


# BMJ Open Prospective, randomised, parallel-group, open-label study to evaluate the effectiveness and safety of IMU-838, in combination with oseltamivir, in adults with COVID-19: the IONIC trial protocol

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## ABSTRACT

**Background** Globally, there is a scarcity of effective treatments for SARS-CoV-2 infections (causing COVID-19). Repurposing existing medications may offer the best hope for treating patients with COVID-19 to curb the pandemic. IMU-838 is a dihydroorotate dehydrogenase inhibitor, which is an effective mechanism for antiviral effects against respiratory viruses. When used synergistically with oseltamivir, therapeutic effects have been observed against influenza and SARS-CoV-2 in rodents. The IMU-838 and Oseltamivir in the Treatment of COVID-19 (IONIC) trial is a randomised controlled trial that will investigate whether time to clinical improvement in patients with COVID-19 is improved following a 14-day course of IMU-838+oseltamivir versus oseltamivir alone.

**Methods** IONIC trial is an open-label study in which participants will be randomised 1:1 in two parallel arms: the intervention arm (IMU-838+oseltamivir) and the control arm (oseltamivir only). The primary outcome is time to clinical improvement; defined as the time from randomisation to a two-point improvement on WHO ordinal scale; discharge from hospital, or death (whichever occurs first). The study is sponsored by the University Hospitals Coventry and Warwickshire NHS Trust and funded by LifeArc.

**Discussion** The IONIC protocol describes an overarching trial design to provide reliable evidence on the effectiveness of IMU-838 (vidofludimus calcium) when delivered in combination with an antiviral therapy (oseltamivir) (*IONIC intervention*) for confirmed or suspected COVID-19 infection in adult patients receiving usual standard of care.

**Ethics and dissemination** This study has been independently reviewed and approved by Wales Research Ethics Committee. In addition, required regulatory approvals were received from Medicines and Healthcare products Regulatory Agency.

**Trial registration number** EudraCT 2020-001805-21, ISRCTN53038326, NCT04516915.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ It is the only trial exploring the effectiveness of IMU-838 and its potential synergy with oseltamivir (Tamiflu) when given alongside standard care in patients with moderate to severe COVID-19.
- ⇒ Open-label trial design.
- ⇒ Trial design will not be able to explore the isolated effect of IMU-838 in COVID-19.

## BACKGROUND

### Background and justification

WHO declared SARS-CoV-2 infection (causing COVID-19) a pandemic on 11 March 2020. Main clinical symptoms include fever, cough, myalgia or fatigue, expectoration and dyspnoea.<sup>1</sup> While a majority of patients do not experience severe symptoms, one early meta-analysis found that approximately 18% of cases were severe with a fatality rate estimated to be ~4%–7% at this time.<sup>2</sup> A more recent meta-analysis suggests fatality rates of COVID-19 are around 0.68%.<sup>3</sup>

At the time of study conception, there were no known treatments for COVID-19; while the anticipated scale of the epidemic is such that hospitals, and particularly intensive care facilities, may be massively overstretched. As described by a few models of pandemic spread, up to 50% of an adult population may fall sick over a period of 8–12 weeks without intervention, of whom around 10% may require hospitalisation. This figure could imply 2 million hospital admissions in the UK alone. Considering this scenario, therapies which may only have a moderate impact

on survival or on hospital resources should be worth investigating.<sup>4</sup>

The IMU-838 and Oseltamivir in the Treatment of COVID-19 (IONIC) protocol describes an overarching trial design to provide reliable evidence on the effectiveness of IMU-838 (vidofludimus calcium) when delivered in combination with an antiviral therapy (oseltamivir) (*IONIC intervention*) for confirmed or suspected COVID-19 infection in hospitalised adult patients receiving usual standard of care (table 1).

### Choice of intervention

#### IMU-838

IMU-838 (vidofludimus) is a selective dihydroorotate dehydrogenase (DHODH) inhibitor. Vidofludimus free acid (SC12267) was previously developed by 4SC AG using capsules or tablets containing amorphous vidofludimus (4SC-101). Immunic AG acquired all rights and data of SC12267 and have developed a new pharmaceutical form containing the calcium salt of vidofludimus (vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

#### Safety of IMU-838

To date, 351 individuals have been exposed to vidofludimus (not including the ongoing and still blinded phase II trial in relapsing-remitting multiple sclerosis (RRMS)). Of these 351 subjects, 299 were dosed with 4SC-101 and 52 with IMU-838.

The safety analysis of all exposed subjects provided the following findings: no deaths, no serious adverse events (SAE) during phase I with IMU-838.

The most frequent adverse events (AE) for IMU-838 during phase I were headaches, flatulence, common cold symptoms and positive urine dipstick for haemoglobin. Importantly, vidofludimus (free acid) at a daily dose of 35 mg showed no increase in adverse reactions compared with placebo, and no increased infection rate.

#### IMU-838 and COVID-19 (SARS-CoV-2)

IMU-838 selectively inhibits pyrimidine synthesis via inhibition of DHODH, which may be a promising approach to treat COVID-19. Inhibition of de novo pyrimidine biosynthesis is a well-recognised mechanism of action associated with antiviral effects against respiratory viruses.<sup>5-7</sup> The presumptive explanation is attributed to the direct depletion of host nucleosides necessary for replication of the viral genome; however, secondary activation of the innate immune response has also been described as a relevant downstream mechanism.<sup>6 8</sup> Pyrimidine depletion is primarily achieved by blocking DHODH, an enzyme involved in the rate-limiting step of pyrimidine biosynthesis. Therefore, DHODH inhibition ameliorates and blocks the viruses' ability to 'hijack' the human host cells mechanism of RNA production to virus replication. Further detail of in vitro and in vivo trials is shown in online supplemental appendix 1 table 1 and online supplemental appendix 1 figures 1-4.

#### IMU-838 and oseltamivir (Tamiflu)

The data described by Xiong *et al*<sup>8</sup> described the synergistic response between a DHODH inhibitor (where IMU-838 is one such example) and oseltamivir in influenza-infected mice. Specific inhibition of SARS-CoV-2 was shown with DHODH inhibitors alone but not with oseltamivir. In particular, IMU-838 was shown to have a clear activity against SARS-CoV-2 in cellular assays at mid-range single-digit micromolar range. This activity is well below the plasma concentrations of IMU-838 with the dosing regimen proposed in this trial (see online supplemental appendix 1 figure 1).

While there are no data at present demonstrating direct activity of oseltamivir against SARS-CoV-2, the IONIC trial is investigating the combination effect of IMU-838 and oseltamivir and in this regard, the oseltamivir-only arm represents the control arm. The trial is not about investigating the effect of oseltamivir on SARS-CoV-2.

An important consideration is that influenza is a recurring infection with reports of coinfection with SARS-CoV-2.<sup>9 10</sup> Hence, it would seem prudent to protect patients in both arms including the 'control arm' of this possibility. In fact, Ding *et al*<sup>9</sup> reported use of oseltamivir in addition to standard care in patients with SARS-CoV-2 coinfecting with influenza. Of note, oseltamivir is usually given early in a viral infection.<sup>8</sup> Data show that IMU-838 resensitises oseltamivir to also be effective in the later stages of virus infection which is very important for this proposed trial. We can extrapolate its effects to that of SARS-CoV-2 based on the assumption that another drug (favipiravir) of the same class as oseltamivir has shown a clinical relevant effect in patients with COVID-19 in a trial in China.<sup>11</sup> Moreover, the recent report by Costanzo *et al*<sup>12</sup> demonstrates the synergistic effect of oseltamivir (in this case when combined with lopinavir/ritonavir) in the treatment of COVID-19 lending support to our rationale that it is the synergistic effect of oseltamivir with either an antiviral or DHODH inhibitor that seems effective. A further consideration: we also know that gastrointestinal symptoms can affect up to 60% of those with COVID-19<sup>13</sup> and a systematic review of oseltamivir (in influenza) has shown reduction in the proportion with diarrhoea.<sup>14</sup> Hence, we perceive this to be an added therapeutic benefit.

If this fixed combination therapy (IMU-838 and oseltamivir) is proven to be effective against COVID-19, it would also offer a more cost-effective treatment option in the long term compared with other antivirals as oseltamivir is cheap and is easily available. We did explore other antiviral remedies such as remdesivir and favipiravir, but these are not available in UK or Europe at the time of study conception. Hence, the practicalities of having an available drug in stock in the UK have been given considerable weighting when designing this project.

In an ideal scenario, we would repeat the experiments of Xiong *et al*<sup>8</sup> against SARS-CoV-2 using oseltamivir but the urgency of this pandemic precludes this, hence we have adopted a practical approach based on the best

**Table 1** Administrative details and trial summary

Short study title	IMU-838 and oseltamivir (Tamiflu) in the treatment of novel coronavirus: the IONIC trial		
Primary registration	ClinicalTrials.gov NCT04516915		
Date of registry in primary registration	18 August 2020		
Secondary identifiers	ISRCTN: ISRCTN53038326, EudraCT: 2020-001805-21		
Sponsor	University Hospitals Coventry and Warwickshire NHS Trust		
Funder	LifeArc (COVID-19 Call) and Immunic Therapeutics, Germany (no award number)		
Ethics/REC	Wales.REC1		
REC and HRA approval date	15 May 2020		
MHRA approval date	15 May 2020		
Version and date	4.0_11.01.2021		
<b>Amendment number</b>	<b>Protocol version</b>	<b>Date of amendment</b>	<b>Date of approval</b>
Substantial amendment (SA) 1.0	2.0	1 June 2020	9 June 2020
SA 2.0	3.0	15 July 2020	23 July 2020
SA 3.0	4.0	23 November 2020	26 January 2021
Contact for public queries	Kavi Sharma Email: kavi.sharma@uhcw.nhs.uk Contact number: 024769 26 197		
Contact for scientific queries	Professor Ramesh Arasaradnam Email: ramesh.arasaradnam@uhcw.nhs.uk		
Countries of recruitment	UK (single site)		
Health condition studied	COVID-19		
Study aim	To explore the effectiveness of IMU-838 in combination with antiviral (oseltamivir) therapy in treating COVID-19.		
Clinical phase	Phase IIb		
Trial design	Interventional, open-label, prospective, randomised trial		
Key inclusion and exclusion criteria	<p><b>Inclusion:</b> male or non-pregnant female patients at least 18 years old, patients having confirmed or suspected COVID-19, moderate to severe COVID-19 requiring hospitalisation</p> <p><b>Exclusion:</b> allergic or hypersensitive to IMU-838, oseltamivir or any of the ingredients; pregnant or breast feeding or with intention to become pregnant during the study; medical or concomitant disease history preventing participation</p>		
Interventions	<p><b>Control group:</b> oseltamivir (75 mg two times per day) plus standard care</p> <p><b>Intervention group:</b> loading dose of 45 mg IMU-838 followed by 22.5 mg two times per day plus oseltamivir (75 mg two times per day) and standard care (<i>IONIC intervention</i>)</p>		
Sample size	120 (60 in each arm)		
Treatment duration	14 days		
Follow-up duration	14 days		
Long COVID-19 follow-up	12 months		
Date of first enrolment	10 July 2020		
Recruitment status	Recruiting		
	<b>Objectives</b>	<b>Outcome measures</b>	
Primary	To evaluate whether clinical time to improvement is significantly better in IMU-838 plus oseltamivir ( <i>IONIC intervention</i> ) and standard care versus oseltamivir and standard care in adult subjects with COVID-19	Time to clinical improvement; defined as the time from randomisation to a 2-point improvement on an ordinal scale, discharge from hospital or death (whichever occurs first)	

Continued

**Table 1** Continued

Key secondary outcomes	<ul style="list-style-type: none"> <li>▶ To evaluate safety and tolerability of <i>IONIC</i> intervention versus oseltamivir in adult subjects with COVID-19.</li> <li>▶ To determine the effects of <i>IONIC</i> intervention on improvement of at least 2 points in clinical status scale.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Incidence of adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities.</li> <li>▶ Proportion of patients with 2-point change on WHO ordinal scale at days 7 and 28.</li> </ul>
Investigational medicinal product(s)	<p>I. IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase (DHODH).</p> <p>II. Oseltamivir is an influenza neuraminidase inhibitor (NAI).</p>	
HRA, Health Research Authority; IONIC, IMU-838 and Oseltamivir in the Treatment of COVID-19; MHRA, Medicines and Healthcare products Regulatory Agency; REC, Research Ethics Committee.		

available evidence. It is for the above reasons we have chosen to add oseltamivir within the control arm.

## METHODOLOGY

### Trial procedures

The IONIC trial is an interventional, randomised, parallel-group, open-label phase IIb trial to assess the effectiveness and safety of an oral dose of IMU-838 (22.5 mg two times per day (45 mg/day)) plus oseltamivir (75 mg two times per day (150 mg/day)) (IONIC intervention) in comparison with oseltamivir alone (75 mg two times per day) for 14 days in hospitalised patients with COVID-19. [Figure 1](#) illustrates the design of the trial.

The IONIC trial comprises a screening period, a 14-day treatment period, a 14-day follow-up period and a long-term follow-up to 1 year evaluating the effectiveness of IONIC intervention in comparison to oseltamivir alone. All participants will receive standard care as necessary (eg, supplemental oxygen, antibiotic agent's vasopressor support, etc) in addition to IONIC intervention or oseltamivir, consistent with WHO recommendations. Treatment allocation will be assigned on a 1:1 ratio using variable block randomisation. After day 14, all patients will continue with appropriate standard care as decided by the clinical care team.

The lead site of the study is University Hospital Coventry and Warwickshire NHS Trust. The study will be initiated as a single-centre trial; however, we are actively engaging with other NHS trusts which if interested will be invited to participate.

### Screening and consent

All patients admitted and hospitalised at University Hospitals Coventry and Warwickshire (UHCW) with a confirmed or suspected case of COVID-19 who meet the eligibility criteria will be approached by a member of their immediate care team and offered the chance to participate in the IONIC trial.

Informed consent will be obtained from each patient before enrolment into the study by a delegated and qualified member of the research team. However, if the patient

lacks capacity to give consent due to the severity of their medical condition, then consent may be obtained from next of kin or friend acting as the patient's personal legal representative. Further consent will then be sought with the patients if they recover sufficiently. Due to limitations on visitors on hospital premises consent will be taken verbally by telephone and documented on the consent form (consent form is attached as online supplemental material).

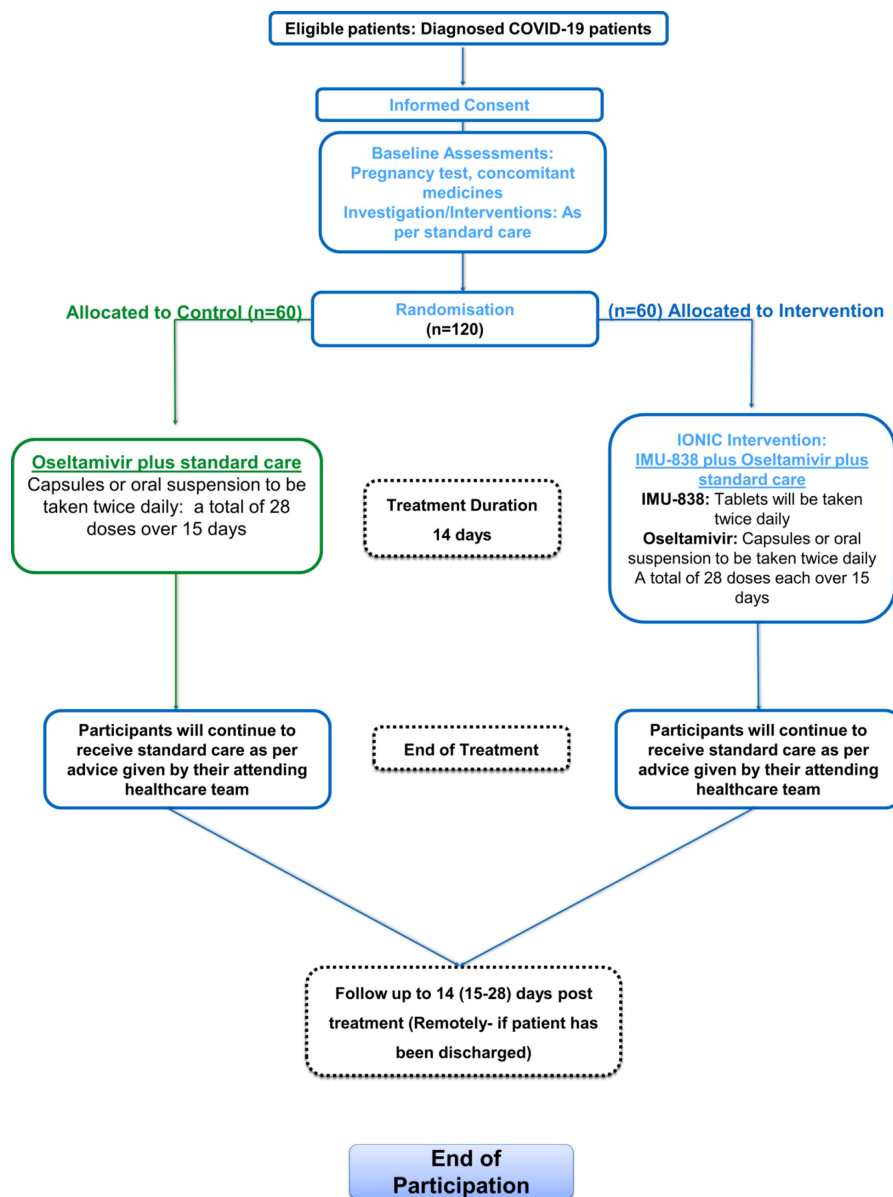
Due to the poor outcomes in patients with COVID-19 who require ventilation (>90% mortality in one cohort<sup>3</sup>), patients who lack capacity to consent due to severe disease (eg, need ventilation), and for whom a personal legal representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the professional legal representative. Consent will then be obtained from the patient's personal legal representative (or directly from the patient if they recover promptly) at the earliest opportunity.

### Eligibility criteria

*Inclusion criteria* will be any male or non-pregnant female who is 18 years or older with either confirmed (positive result from a validated test) or suspected (has been in contact with a confirmed case of COVID-19 AND have mild to severe COVID-19 symptoms AND radiological evidence of pulmonary infiltrates) case of SARS-CoV-2. Hospitalisation must be in clinical status categories 3–5 on the 9-point clinical status category scale proposed by WHO master protocol:

1. Category 3: hospitalised, no oxygen therapy.
2. Category 4: hospitalised, oxygen by mask or nasal prongs.
3. Category 5: hospitalised, non-invasive ventilation or high-flow oxygen.

*Exclusion criteria* will be anyone who is allergic or hypersensitive to IMU-838 or any of its ingredients; pregnant, breast feeding or with the intention to become pregnant during the study, or participants who cannot take the trial



**Figure 1** Flow of participants in trial. IONIC, IMU-838 and Oseltamivir in the Treatment of COVID-19.

medication orally at present; if the attending clinician specifies contraindication to the IONIC intervention or the patient has a specific medical or concomitant disease history preventing them to participate; in addition, if the participant is involved in any other interventional clinical trial for an experimental treatment of COVID-19 (online supplemental appendix 2).

### Objectives and outcome measures/endpoints

#### Primary objective

1. To evaluate the effectiveness of IONIC intervention (IMU-838 plus oseltamivir and standard care) versus oseltamivir and standard care in adult participants with COVID-19 in relation to time to clinical improvement by 2 points on the 9-point WHO ordinal scale (online supplemental appendix 3).

#### Secondary objectives

1. To evaluate safety and tolerability of *IONIC intervention* versus oseltamivir in adult subjects with COVID-19.
2. To determine the effects of *IONIC intervention* on improvement of at least 2 points in clinical status scale.
3. To assess the effects of IONIC intervention versus oseltamivir on the need for invasive ventilation, renal replacement therapy or extracorporeal membrane oxygenation (ECMO).
4. To assess the effects of IONIC intervention versus oseltamivir on the length of hospital and intensive care unit stays.
5. To assess the effects of IONIC intervention versus oseltamivir on the time from treatment initiation to death.

### Primary endpoint

1. Time to clinical improvement; defined as the time from randomisation to a 2-point improvement on WHO ordinal scale, discharge from hospital or death (whichever occurs first). Clinical status will be confirmed daily from randomisation to day 28, hospital discharge or death (whichever occurs sooner), with the worst score for that day recorded.

### Secondary endpoints

1. AEs and SAEs, including COVID-19 worsening and incidence of laboratory abnormalities.
2. Proportion of patients with 2-point change on WHO ordinal scale at days 7, 14 and 28 ( $\pm 2$  days).
3. Proportion of patients free of invasive ventilation, renal replacement therapy or ECMO at days 7 and 14.
4. Hospital length of stay and length of stay in intensive care.
5. Mortality at day 28.
6. Time from treatment initiation to death (days).

### Randomisation

Variable block randomisation will be conducted using an online validated randomisation sequence generator, as part of the electronic data capture (EDC) system where the treatment allocation will be. The block sizes to be used in the randomisation sequence will be selected by the trial statistician.

Participants will be randomised on a 1:1 basis to IONIC intervention or control group, stratified by centre, age groups and sex. Data validation will be built into the EDC system to prevent randomisation unless the participant is eligible.

Only trained staff with the assigned user rights will be able to randomise participants using their unique username and password. An email notification will be automatically generated once the participant has been randomised. This email confirmation of the participant's allocation will be sent to the chief investigator and trial team.

### Blinding and allocation concealment

This is an open-label study; therefore, both the patients and the trial staff will be aware of the patient's allocated treatment. Allocation concealment will be maintained by using an independent online randomisation sequence generator. The statisticians will be blind to treatment allocation to conduct and a blinded outcome assessment.

### Follow-up

Follow-up information is to be collected on all study participants, irrespective of whether they complete the scheduled course of allocated study treatment. Study staff will seek follow-up information through various means (via telephone if discharged), including reviewing information from medical notes, routine healthcare systems and registries.

Participants who are discharged during treatment (14 days) and are continuing to take the investigational

medical product will be followed up remotely (via telephone) every 4 days ( $\pm 24$  hours) to monitor AEs and drug compliance by a delegated research team member.

### Long-term follow-up

There are emerging data to show that a percentage of patients experience long-lasting effects of infection after recovering from COVID-19 infection referred to as 'Long COVID'.<sup>15–17</sup> In an attempt to explore the prevalence of these long-lasting effects in patients participating in the IONIC trial the study participants will be invited to remote follow-ups at three time points, that is, 3 months ( $\pm 2$  weeks), 6 months ( $\pm 2$  weeks) and 12 months ( $\pm 2$  weeks). Each follow-up will record the participants' WHO clinical status, health-related quality of life questionnaire (5-Level version of EuroQol-5 Dimension)<sup>18 19</sup> and any further relevant medical history since discharge. All follow-up activities will be conducted by a delegated member of the research team remotely and questionnaires will be delivered via telephone.

Prospective participants will have the option to only participate in the main trial by choosing not to participate in the long-term follow-up. A full schedule of events is available in [table 2](#).

### Patient withdrawal criteria

Patients must be withdrawn from the trial for any of the following reasons: patient withdraws consent; investigator decision due to deterioration in renal or liver function (1.5 times increase in the values from baseline) which in the opinion of the investigator is not related to COVID-19; AE which, in the opinion of the investigator, may jeopardise the patient's health or may compromise the trial objectives; relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardise the trial integrity or scientific goals of the trial.

If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. However, the patient may agree to continuing non-interventional follow-up procedures.

Reasonable efforts will be made to contact any patient lost to follow-up, to complete assessments and to retrieve any outstanding data and investigational medicinal product (IMP) and supplies. Patients who discontinue therapy with IMP will be encouraged to continue with trial-related assessments (including end-of-study (EoS) visit) until their trial completion.

### EoS definition

The EoS will be defined as the date of the last participant's EoS assessment or the last long-term follow-up date due, whichever comes later.

## TRIAL TREATMENTS

### IMU-838 (vidofludimus calcium)

IMU-838 will be supplied by Immunic AG and will be manufactured, tested and released according to current

**Table 2** Schedule of events

	Phase I		Phase II (long-term follow-up)				
	Screening/ baseline	Treatment period*	End of trial/early withdrawal	Day 15 (EoT)	3 months	6 months	12 months
Evaluation	Days -4 to 0†	Day 1†	Days 2-6	Day 7	Days 8-14	Day 15 (EoT)	Days 15-28 or up to 14 days after last assessment (discharge/ withdrawal)
<b>Assessments</b>							
Eligibility assessment	X						
Informed consent	X						
Demographics	X						
Relevant clinical history (including COVID-19)	X						
Current medication	X						
Inclusion/exclusion criteria	X						
Randomisation	X						
Concomitant medications/ interventions	X						
Physical examination	X						
Clinical status	X	X	X (daily)	X	X (daily)	X‡	X‡
<b>Laboratory assessments</b>							
Screening labs (including pregnancy test)§	X§						
Routine blood tests—U&E (sodium, potassium, urea and creatinine), GFR, glucose and HbA1c*	X§	X*	X*	X§	X*	X§	
Liver function test (LFT)§	X§	X*	X*	X§	X*	X§	
RBC urine (dipstick)§		X*	X*	X§	X*	X§	
Viral load¶	¶X	X*	X*	¶X	X*	¶X	¶X
<b>Safety assessments</b>							
AE and SAE assessment			‡X	‡X	‡X	‡X	‡X
<b>IMP</b>							

Continued

Table 2 Continued

Evaluation	Phase I		Treatment period*				End of trial/early withdrawal		Phase II (long-term follow-up)		
	Screening/ baseline						Days 15–28 or up to 14 days after last assessment (discharge/ withdrawal)				
	Days -4 to 0†	Day 1†	Days 2–6	Day 7	Days 8–14	Day 15 (EoT)	3 months	6 months	12 months		
IMP administration	X	X (IMU-838 loading dose/ oseltamivir single dose, PM)	X (two times per day)	X (two times per day)	X (two times per day)	X (oseltamivir single dose, AM)					
<b>Long-term follow-up</b>											
HRQOL EQ-5D							X‡	X‡	X‡		
Clinical status							X‡	X‡	X‡		
All-cause mortality and morbidity							X‡	X‡	X‡		
<p>*Standard treatment pathway: Assessments/laboratory assessments/investigations (eg, clinical, laboratory) conducted as per standard care/requested by the healthcare team. Existing local lab values obtained within 48 hours of randomisation can be used for the assessment of eligibility.</p> <p>†Screening, randomisation and first IMP administration can be performed on the same day. If these occur on the same day, treatment will start with the evening dose (loading dose of IMU-838/single dose of oseltamivir) on day 1.</p> <p>‡Follow-up assessment: Conducted remotely by reviewing medical history, patient notes and/or by telephone if the patient has been discharged from hospital. Long-term follow-up will be conducted remotely: by reviewing patient notes and medical records, clinical status and HRQOL questionnaires will be conducted via telephone, based on capacity and capability of the delivery team.</p> <p>§Research activity: Conducted if not assessed as part of standard care for participants in intervention arm. No further laboratory assessments are required following discharge.</p> <p>¶Research activity: Conducted if not assessed as part of standard care, however may be dependent on capacity and availability of kits. No further assessment required following discharge.</p> <p>AE, adverse event; EoT, End of Treatment; EQ-5D, EuroQol-5 Dimension; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin ; HRQOL, health-related quality of life ; IMP, investigational medicinal product; RBC, red blood cell; SAE, serious adverse event.</p>											



**Table 3** Proposed dosing scheme for IMU-838 used in COVID-19 therapeutic trials

Time	Day 1		Days 2–13		Day 14	
	AM	PM	AM	PM	AM	PM
Tablets (n)		2	1	1	1	1
Dose of IMU-838 (mg)		45	22.5	22.5	22.5	22.5
		*	†	†	†	†

\*Day 1: loading dose of 45 mg IMU-838 once daily given in the evening of day 1.

†Days 2–14: dosing 22.5 mg of IMU-838 two times per day.

Good Manufacturing Practice guidelines and local requirements. IMU-838 will be administered two times per day as oral tablets starting with a loading dose of 45 mg on the first day (day 1, [table 3](#)).

The highest dose of IMU-838 used in this trial will be 45 mg/day. The area under the concentration time curve of this dose is expected to be far lower than that of 70 mg/day 4SC-101, which was associated with increased red blood cell in urine. An elimination half life of 30–40 hours allows a once-daily administration with minimal accumulation (see [figure 2](#)).

Days 2–14: once in the morning (15–60 min before a meal) and once in the evening (at least 2 hours after any meal and 15–60 min before any meal). The participants will be encouraged to drink sufficiently (approximately 1.5 L/day throughout the trial).

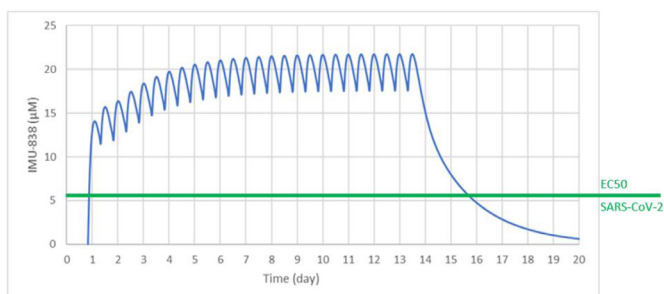
### Oseltamivir

Oseltamivir will be taken from commercially available stock with a UK marketing authorisation. Twenty-eight doses of 75 mg oseltamivir will be administered over 15 days as defined in [table 4](#). Dose adjustments for renal impairment are outlined in online supplemental appendix 4.

## STATISTICS AND DATA ANALYSIS

### Sample size calculation

There will be a sample size of 60 participants in each arm of the study. The sample size calculation is based on the analysis of the primary outcome, the time to clinical improvement. Current clinical knowledge suggests that patients in the control arm take about 14 days to improve by 2 points (ie, a clinically significant improvement).



**Figure 2** Pharmacokinetic (PK) profile for 22.5 mg two times per day of IMU-838 over a 14-day treatment period.

Therefore, we motivated the power analysis using the expected percentage of the study population to have improved within the planned study follow-up time of 14 days, under an assumed proportional hazards model.

We assume that 50% of patients in the control arm will improve within 14 days and we hypothesise that 75% of patients will improve in the intervention arm; this results in an HR of 2.<sup>20</sup> Using the standard formula for sample sizes of time-to-event outcomes suggests that 52 patients are required in each arm of the study to detect an HR of this size with 80% power at the 5% level of significance. Allowing 10% loss to follow-up, the study would require approximately 120 participants.

### Statistical analysis plan

The primary analysis will be on an intention-to-treat basis (ie, as allocated), and will compare the time to clinical improvement between study arms using the proportional hazards survival model. The model will include terms to adjust for the status of the patients (ordinal assessment) at recruitment and other baseline data available such as age and sex. Patients who do not clinically improve or who die during the 14-day period will be right censored. We will report HRs and their 95% CIs, and plot Kaplan-Meier curves to illustrate the time to improvement for both arms. For each intervention group and overall, we will report mean and SD values (or proportions for dichotomous or ordinal measures) of baseline data. Analogous survival models will be fitted to the secondary outcomes that investigate time-to-event data. Linear regression models will be fitted to the continuous secondary outcomes. Secondary analyses will also include a per-protocol (ie, as treated) analysis, and sensitivity analyses to explore the effect of the censored observations, due to death or deterioration, on the overall conclusions.

Although data ‘missingness’ is not expected to be an issue in this study, some outcome data are likely not to be available due to lack of completion of individual data items, declining consent for further follow-up or general loss to follow-up. Where possible, the reasons for data missingness will be ascertained and reported. The nature and pattern of the missingness will be carefully considered—including whether data can be treated as missing at random. Missing data may be imputed in sensitivity analyses if considered beneficial to the interpretation of the main findings. Any imputation methods used for scores

**Table 4** Proposed dosing scheme for oseltamivir use in COVID-19 therapeutic trials

Time	Day 1		Days 2–14		Day 15	
	AM	PM	AM	PM	AM	PM
Tablets (n)		1	1	1	1	
Dose of oseltamivir (mg)		75	75	75	75	
		*	†		‡	

\*Day 1: single dose of 75 mg in the evening of day 1.

†Days 2–14: dosing 75 mg two times per day of oseltamivir.

‡Day 15: single dose of 75 mg in the morning of day 15.

and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarised. All analyses will be undertaken in R V.4.0.0.

### Interim analysis

We will conduct key event analysis after data are available on 30 participants (15 in each arm). This will allow the independent Data Monitoring Committee to make recommendations about adjustments to the study in the light of data on recruitment and outcome incidence, and to reassess our assumptions about sample size considering early data on the observed differences between the groups and safety information.

### Data management

Trial data will be collected on case report forms (CRFs) and validated questionnaires, either on paper or electronically. An online validated, (GCP) Good Clinical Practice-compliant EDC system will be used to record and store trial data. Individual user log-in access to this database will be granted to only those in the study team that require it for the performance of their role. Any paper copy of the CRFs and trial forms will be securely saved for 25 years in accordance with the UHCW NHS Trust archiving procedures. The information from these paper forms will also be recorded onto the database. All information stored on the database will be pseudonymised.

### PATIENT AND PUBLIC INVOLVEMENT

Fourteen members of the UHCW patient and public involvement (PPI) group reviewed the draft lay summary for this study, commenting on the concept of the study. Most reviewers confirmed that they would be 'happy' to take part or 'had no objections' to taking part in this study. The feedback was instrumental in designing the trial and producing the protocol.

A member of the UHCW PPI group was coapplicant on the funding application and continues to be part of the research team as a coinvestigator, reviewing the trial design, protocol and additional documentation, and also being a member of the Trial Steering Committee.

All patient's facing documentation has also been reviewed by members of the UHCW PPI group and

feedback from this group has been taken into account in developing these documents.

### ETHICS AND DISSEMINATION

#### Dissemination policy

All data arising from the conduct of this study will remain the property of UHCW NHS Trust. All efforts will be made to ensure that the results arising from the study are published in a timely fashion, in established peer-reviewed journals. Results will be disseminated to collaborators, colleagues, health professionals and participants via internal and external conferences and seminars, newsletters, and via interested groups, including local health-care commissioning groups.

#### Monitoring, audit and inspection

The study will be monitored by the Research and Development Department at UHCW as representatives of the sponsor, to ensure that the study is being conducted as per protocol, adhering to research governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.

#### Ethics approval

This study has been independently reviewed and approved by Wales Research Ethics Committee (reference number: 20/WA/0146). Health Research Authority approval was granted on 15 May 2020. In addition, required regulatory approvals were received from Medicines and Healthcare products Regulatory Agency.

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**Contributors** AA and KS conceived the presented idea to the funder. AA, LB and EV helped in developing the theory and delivery of the idea. NP and AN verified the analytical methods and the data analysis plan. LB and BL encouraged and assisted RA to investigate specific aspects (viral load) of the trial. KS has led on the project management with significant support from BH and CB. MT has led the research delivery team and assisted in recruitment. All authors discussed the results and contributed to the final manuscript.

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