## Appendix 1

**Table 1: Broad-spectrum antiviral efficacies of DHODH inhibitors (from Xiong et al. [2020][1])**

<table>
<thead>
<tr>
<th>IC₅₀ (µM) (SI*)</th>
<th>Virus type</th>
<th>H1N1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>H3N2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>H9N2&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Zika virus</th>
<th>Ebola replicon</th>
</tr>
</thead>
<tbody>
<tr>
<td>S312</td>
<td></td>
<td>2.36 (25)</td>
<td>8.43 (7)</td>
<td>13.2 (4)</td>
<td>2.29 (26)</td>
<td>15.0 (7.9)</td>
</tr>
<tr>
<td>S416</td>
<td></td>
<td>0.0161 (27)</td>
<td>0.013 (126)</td>
<td>0.020 (82)</td>
<td>0.021 (1090)</td>
<td>0.018 (4750)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td></td>
<td>29.3 (6)</td>
<td>2.73 (32)</td>
<td>3.36 (26)</td>
<td>17.7 (3)</td>
<td>6.43 (32)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>&gt;25.0 (&lt;2.7)</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>7.68 (680)</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Brequinar</td>
<td>0.240 (11.9)</td>
<td>0.022 (130)</td>
<td>0.060 (48)</td>
<td>0.268 (48)</td>
<td>0.102 (127)</td>
<td></td>
</tr>
</tbody>
</table>

SI* value was equal to CC₅₀/IC₅₀; values were rounded for significant figures from Xiong et al. 2020[1]

<sup>a</sup>A/WSN/33; <sup>b</sup>A/DongHu/06; <sup>c</sup>A/GuangZhou/99 NT (not tested)
Figure 1: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]11)

Note: (A) Anti-Ebola replication efficacy. BSR-T7/5 cells were transfected with the EBOV mini-genome replication system (NP, VP35, VP30, MG, and L) in the presence of increasing concentrations of Teriflunomide, Brequinar, S312 and S416 respectively. Inhibitory effects of these compounds (EC50) to EBOV mini-genome replication were determined using Bright-Glo Luciferase Assay (left-hand scale, red curve). CC50 of compounds were determined by analyzing BSR-T7/5 cell viability using CellTiterGlo Assay (righthand scale, green curve). The results are presented as a mean of at least two replicates ± SD. (B) Anti-Zika virus efficacy. Huh7 cells were infected with Zika virus (MOI=0.05) for 4 hours and then treated with increasing concentrations of compounds Teriflunomide, Brequinar, S312 and S416 respectively. The viral yields in cell supernatants were then quantified by qRT-PCR to reflect the replication efficiency of Zika virus. (C) Anti-SARS-CoV-2 virus efficacy. Aliquots of Vero E6 cells were seeded in 96-well plates and then infected with Beta CoV/Wuhan/WIV04/2019 at MOI of 0.03. At the same time, different concentrations of the compounds were added for co-culture. Cell supernatants were harvested 48 h.p.i. and RNA was extracted and quantified by qRT-PCR to determine the numbers of viral RNA copies. (D) Immuno-
fluorescence assay of SARS-CoV-2-infected cells. Vero E6 cells were infected with SARS-CoV-2 under the same procedure of C. Cells were fixed and permeabilized for staining with anti-viral NP antibody, followed by staining with Alexa 488-labeled secondary antibody. Green represents infected cells. Nuclei were stained by DAPI, and the merge of NP and nuclei were shown. Scale bar, 400uM. The results (B, C) are presented as a mean of at least three replicates ± SD. Statistical analysis, One-way ANOVA for (B). NS, p >0.05; *, p <0.05; **, p <0.01; ***, p <0.001.

Figure 2: The in vivo antiviral activity of S312 in influenza A virus-infected mice (from Xiong et al. [2020][11])

Note: (A) Diagram of the experimental procedure. (B) BALB/c mice were intranasal infected with 4000PFU of WSN virus and then intraperitoneal injected (i.p.) with PBS, S312 (2.5, 5, 10mg/kg), Oseltamivir (20mg/kg) and S312+Oseltamivir (10mg/kg+20mg/kg) once per day from D1-D14.
respectively. The body weight and survival were monitored for 14 days or until body weight reduced to 75% (n = 4 mice per group). (C) Mice were inoculated intranasally with 600 PFU of A/SC/09 (H1N1) and then i.p. with S312 (10mg/kg), Oseltamivir (20mg/kg) and S312+Oseltamivir (10mg/kg+20mg/kg) once per day from D1 to D14. The body weight and survival were monitored until 14 days post-infection or when the bodyweight reduced to 75%. The dotted line indicates endpoint for mortality (75% of initial weight). The body weights are present as the mean percentage of the initial weight ±SD of 4-5 mice per group and survival curve were shown.

**Figure 3:** S312+oselamivir is more effective at the late and severe infection phase as compared to the direct-acting antiviral drug oseltamivir (from Xiong et al. [2020][11])

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Note: (A) Diagram of the experimental procedure. (B-E) BALB/c mice were inoculated intranasally with 4000PFU of WSN virus and then i.p. with S312 (10mg/kg), Oseltamivir (20mg/kg), or S312+Oseltamivir (10mg/kg+20mg/kg) once per day from D3-7 (B), D5-9 (C), D7-11 (D). Another groups of S312 (5mg/kg) or S312+Oseltamivir (5mg/kg+20mg/kg) were given i.p. once per day from D6 to D13 in (E). The green bars indicate the period of drug administration. The body weight and survival were monitored until 14 days post-infection or when the bodyweight reduced to 75%, respectively (n = 4-5 mice per group). The dotted line indicates endpoint for mortality (75% of initial weight). The body weights are present as the mean percentage of the initial weight ± SD of 4-5 mice per group and survival curve were shown.

Figure 4: Cytokine and chemokine measurements following antiviral therapy (from Xiong et al. [2020][11])

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Note: (A) BALB/c mice were intranasally infected with 2000 PFU of influenza virus A/WSN/33 H1N1. Then, give mice intraperitoneal injection (i.p.) with Oseltamivir (20mg/kg), S312 + Oseltamivir (5mg/kg + 20mg/kg) once a day. Bodyweight loss and survival of the mice were monitored for 14 days or until body weight reduced to 75%, respectively (n = 5 mice per group). And dotted line indicates endpoint for mortality (75% of initial weight). (B) The cytokines and chemokines were measured by Meso Scale Discovery (MSD). The data were expressed as mean ± SD and were used to create the bar charts with error bars. The statistical analyses were performed using one-way ANOVA followed by Turkey post-hoc test. The plot function, ANOVA and the post-hoc functions were provided by OriginPro 2020 SR1 (9.7.0.188). P<0.05 was considered statistically significant and therefore the "significance level" parameters of the above functions were set to 0.05.
APPENDIX 2

**WHO Ordinal Scale for Clinical Improvement**

<table>
<thead>
<tr>
<th>Patient State</th>
<th>Descriptor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>No clinical or virological evidence of infection</td>
<td>0</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>No limitation of activities</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Limitation of activities</td>
<td>2</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Hospitalized, no oxygen therapy</td>
<td>3</td>
</tr>
<tr>
<td>Mild disease</td>
<td>Oxygen by mask or nasal prongs</td>
<td>4</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>Non-invasive ventilation or high-flow oxygen</td>
<td>5</td>
</tr>
<tr>
<td>Severe Disease</td>
<td>Intubation and mechanical ventilation</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Ventilation + additional organ support – pressors, RRT, ECMO</td>
<td>7</td>
</tr>
<tr>
<td>Dead</td>
<td>Death</td>
<td>8</td>
</tr>
</tbody>
</table>
Appendix 3

Concomitant Medications & Medical History

1. Therapy exclusion criteria

- Undergoing active chemotherapy or radiotherapy.
- Use of the following concomitant medications is prohibited at Screening Visit and throughout the duration of the trial:
  
  a) Use of Oseltamivir for more than 48 hrs prior to the first treatment dose
  
  b) Use of antiviral drugs (e.g. nucleoside analogue reverse-transcriptase inhibitors, protease inhibitors, etc.)
  
  c) History of long-term or concurrent use of mycophenolate mofetil, methotrexate exceeding 17.5 mg weekly
  
  d) Chloroquine or hydroxychloroquine
  
  e) Any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad as well as uricosuric drugs such as probenecid
  
  f) Treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafenib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
  
  g) Any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogues
  
  h) Use of rosuvastatin at daily doses higher than 10 mg
2. Medical history and concomitant disease exclusion criteria

- Critical patients whose expected survival time < 48-72 hours
- Evidence of pancytopenia or immunosuppression
- Any contraindication to Oseltamivir or standard of care

Presence of the following laboratory values at Screening (samples taken to taken at Screening or any routine assessment performed within the last 5 days can be used to determine eligibility, where several the most recent should be reviewed):

- Platelet count < 100,000/mm³ (<100 x 10⁹/L)
- Total bilirubin > 2 x ULN or ALT or GGT > 5 x ULN
- Elevated indirect (unconjugated) bilirubin > 1.2 x ULN (i.e. >1.1 mg/dL)
- Serum uric acid levels at Screening Visit > 1.2 x ULN (for women > 6.8 mg/dL, for men > 8.4 mg/dL)
- Renal impairment defined as estimated glomerular filtration rate ≤ 30 mL/min/1.73m²
- Decompensated liver cirrhosis (Child-Pugh score B and C)
- History or presence of serious or acute heart disease such as uncontrolled cardiac dysrhythmia or arrhythmia, uncontrolled angina pectoris, cardiomyopathy, or uncontrolled congestive heart failure (New York Heart Association [NYHA] class 3 or 4)
  - Note: NYHA class 3:
    - Cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. NYHA class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
- History or presence of any major medical or psychiatric illness (such as severe depression, psychosis, bipolar disorder), history of suicide attempt, or current suicidal ideation, if any of those conditions in the opinion of the investigator could create undue risk to the patient or could affect adherence with the trial protocol
3. **Women of child-bearing potential**

If of child-bearing potential, must have a negative pregnancy test at Screening (blood test). They must agree not to attempt to become pregnant, must not donate ova, and must use a highly effective contraceptive method (see below) together with a barrier method between trial consent and 30 days after the last intake of the investigational medicinal product (IMP).

a) Highly effective forms of birth control are those with a failure rate less than 1% per year and include:

b) Oral, intravaginal, or transdermal combined (oestrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation

c) Oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation

d) Intrauterine device or intrauterine hormone-releasing system

e) Bilateral tubal occlusion performed at least 6 months prior to study randomization

f) Vasectomised partner (i.e. the patient's male partner underwent effective surgical sterilization before the female patient entered the clinical trial and is the sole sexual partner of the female patient during the clinical trial)

g) Sexual abstinence (acceptable only if it is the patient's usual form of birth control/lifestyle choice; periodic abstinence [e.g. calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception)

h) Barrier methods of contraception include:

- Condom (without spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants)
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository
4. **Male participants of child bearing age**

Male patients must agree not to father a child or to donate sperm starting at Screening Visit, throughout the clinical trial and for 30 days after the last intake of IMP. Male patients must also:

   a) Abstain from sexual intercourse with a female partner (acceptable only if it is the patient’s usual form of birth control/lifestyle choice), or

   b) Use adequate barrier contraception during treatment with IMP and until at least 30 days after the last intake of IMP, and

   c) If they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined above

   d) If they have a pregnant partner, they must use condoms while taking IMP to avoid exposure of the foetus to the IMP

5. **Drug-drug interactions for IMU-838**

   a) The exposure to drugs metabolized by CYP2C8 may be increased by concomitant IMU-838 treatment. Concomitant administration of these drugs (especially those metabolized by more than 70% by CYP2C8) must, thus, be carefully considered. If possible, dose and treatment duration should be restricted or alternative drugs should be used. These drugs include:

      • Metabolized for more than 70% by CYP2C8: amodiaquine (anti-malarial), dasabuvir (anti-viral), enzalutamide (anti-cancer), montekulast (anti-asthmatic) and pioglitazone and repaglinide (anti-diabetics).

      • Metabolized for less than 70% by CYP2C8: paclitaxel, chloroquine, loperamide, ibuprofen and possibly diclofenac.

   In turn, strong CYP2C8 inhibitors such as gemfibrozil, glitazones, quercetin and trimethoprim may increase plasma concentrations of vidofludimus.

   b) Medications with a metabolism and elimination being mainly dependent on CYP2C8 and CYP2C9 (with few alternative ways of elimination) should be taken with caution and should be monitored carefully. Given the known hepatotoxic potential of ibuprofen, the use of ibuprofen should be carefully considered or, if possible, therapeutic alternatives should be used.

   c) The induction potential of IMU-838 for CYP1A2 may not lead to clinically relevant drug-drug interactions, however, they cannot be fully excluded. Although clopidogrel activation is performed via CYP1A2, the contribution of CYP1A2 is relatively small. It is known that some
antipsychotic drugs, in particular clozapine, are partially eliminated via CYP1A2 and an induction of this enzyme may potentially reduce their drug efficacy.

d) In-vitro assays have shown synergistic effects of vidofludimus with infliximab.

e) Recent or concurrent treatment with uricosuric drugs such as probenecid or lesinurad may result in an increased risk of renal AEs since these drugs also inhibit URAT-1 and are expected to further elevate uric acid excretion. Therefore, uricosuric drugs should not be administered in combination with IMU-838. If uratelowering therapy is required, e.g. for gout flare prophylaxis, patients should be using xanthine oxidase inhibitors (allopurinol, febuxostat) or uricases (pegloticase, rasburicase) and should be monitored closely for changes in serum uric acid levels and renal function.

f) Because it cannot be excluded that vidofludimus interacts with protein binding of drugs that are strongly bound to plasma proteins, the plasma concentration of these drugs could be increased by vidofludimus. Similarly, vidofludimus plasma levels could increase by concomitant treatment with such drugs.

g) Vidofludimus has been shown in in-vitro studies to be a potent inhibitor of the organic anion transporters OAT1 and OAT3, and may therefore reduce the excretion of some drugs also using these transport systems.

h) IMU-838 is a strong inhibitor of BCRP (IC50 = 0.02 µM). If drugs that heavily depend on the BCRP transport system for elimination are co-administered with vidofludimus, patients should be closely monitored for signs and symptoms of excessive exposure to these drugs and their dosing should be carefully considered. This is particularly true for statins, and their dose should be lowered to the lowest possible dose. Specifically, doses of rosuvastatin are not to exceed 10 mg daily.

i) MTX doses of 17.5 mg/week or higher may slightly lower trough levels of vidofludimus and should not be used concomitantly with IMU-838.

j) Patients with UGT1A1 enzyme underexpression are at greater risk for irinotecan-induced severe diarrhea or neutropenia. Because vidofludimus inhibits UGT1A1, caution should be used when using vidofludimus in a patient undergoing therapy with irinotecan.

Further details can be found in the Investigator Brochure section 6.2.4.
Appendix 4

Dose adjustment in renal impairment

Considering that COVID-19 patients can suffer multi-organ failure which may include renal impairment the dose regime can be modified as per recommendations provided in the Renal Drug Database as follows, unless clinically indicated otherwise at the discretion of the treating physician:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Recommended dose for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>&gt; 30 to 60</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>&gt; 10 to 30</td>
<td>75 mg once daily</td>
</tr>
<tr>
<td>≤ 10</td>
<td>75 mg as single dose *</td>
</tr>
</tbody>
</table>

Note: This is in line with the Renal Drug database which differs from that in the SmPC and Public Health England and Scotland (updated September 2017) and is based on clinical experience and the good tolerability of oseltamivir.

* In the event that GFR goes below the stated level and the participant has already received one or more doses as part of ongoing treatment during the trial they will not receive any more doses.

8.2.6 Deterioration and requirement for NG tube

As the disease develops an NG tube may be inserted. For patients on the combination treatment arm, the IMU-838 tablets cannot be crushed and will not be administered via the NG tube. The oseltamivir will, however, continue to be administered.

The oseltamivir capsules can be opened and its contents mixed with a little bit of water for administration via an NG tube. The mixture should be stirred and given entirely to the patient. The mixture must be swallowed immediately after its preparation. For more details refer to the Oseltamivir SmPC (end of section 6.6). If the patient is discharged from the hospital before Day 14, the patient will receive the IMP(s) and will take the remaining doses of IMP at home. They will be given a medication card detailing their remaining treatment and administration.