FDA did not consider this oral lead-in to be mandatory).

A significant advantage of CAB-LA for PrEP over oral PrEP options is that its long-acting formulation allows for less frequent administrations, which circumvents adherence challenges (as well as stigma) that are often associated with consistently taking daily oral pills. During the initiation period, CAB-LA for PrEP is administered:

1. one month apart for two consecutive months; and
2. after the second administration, once every two months.

Indeed, CAB-LA for PrEP reduces dosing from 365 doses as with oral PrEP to as few as six doses per year after the initiation period. This is advantageous particularly in light of research that has shown that teenage girls and young women often do not adhere to a daily dose regimen.²

From an access perspective, the market for PrEP is growing substantially by approximately 1 million people in 2020. CAB-LA for PrEP, if made available at low-cost prices, could be a strong candidate for inclusion in national PrEP HIV programs. CAB-LA for PrEP is considered as a key tool in HIV prevention and access to a low-cost generic version of CAB-LA for PrEP could significantly contribute towards the goal of ending HIV transmission by 2030.

(c) Licensing terms

The key aspects of the proposed Agreement are as follows:

Scope of Grant of Licence. The proposed Agreement would grant MPP a non-exclusive licence over ViiV's patents with the ability for MPP to enter into sublicences with a maximum of three sublicensees. MPP would grant sublicensees a non-exclusive licence over ViiV's patents to the extent necessary to:

1. obtain regulatory approval for the licensed product;
2. manufacture, sell and supply the licensed product for use in the Territory; and
3. sell and supply the cabotegravir compound between sublicensees for use in the Territory.

Eligibility for sublicensees. Sublicences can be issued to any qualified entity worldwide to a maximum of three. The Agreement foresees the possibility to have additional sublicensees if MPP notifies ViiV of a need for more sublicensees to meet public health demand.

Patents. The patent exhibit lists four PCT applications relating to cabotegravir, specifically the (1) cabotegravir compound patent, (2) a patent on the process for preparing cabotegravir derivatives and intermediates, (3) a patent on a cabotegravir long-acting injectable formulation, and (4) a patent on cabotegravir crystalline forms (applicable only to a tablet formulation). The proposed Agreement defines ViiV's 'Patent Rights' to include all foreign national equivalent patents of those PCT applications.

Manufacturing: The proposed Agreement allows for the manufacturing of cabotegravir anywhere in the world in a form of a tablet containing 30 mg of cabotegravir as its sole active pharmaceutical ingredient and/or an extended-release injectable suspension form.

Field of Use. The Field of Use in the proposed Agreement is for PrEP of at-risk persons weighing at least 35 kg to reduce the risk of sexually acquired HIV-1 infection.

² See <https://pubmed.ncbi.nlm.nih.gov/33389323/>.

Territory.

- **Named territory:** The Territory of the proposed Agreement consists explicitly of 90 countries, comprising of all low-income countries, lower middle-income countries, sub-Saharan African countries, and least-developed countries (as defined by the UN) (see Appendix B of the draft sublicense agreement of the Proposed Agreement for the list of countries).
- There are additional countries outside the territory in which ViiV has not filed for any of the relevant patents and thus where sublicensees could sell the product in line with Section 3.5 of the draft sublicense agreement of the Proposed Agreement.
- Countries where the licence is limited to the public market: Algeria, Egypt, India, Indonesia, Kyrgyzstan, Morocco, Philippines, Tajikistan, Ukraine, and Vietnam. ViiV will make a decision on whether it would like to keep the private market in these countries or whether it will be included in the Agreement. The proposed Agreement is structured in a manner that allows MPP and ViiV to include the private market of these countries without a formal amendment process of the license agreement.
- Countries with EU candidate status: Section 31.3 of the draft sublicense agreement of the Proposed Agreement stipulates that if a country in the Territory has been accepted as an official candidate for membership of the European Union and if ViiV is of the reasonable opinion that there is a risk that the licensed product will become subject to free movement of goods within the European Union, ViiV can request the MPP to remove such country from the Territory. This applies to Ukraine who has become an official candidate for membership of the European Union.

Royalties. The proposed Agreement is royalty-free for most countries within the Territory for both the private and public market. It is royalty-bearing for 10 countries³ where the licensed product falls within the scope of ViiV's patent rights in such countries. In those royalty countries the rate is 5% of net sales of the licensed product in the public market.

Compatibility with TRIPS flexibilities. The proposed Agreement in Section 3.5 of the draft sublicense agreement of the Proposed Agreement contains language that provides that nothing in it shall be construed to prevent the sublicensee from undertaking any activity anywhere in the world where such activity (i) is outside the scope of ViiV's patent rights or (ii) is permitted pursuant to a compulsory license of ViiV's patent rights.

Other key public health-oriented terms and conditions. The proposed Agreement contains other important public health-oriented terms and conditions, such as the requirement that (i) ViiV provides regulatory waivers, (ii) the manufacture of the licensed product is in a manner consistent with WHO PQ or SRA⁴ standards, and (iii) the sale of the licensed product must have received prior WHO PQ or SRA approval.

(d) Other relevant considerations

The WHO has opened submissions for WHO Prequalification for cabotegravir products and has published a guidance document entitled 'Notes on the Design of Bioequivalence Study: Cabotegravir',⁵ which provides notes on the design of bioequivalence studies with cabotegravir products that can aid manufacturers with the development of their product dossier.

³ Algeria, Egypt, India, Indonesia, Kyrgyzstan, Morocco, Philippines, Tajikistan, Ukraine, and Vietnam.

⁴ Full list of countries found at <https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs>.

⁵ See https://extranet.who.int/pqweb/sites/default/files/documents/BE_cabotegravir_July2022.pdf.

MPP estimates that the lead time for generic manufacturers to develop a low-cost generic version of CAB-LA for PrEP to be four to five years due to the complexity of the product. It also anticipates large capital expenditure to be required for its development.

The proposed Agreement does not require the provision of a technology transfer package. MPP and ViiV intend to enter into further discussions for technology transfer support from ViiV after the execution of the proposed Agreement.

Assessment of the Proposed Agreement in light of MPP's Statutes

The Terms of Reference for the EAG define two requirements against which the EAG has to assess the results of the final negotiations: (i) do the results sufficiently meet the requirements set out in the Statutes, and (ii) do the negotiation results offer sufficient added value over the *status quo*?

Relevant Considerations in the Statutes of the Medicines Patent Pool

The EAG finds that the proposed Agreement meets the requirements in the Statutes, as summarised in the table below.

Statutes	Terms in Proposed Licence
Negotiating terms and conditions of licence agreements with the aim to maximise public health benefits, taking into account the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of the WHO (GSPOA); WTO Doha Declaration	<ul style="list-style-type: none"> Provisions ensuring that sales anywhere in the world are not a breach of the Agreement if the sales do not infringe ViiV's patent rights, including where a compulsory licence has been granted over ViiV's patent rights The Agreement waives data exclusivity in countries of the Territory with such form of protection, thus facilitating regulatory approval of generics
Entering into licence agreements with patent holding entities, and sublicense agreements with generic manufacturers and other appropriate sublicensees on a non-exclusive and non-discriminatory basis	<ul style="list-style-type: none"> MPP to enter into non-exclusive sublicences with up to three sublicensees (unless additional sublicensees are permitted pursuant to the Agreement) chosen through MPP's Expression of Interest Portal No parallel bilateral licence agreements with generic companies
As and when necessary, enforcing terms and conditions of licence agreements, with appropriate dispute resolution mechanisms	<ul style="list-style-type: none"> MPP takes on significant obligations to monitor and enforce terms of agreements; specifies dispute resolution through ICC arbitration
Requiring stringent quality criteria for licensed products	<ul style="list-style-type: none"> Requires all licensed products to be made in accordance with WHO PQ or SRA standards, or through any provisional or emergency use authorisations available from WHO or an SRA
Including anti-diversion and traceability mechanisms	<ul style="list-style-type: none"> Sublicensees required to maintain a quick and efficient batch trace procedure as a means of tracing licensed products to monitor potential diversions

Assessment of the Proposed Agreement in light of the *Status Quo*

During the consultation, the EAG raised a number of questions, including with respect to the Territory, the situation of Ukraine with respect to its EU candidate status, and the limitation to a maximum of three sublicensees.

- With respect to the royalty-bearing countries of which the private market is not included, the MPP clarified that this question is still open for negotiation.
- With respect to Ukraine, MPP clarified that the provision addresses only the question of stockpiling in view of the country entering the EU free market. Given the average length of the EU accession process, at this point in time, MPP considers it unlikely that this provision will be used.
- With respect to the maximum number of sublicensees, MPP clarified that it considered that up to three sublicensees was an adequate number due to the uncertain demand and forecast of CAB-LA for PrEP in the Territory, the complexity in the development of CAB-LA for PrEP, the potential capital expenditure required for its development, and MPP's capacity to assist generics during its development.

In view of these clarifications, the EAG concluded that the terms and conditions of the proposed Agreement represent a significant added value over the *status quo*. The EAG considered it a major improvement over the status quo that the proposed Agreement would allow for affordable access to a long-acting injectable formulation of cabotegravir for PrEP in a significant number of LMICs although the defined Territory is smaller than in many other HIV-related licence agreements.

The EAG notes that the following public health-oriented licensing terms and conditions, together represent an advance over the *status quo*:

1. a defined territory that provides coverage for 90 countries, which represents a relatively high percentage of worldwide HIV infections annually;
2. a broad provision that allows for sales of the licensed product outside the proposed CAB-LA for PrEP territory where ViiV's patent rights are not implicated;
3. provisions that ensure quality manufacturing of the licensed products and that the licensed products cannot be sold prior to WHO PQ or SRA approval; and
4. provisions that allow MPP to monitor, manage and enforce the licence agreements vis-a-vis its licensees.

The EAG urges ViiV to consider expanding the licence to cover the private market in the ten royalty-bearing countries. The EAG also considers it essential and a matter of urgency that MPP and ViiV agree on technology transfer support for the sublicensees from ViiV after the execution of the proposed Agreement. The EAG considers the provision of a technology transfer package to support sublicensees in the manufacture of the licensed product to be an important component for ensuring that people have access to low-cost generic CAB-LA for PrEP as quickly as possible.

The EAG is encouraged by the fact that ViiV worked directly with MPP and did not opt to engage in any bilateral licence agreements.

Lastly, whilst the EAG is satisfied with its assessment of the proposed Agreement, it notes that it was provided with limited time to consider the proposed Agreement. The EAG reminds the Board that in order to fulfill its mandate, it needs sufficient time and information to appropriately assess the proposed agreements.

Recommendation

The EAG concludes that the proposed Agreement with ViiV is consistent with MPP's mandate as defined in its Statutes and represents a significant improvement over the *status quo* in terms of the public health-oriented nature of the licensing terms and conditions. Therefore, the EAG recommends that the



Medicines Patent Pool Governance Board request the Executive Director to sign the proposed Agreement between ViiV and MPP while urging ViiV to work with MPP on a further expansion of the Territory, including with respect to the private market of the royalty-bearing countries.

Signed,

A handwritten signature in black ink, appearing to read "P. Beyer". The signature is written in a cursive style with a prominent vertical stroke at the end.

Peter Beyer
Chair, Expert Advisory Group
Date: 19 July 2022