

## Report of the Medicines Patent Pool Expert Advisory Group on the Proposed Licence Agreement between MPP and Shionogi & Co., Ltd (Shionogi) on ensitrelvir fumaric acid for SARS-CoV-2

### 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 Shionogi for ensitrelvir fumaric acid (**ensitrelvir**) for Covid-19 (the **Agreement**).

This report reflects the outcome of consultations with the EAG on 16 September 2022, chaired by Peter Beyer and joined by EAG members Deus Mubangizi, Ellen 't Hoen, Giten Khwairakpam, Gugu Mahlangu, Fatima Suleman, Jennifer Cohn, Luis Gil Abinader, Martha Gyansa-Lutterodt, and Zeba Aziz. The EAG was joined by two members of the Scientific Advisory Panel, Wim Vandeveld and Francois Venter. 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

In March 2020, the Board of MPP expanded its mandate to any Covid-19 related health technologies that could contribute to the global response to COVID-19 and where licensing could facilitate innovation and access. In May 2021, the Board of MPP decided to permanently expand its mandate into the licensing of Covid-19 related health technologies.

In October and November 2021, MPP entered into licence agreements with MSD for molnupiravir and Pfizer for nirmatrelvir, respectively. In May 2022, under the auspices of WHO's COVID-19 Technology Access Pool (C-TAP), MPP signed two licensing agreements with the US National Institutes of Health for the development of 11 innovative therapeutics, early-stage vaccines and diagnostic tools for COVID-19.

Ensitrelvir has been prioritised by the ACT-A therapeutics pillar, which is co-coordinated by UNITAID, the Wellcome Trust and the Global Fund. The ACT-A therapeutics pillar has been the mechanism that MPP has relied on to prioritise Covid-19 medicines for licensing.

Subject to the results of the ongoing clinical trials, ensitrelvir could be an important all-oral treatment for Covid-19.

MPP entered into negotiations with Shionogi for ensitrelvir in July 2022. Shionogi did not engage in bilateral negotiations with generic companies and does not plan to issue bilateral license agreements outside the MPP license.

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 Shionogi's patents and know-how with the ability to grant nonexclusive, royalty-bearing sublicences to eligible API and finished product manufacturers anywhere in the world for purposes of supplying API or finished product into the Territory for use in the prevention and/or treatment of Covid-19.

**Field of Use.** The Field of Use in the proposed Agreement is the treatment and/or prevention of Covid-19.

**Patents.** As evidenced by the patent exhibit in the proposed Agreement, Shionogi pursues patents in many different jurisdictions.

**Manufacturing.** The license agreement allows worldwide manufacturing for the territory (thus manufacturing could take place outside the territory for shipping to the territory).

**Royalties.** Royalties are set at 5% of net sales for governments and other public purchasers (including NGOs) in the Territory, and at 10% of net sales to commercial entities in the Territory, except that there are no royalties for sales in LICs. Royalties are only payable where there is a patent/patent application in the country of manufacture or sale, or for the duration of regulatory exclusivity in place. The Agreement is royalty-free until the World Health Organization (**WHO**) declares the end of the Public Health Emergency of International Concern regarding COVID-19 (**PHEIC**).

**Territory.**

- Named territory: The Territory of the proposed Agreement consists explicitly of 117 countries, comprising of all low-income countries, lower-middle income countries, upper-middle income countries in Sub Saharan Africa, and upper-middle income countries (see Exhibit C of the proposed Agreement for the list of countries).
- There will be additional countries outside the territory in which Shionogi has not filed for any of the relevant patents and thus where sublicensees could sell the product in line with Section 2.4 of the proposed Agreement.

**Compatibility with TRIPS flexibilities.** The proposed Agreement contains language that provides that nothing in the Agreement shall be interpreted as preventing activities by the sublicensees that would not (a) infringe upon Shionogi's patents and/or any other IPRs of Shionogi and/or (b) use or misappropriate Shionogi's know-how and/or (c) use or require the use of Shionogi's Confidential Information. It also expressly makes clear that there is no breach by a Sublicensee to supply the API or licensed product outside the Territory into a country that has issued a compulsory licence.

**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) Shionogi provides regulatory waivers, (ii) the manufacture of the licensed product is in a manner consistent with WHO prequalification or stringent regulatory authority<sup>1</sup> standards, and (iii) the sale of the licensed product must have received prior WHO prequalification or stringent regulatory authority approval. Anti-diversion restrictions are limited to those countries outside the Territory where there is a non-Territory Patent.

**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	<ul style="list-style-type: none"> <li>• Provisions ensuring that sales inside or outside the Territory are not a breach of the Agreement if the sales do not infringe</li> </ul>

<sup>1</sup> Full list of countries found at <https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs>.

Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of the WHO (GSPOA); WTO Doha Declaration	Shionogi's intellectual property and/or misappropriate Shionogi know-how and/or use Shionogi's Confidential Information. Explicitly references compulsory licences. No limitations to use TRIPS flexibilities
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"> <li>• MPP to enter into non-exclusive sublicences chosen through MPP's Expression of Interest Portal</li> <li>• No parallel bilateral licence agreements with generic companies</li> </ul>
As and when necessary, enforcing terms and conditions of licence agreements, with appropriate dispute resolution mechanisms	<ul style="list-style-type: none"> <li>• MPP takes on significant obligations to monitor and enforce terms of agreements; specifies stepwise escalation of disputes, including resolution with executives and arbitration</li> </ul>
Requiring stringent quality criteria for licensed products	<ul style="list-style-type: none"> <li>• 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</li> </ul>
Including anti-diversion and traceability mechanisms	<ul style="list-style-type: none"> <li>• Sublicensees required to implement a system of batch control and tracing as a means of identifying and tracing licensed products to monitor potential diversions</li> </ul>

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

The EAG finds that the terms and conditions of the proposed Agreement represent a significant added value over the *status quo*. The terms and conditions of the proposed Agreement are comparable to the licence agreement between MPP and Pfizer for nirmatrelvir that the EAG reviewed and recommended for approval on 12 November 2021. The key difference is that the proposed Agreement has a broader territory. In light of this, subject to the final outcome and the assessment of the clinical trial data once published, the added value would consist of:

- the potential medical significance of enabling affordable access to an effective oral antiviral treatment in 117 countries;
- the strategic significance of demonstrating MPP's contribution in meaningfully engaging in the fight against COVID-19;
- building on previous MPP licence agreements with MSD for molnupiravir and Pfizer for nirmatrelvir by expanding the territory; and
- establishing a working relationship between MPP and Shionogi in promoting access to medicines, which may encourage other Japanese companies to also collaborate with MPP.

From a medical standpoint, the EAG notes that ensitrelvir is a new compound and its efficacy is relatively unknown beyond early phase clinical trials (compared to nirmatrelvir, for which there is significantly more clinical data). The EAG stresses the importance of a rigorous review of all the clinical trial data once they become available to make a full assessment on the medical significance of the product. In principle, an effective all-oral antiviral treatment available to Covid-19 patients outside the hospital setting would form an important component of the Covid-19 response by reducing the risk of hospitalisation and death.

The EAG views very positively the willingness of Shionogi to engage in licensing discussions with MPP for ensitrelvir, which is early in its clinical development process. This allowed MPP and Shionogi to move forward with this proposed Agreement even before ensitrelvir has been granted emergency use approval to enable early access to generic treatments if the clinical development is ultimately successful and ensitrelvir is finally approved by regulatory authorities. The EAG notes the importance of generating and

reviewing data regarding certain populations not included in the trials (e.g. pregnant or breastfeeding women, potentially people of African origin depending on the current study population). These are important clinical considerations to monitor closely.

As compared to MPP's previously announced Pfizer licence agreement for nirmatrelvir, the proposed Agreement is largely similar but with an expanded territory. The territory of the proposed Agreement covers 117 countries compared to 95 countries in the Pfizer Agreement. It comprises of an additional 23 countries,<sup>2</sup> which will allow for a broader public health reach and impact. However, it does not include Indonesia. MPP informed the EAG that Shionogi has a partnership with a company that owns the exclusive rights to Shionogi's patents relating to the ensitrelvir compound in Indonesia, and currently is not able to include this country in the territory. However, understands that Shionogi plans to commence negotiations for the inclusion of Indonesia in the territory after the execution of the proposed Agreement.

The EAG was also informed that the territory of the proposed license agreement includes both the public and private market in South Africa. The EAG views positively the inclusion of the private market in South Africa in the territory, particularly given that both the MPP-MSD licence agreement for molnupiravir and the MPP-Pfizer licence agreement for nirmatrelvir excluded the private market in South Africa (although, after the execution of the MPP-MSD licence agreement, MSD expanded to the private market of South Africa).

MPP informed the EAG that the proposed license agreement contains non-infringement language that could make the product available in countries outside the territory where the sublicensees activities do not infringe Shionogi's patents or other IP rights (including where a compulsory license has been issued) and/or use or misappropriate licensed know-how and/or use any of Shionogi's confidential information. However, at the time of this EAG consultation, Shionogi has filed three international PCT applications, with one having entered the national phase. As such, the patent landscape and the number of additional countries that could be indirectly covered under the proposed license agreement is currently unclear, but will become clearer in the coming months.

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

1. a broad provision that allows for sales of the licensed product outside the proposed territory where the sales do not infringe Shionogi's IPRs, misappropriate Shionogi know-how, and/or use Shionogi's Confidential Information;
2. provisions that ensure quality manufacturing of the licensed products and that the licensed products cannot be sold prior to WHO Prequalification or Stringent Regulatory Authority approval; and
3. provisions that allow MPP to monitor, manage and enforce the licence agreements vis-a-vis its licensees.

The EAG hopes that the proposed Agreement will offer the opportunity to further expand the territory of the MPP-MSD agreement and the MPP-Pfizer agreement.

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

## Recommendation

The EAG concludes that the proposed Agreement with Shionogi 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

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<sup>2</sup> Azerbaijan, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, Fiji, Grenada, Guyana, Iraq, Jamaica, Kazakhstan, Libya, Maldives, Marshall Islands, Mauritius, Paraguay, Peru, Saint Lucia, Saint Vincent and the Grenadines, Seychelles, Suriname, and Tuvalu



Medicines Patent Pool Governance Board request the Executive Director to sign the proposed Agreement between Shionogi and MPP.

Signed,

A handwritten signature in black ink, appearing to read "P. Beyer".

Peter Beyer  
Chair, Expert Advisory Group  
Date: 26 September 2022