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Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Efficacy and Safety of IMU-838, in Combination with Oseltamivir, in Adults with Coronavirus-19 – The **IONIC Trial Protocol**

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ABSTRACT

Introduction: 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 COVID 19 patients to curb the pandemic. IMU-838 is a dihydroorotate dehydrogenase (DHODH) 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.[13] The IONIC trial is a randomized control trial that will investigate whether time to clinical improvement in COVID 19 patients is improved following a 14 day course of IMU-838 + Oseltamivir versus Oseltamivir alone.

Methods and Analysis: Participants will be randomised 1:1 in two parallel arms; the intervention arm (IMU-838 + Oseltamivir + standard care) and control arm (Oseltamivir only + Standard care). The primary outcome is 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). The IONIC Protocol describes an overarching trial design to provide reliable evidence on the efficacy 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: The study, is sponsored by UHCW NHS Trust and funded by LifeArc and Immunic Ag, is independently reviewed and approved by Wales Research Ethics Committee. The trial is registered with EudraCT (2020-001805-21), ISRCTN (ISRCTN53038326) and Clinicaltrials.gov (NCT04516915)

Strengths and Limitations:

- First to recruit participants in the trial exploring the effectiveness of IMU-838 in COVID-19.
- The only trial exploring the effectiveness of IMU-838 in combination with Oseltamivir (Tamiflu) in patients with moderate to severe COVID-19.
- However, to make the trial design flexible due to the on-going pandemic the trial methodology is un-blinded.

Table 1: Administrative details and Trial Summary

Short study title		**I**MU-838 and **O**seltamivir in the treatment of **N**ovel **C**oronovirus: **The IONIC Trial**	
Primary Registration		Clinicaltrials.gov NCT04516915	
Date of Registry in primary registration		18th Aug 2020	
Secondary identifiers		ISRCTN: ISRCTN53038326 on (23.09.2020), EudraCT: 2020-001805-21	
Sponsor		University Hospitals Coventry & Warwickshire NHS Trust	
Funder		Life Arc & Immunic Therapeutics, Germany	
Ethics/REC Comitte		Wales.REC1	
REC & HRA Approval date		15.05.2020	
MHRA Approval date		15.05.2020	
Version & Date		4.0_11.01.2021	
Amendment Number	**Protocol Version**	**Date of Amendment**	**Date of Approval**
Substantial Amendment (SA) 1.0	2.0	01.06.2020	09.06.2020
SA 2.0	3.0	15.07.2020	23/07/2020
SA 3.0	4.0	23.11.2020	26.01.2021
Contact for public queries		Kavi Sharma Email: kavi.sharma@uhcw.nhs.uk Contact number: 024769 26197	
Contact for scientific queries		Professor Ramesh Arasaradnam, Email: ramesh.arasaradnam@uhcw.nhs.uk	
Countries of recruitment		United Kingdom (single site)	
Health condition studied		COVID-19	
Study aim		To explore the efficacy 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		**Inclusion:** 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. **Exclusion criteria:** Allergic or hypersensitivity to the IMU-838,	

	Oseltamivir, or any of the ingredients, Pregnant or breastfeeding or with intention to become pregnant during the study, medical or concomitant disease history preventing participation	
Interventions	**Control Group:** Oseltamivir (75mg BID)plus standard care **Interventional Group:** Loading dose of 45mg IMU-838 followed by 22.5mg BID plus Oseltamivir (75mg BID) and standard care ***(IONIC Intervention)***	
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	10.07.2020	
Recruitment Status	Recruiting	
	Objectives	**Outcome Measures**
Primary	To evaluate whether clinical time-to-improvement is significantly better in IMU-838 plus Oseltamivir *(IONIC Intervention)* and standard care vs. 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)
Key Secondary Outcome	• To evaluate safety and tolerability of *IONIC intervention* vs. Oseltamivir in adult subjects with COVID-19. • To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale	• Incidence of Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities • Proportion of patients with two-point change on WHO ordinal scale at Day 7 and 28
Investigational Medicinal Product(s)	I. IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase (DHODH). II. Oseltamivir is an influenza neuraminidase inhibitor (NAI)	

1. Background

1.1 Background and Justification

The World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus (SARS-CoV-2) infections (causing coronavirus disease 2019 [COVID-19]) a pandemic on March 11, 2020. Main clinical symptoms include fever, cough, myalgia or fatigue, expectoration, and dyspnoea[1]. While a majority of patients do not experience severe symptoms, one early meta-analysis found that approximately 18% of cases were severe[2] with a fatality rates estimated to be ~4-7% at this time[2,3]. A more recent meta-analysis suggests fatality rates of COVID 19 are around 0.68% (Meyerowitz-Katz & Merone, 2020).

At the time of study conception, there were no known treatments for COVID-19. Whilst 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 nearly 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.

The IONIC Protocol describes an overarching trial design to provide reliable evidence on the efficacy 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.

1.2 Choice of Intervention

IMU-838

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 (INNM: vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

1.3 Safety of IMU-838

To date, 351 individuals have been exposed to vidofludimus (not including the ongoing and still blinded Phase 2 trial in 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 during Phase 1 with IMU-838.

The most frequent adverse events for IMU-838 during Phase 1 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 of adverse reactions compared with placebo, and no increased infection rate.

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

IMU-838 selectively inhibits pyrimidine synthesis via inhibition of DHODH, which may be promising approach to treat COVID-19. Inhibition of de novo pyrimidine biosynthesis is a well-recognized mechanism of action associated with antiviral effects against respiratory viruses. [5–11] 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. [6,11,12] 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 as a means to virus replication. Please refer to Appendix 1 for further detail of in vitro and in vivo trials.

1.5 IMU-838 and Oseltamivir

The data described by Xiong et al. [13] 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 figure 1).

While there is 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 co-infection with SARS-COV-2 [14, 15]. Hence it would seem prudent to protect patients in both arms including the 'control arm' of this possibility. In fact Ding et al.[14] reported use of Oseltamivir in addition to standard care in patients with SARS-COV-2 co-infected with Influenza. Of particular note, Oseltamivir is usually given early in a viral infection. Xiong et al. [13] data shows that IMU-838 re-sensitizes 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 COVID-19 patients in a trial in China [16]. Moreover, the recent report by Costanzo et al. [16] 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% [17] of those with COVID and a systematic review of Oseltamivir (in Influenza) [18] has shown reduction in the proportion with diarrhoea. 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 to other anti-virals as Oseltamivir is cheap and is easily available. We did explore other anti-viral 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. 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 available evidence. It is for the above reasons we have chosen to add Oseltamivir within the control arm.

2. Methodology

2.1. Trial Procedures

The IONIC trial is an interventional, randomised, parallel-group, open-label, Phase IIb trial to assess the efficacy and safety of an oral dose of IMU-838 (22.5 mg twice daily [45 mg/day]) plus Oseltamivir (75mg twice daily [150mg/day]) (IONIC Intervention) in comparison with Oseltamivir alone (75mg twice daily) for 14 days in hospitalised patients with COVID-19.

The IONIC trial comprises of a screening period, a 14-day treatment period, a 14-day follow-up period, and a long term follow up to one year evaluating the efficacy of IONIC intervention in comparison to Oseltamivir alone. All participants will receive standard care as necessary (e.g. 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 (Figure 2).

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.

2.2. Screening and Consent

All patients admitted and hospitalised at UHCW with a confirmed or suspected case of COVID 19, that meet the eligibility criteria will be approached and offered the chance to participate in the IONIC trial.

Informed consent will be obtained from each patient before enrolment into the study. 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 patient 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.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort [5]), patients who lack capacity to consent due to severe disease (e.g. needs 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.

2.3. 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 category 3-5 on the 9 point clinical status category scale proposed by WHO master protocol:

I. Category 3: hospitalized, no oxygen therapy
II. Category 4: hospitalized, oxygen by mask or nasal prongs
III. Category 5: hospitalized, 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, breastfeeding or with the intention to become pregnant during the study, or participants who cannot take the trial 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 (Appendix 2). In addition, if the participant is involved in any other interventional clinical trial for an experimental treatment of COVID 19.

2.4. Objectives and Outcome Measures/Endpoints

Primary objective

(i) To evaluate the efficacy of IONIC Intervention (IMU-838 plus Oseltamivir and standard care) vs. 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 (Appendix 3).

Secondary objectives

(i) To evaluate safety and tolerability of *IONIC intervention* vs. Oseltamivir in adult subjects with COVID-19.

(ii) To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale

(iii) To assess the effects of IONIC Intervention vs. Oseltamivir on the need for invasive ventilation, renal replacement therapy or Extracorporeal membrane oxygenation (ECMO)

(iv) To assess the effects of IONIC Intervention vs. Oseltamivir on the length of hospital and intensive care unit (ICU) stay

(v) To assess the effects of (IONIC Intervention) vs. Oseltamivir on the time from treatment initiation to death.

Primary endpoints

(i) 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

(i) Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities

(ii) Proportion of patients with two-point change on WHO ordinal scale at Day 7, 14 and 28 (± 2 days)

(iii) Proportion of patients free of invasive ventilation, renal replacement therapy or ECMO at Day 7 and 14

(iv) Hospital length of stay and Length of stay in Intensive care

(v) Mortality at Day 28

(vi) Time from treatment initiation to death (days)

2.5. Randomisation

Variable block randomisation will be carried out 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 trial staff will be aware of the patient's allocated treatment. Allocation concealment will be maintained by using an independent online randomisation sequence generator.

2.6. Follow Ups

Follow-up information is to be collected on all study participants, irrespective of whether or not 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 the course of treatment (14 days) and are continuing to take the Investigational medical product will be followed up remotely (via telephone) every 4 days (±24 hours) to monitor adverse events and drug compliance by a delegated research team member.

2.6.1 Long Term Follow-up

There is 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' [21-22]. 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 3 time points i.e. 3 months (±2 weeks), 6 months (±2 weeks) and 12 months (±2 weeks). Each follow up will record the participants WHO clinical status, health related quality of life questionnaire (EQ-5D-5L) 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 1.

2.7. 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; adverse event which, in the opinion of the investigator, may jeopardize the patient's health or may compromise the trial objectives; relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize 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 IMP and supplies. Patients who discontinue therapy with IMP will be encouraged to continue with trial-related assessments (including EoS visit) until their trial completion.

2.8 End of study definition

The end of the study will be defined at the date of the last participant's End of Study assessment.

Table 2: Schedule of events

	PHASE I							PHASE II (Long term Follow-up)		
	Screening/Baseline	Treatment Period[1]					End of Trial/ Early Withdrawal	3 months	6 Months	12 Months
Evaluation	Day -4 to 0[5]	Day 1[5]	Day 2 to 6	Day 7	Day 8 to 14	Day 15 (EoT)	Days 15-28 or up to 14 days after last assessment (Discharge/Withdrawal)			
Assessments										
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**			
Laboratory assessments										
Screening labs (incl. pregnancy test)[3]	**X**[3]									
Routine Blood tests – U&E (sodium, potassium, urea and creatinine), GFR, Glucose, and HbA1c[1]	**X**[3]	**X**[1]	**X**[1]	**X**[3]	**X**[1]	**X**[3]				
Liver Function test (LFT) [3]	**X**[3]	**X**[1]	**X**[1]	**X**[3]	**X**[1]	**X**[3]				
RBC urine (dipstick) [3]		**X**[1]	**X**[1]	**X**[3]	**X**[1]	**X**[3]				
Viral Load[4]	**X**[4]	**X**[1]	**X**[1]	**X**[4]	**X**[1]	**X**[4]	**X**			
Safety assessments										
AEs and SAE assessment			**X**[2]	**X**[2]	**X**[2]	**X**[2]	**X**			
IMP										
IMP administration		**X (IMU-838 loading dose /Oseltamivir single dose pm)**	**X (twice daily)**	**X (twice daily)**	**X (twice daily)**	**X (Oseltamivir single dose AM)**				
Long Term follow Up										
HRQOL EQ-5D									**X**[2]	**X**[2]

Clinical Status		X^2	X^2	X^2
All-cause Mortality & Morbidity		X^2	X^2	X^2

Standard Treatment pathway: Assessments/Laboratory Assessments/Investigations (e.g. 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

[2]**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.

[3] **Research activity:** Conducted if not assessed as part of standard care for participants in intervention arm. No further laboratory assessments are required following discharge.

[4]**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

[5]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 IMU-838 / single dose for Oseltaimivir) on Day 1.

3. TRIAL TREATMENTS

3.1 IMU-838 (Vidofludimus calcium)

IMU 838 will be supplied by Immunic AG and will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines and local requirements. IMU-838 will be administered twice daily as oral tablets starting with a loading dose of 45mg on the first day (Day 1, Table 3).

Day 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 litres per day throughout the trial).

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

	Day 1		Day 2-13		Day 14	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		2	1	1	1	1
Dose of IMU-838		45 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg
		α	β	β	β	β

α Day1: loading dose of 45mg IMU-838 once daily given on the evening of Day 1
β Day 2-14: dosing 22.g mg of IMU-838 BID

3.2 Oseltamivir

Oseltamivir will be taken from commercially available stock with a UK Marketing Authorisation. 28 doses of Oseltamivir 75mg will be administered over 15 days as defined in the table below. Dose adjustments for renal impairment are outlined in Appendix 4.

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

	Day 1		Day 2-14		Day 15	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		1	1	1	1	
Dose of Oseltamivir		75 mg	75 mg	75 mg	75 mg	
		α	β		¥	

α Day1: Single dose 75mg on the evening of Day 1
β Day 2-14: dosing 75 mg of BID of Oseltamivir
¥ Day 15**:** Single dose 75mg on the morning of Day 15

4. STATISTICS AND DATA ANALYSIS

4.1 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 (i.e. a clinically significant improvement). Therefore, we motivated the power analysis using the expected percentage of the study population to have improved within the planned study follow-up time period of 14 days, under an assumed proportional hazards model.

We assume that 50% of patients in the control arm will improve within 14 days [13] and we hypothesise that 75% of patients will improve in the intervention arm; this results in a hazard ratio of 2. Using the standard formula for sample sizes of time-to-event outcomes [13] suggests that 52 patients are required in each arm of the study to detect a hazard ratio 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.

4.2 Statistical analysis plan

The primary analysis will be on an intention-to-treat basis (i.e. 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-days period will be right-censored. We will report hazard ratios and their 95% confidence intervals, 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 standard deviation 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 (i.e. as treated) analysis, and sensitivity analyses to explore the effect of the censored observations, due to death or deterioration, on the overall conclusions. All analyses will be undertaken in R4.0.0.

4.3 Interim Analysis

We will conduct key event analysis after data are available on 30 participants (15 in each arm) participants. This will allow the independent Data Monitoring Committee (DMEC) 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 taking into account early data on the observed differences between the groups and safety information.

4.4 DATA MANAGEMENT

Trial data will be collected on CRFs and validated questionnaires, either on paper or electronically. An online validated, GCP compliant, Electronic Data Capture 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.

5. Declarations

5.1 DISSEMINATION POLICY

All data arising from the conduct of this study will remain the property of University Hospitals Coventry and Warwickshire 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 healthcare commissioning groups.

5.2 MONITORING, AUDIT & INSPECTION

The study will be monitored by the Research & 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.

5.3 Ethics approval

This study has been independently reviewed and approved by Wales Research Ethics Committee – (Ref No: 20/WA/0146); Health Research Authority (HRA) Approval was granted on 15/05/2020. In addition, required regulatory approvals were received from Medicines and Healthcare products Regulatory Agency (MHRA).

5.4 Consent for publication

Not applicable

5.5 Availability of data and materials

Data from this study will be made available to researchers who provide a methodologically sound proposal in writing to the Sponsor, following the publication of the main study paper. Anonymised, individual participant data, data dictionary, study protocol and statistical analysis plan will be accessible upon application.

5.6 Competing interests

The authors declare that they have no competing interests

5.7 Funding

The main phase of the study has received funding from LifeArc organisation through the *'COVID-19 Call'*. Immunic Therapeutics the manufacturer of IMU-838 has provided the funding for the trial drug used for this trial (Gant No N/A). The funding source had no role in the design of this study and will not have any role during its execution, analysis, interpretation of the data, or decision to submit results

5.8 Public and Patient Involvement

14 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. The majority of 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 co-applicant on the funding application and continues to be part of the research team as a co-investigator, reviewing the trial design, protocol and additional documentation, and also being a member of the Trial Steering Committee.

All patients 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.

5.9 Author contributions

AA and KS conceived of the presented idea. 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 lead on the project management with significant support from BH and CB. TM has lead the research delivery team and assisted in recruitment. All authors discussed the results and contributed to the final manuscript.

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The clinical research delivery team
Research participants

[2] Patient and public representative
[3] Independent chair IONIC Data monitoring Committee / Trial Steering Committee
[4] Independent Members IONIC Data monitoring Committee / Trial Steering Committee
[5] This publication presents independent research funded by LifeArc and carried out with the support of the National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of LifeArc, the NHS, the NIHR or the Department of Health

Figure 1: Pharmacokinetic profile for 22.5 mg BD of IMU-838 over a 14 day treatment period

Figure 2: Flow of participants in trial

REFERENCES

1. Li L-Q, Huang T, Wang Y-Q, Wang Z-P, Liang Y, Huang T-B, et al. 2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis. J Med Virol. 2020 Mar 12;

2. Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection. J Med Virol. 2020 Feb 28;

3. Research AA for C. Nucleotide Stress Controls Transcriptional Regulation through HEXIM1. Cancer Discov. 2016 Jun 1;6(6):OF17–OF17.

4. Hoffmann H-H, Kunz A, Simon VA, Palese P, Shaw ML. Broad-spectrum antiviral that interferes with de novo pyrimidine biosynthesis. Proc Natl Acad Sci U S A. 2011 Apr 5;108(14):5777–82.

5. Broad-spectrum inhibition of common respiratory RNA viruses by a pyrimidine synthesis inhibitor with involvement of the host antiviral response | Microbiology Society [Internet]. [cited 2020 Apr 24]. Available from: https://www.microbiologyresearch.org/content/journal/jgv/10.1099/jgv.0.000758

6. Lucas-Hourani M, Dauzonne D, Jorda P, Cousin G, Lupan A, Helynck O, et al. Inhibition of pyrimidine biosynthesis pathway suppresses viral growth through innate immunity. PLoS Pathog. 2013;9(10):e1003678.

7. Luthra P, Naidoo J, Pietzsch CA, De S, Khadka S, Anantpadma M, et al. Inhibiting pyrimidine biosynthesis impairs Ebola virus replication through depletion of nucleoside pools and activation of innate immune responses. Antiviral Res. 2018 Oct 1;158:288–302.

8. Xiong R, Zhang L, Li S, Sun Y, Ding M, Wang Y, et al. Novel and potent inhibitors targeting DHODH, a rate-limiting enzyme in de novo pyrimidine biosynthesis, are broad-spectrum antiviral against RNA viruses including newly emerged coronavirus SARS-CoV-2. bioRxiv. 2020 Mar 12;2020.03.11.983056.

9. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro | Cell Research [Internet]. [cited 2020 Apr 24]. Available from: https://www.nature.com/articles/s41422-020-0282-0

10. Grossfeld GD, Wolf JS, Litwin MS, Hricak H, Shuler CL, Agerter DC, et al. Asymptomatic microscopic hematuria in adults: Summary of the AUA best practice policy recommendations. Am Fam Physician. 2001 Mar 15;63(6):1145–54.

11. Guideline: Diagnosis, evaluation and follow up of asymptomatic mircrohematuria (AMH) in adults. [Internet]. 2012 [cited 2020 Mar 31]. Available from: https://www.auanet.org/guidelines/asymptomatic-microhematuria-(amh)-guideline

12. Cao, Bin and Wang, Chen}. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19}, New England Journal of Medicine 10.1056/NEJMoa2001282

13. Modelling Survival Data in Medical Research. Chapman & Hall London 1993. ISBN10 0412448904

14. Rui Xiong LZ, Shiliang Li et al. Novel and potent inhibitors targeting DHODH, a rate-limiting enzyme in de novo pyrimidine biosynthesis, are broad-spectrum antiviral against RNA viruses including newly emerged coronavirus SARS-CoV-2. bioRxiv. 2020;1(1):1.

15. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol. 2020.

16. Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of Coronavirus Disease 2019 and Influenza A: A Report from Iran. Arch Iran Med. 2020;23(4):239-43.

17. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020.

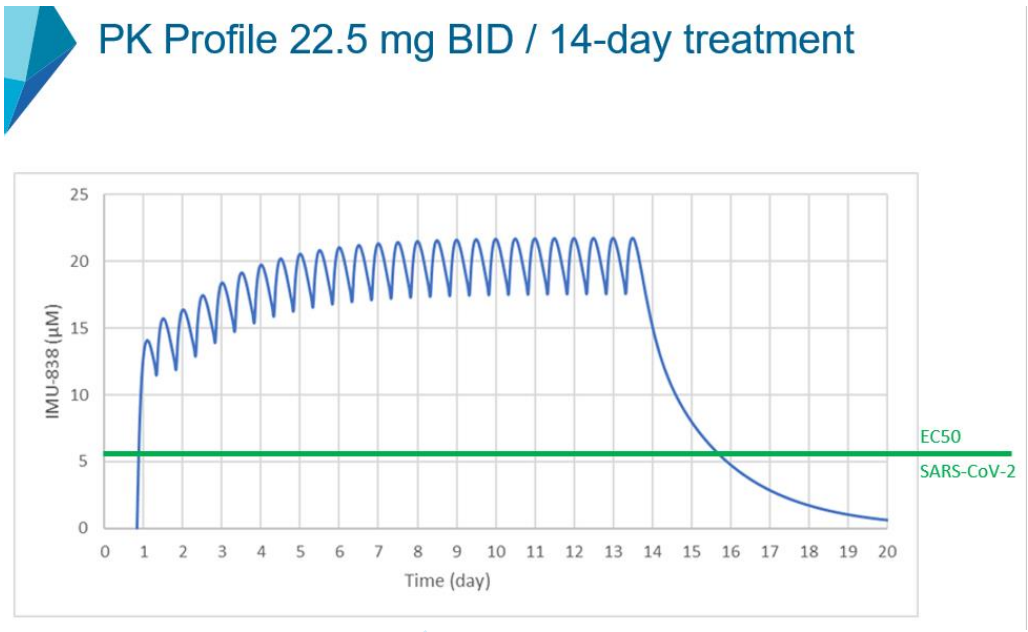
18. Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and Other Drugs for the Treatment of the New Coronavirus. Curr Med Chem. 2020.

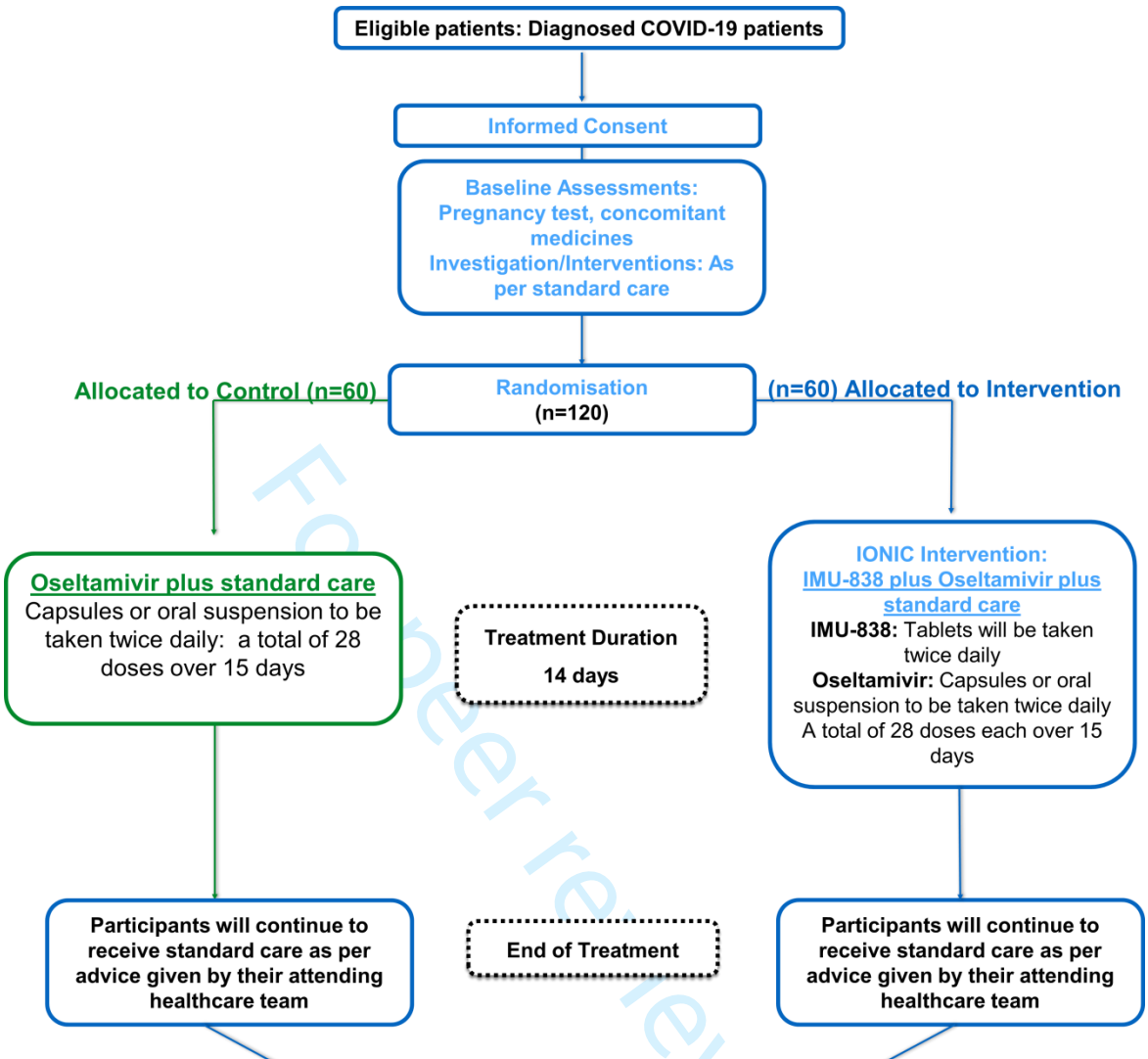
19. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020.

20. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.

21. Garner P. For 7 weeks I have been through a roller coaster of ill health, extreme emotions, and utter exhaustion. BMJ Opinion. 5 May 2020. https://blogs.bmj.com/bmj/2020/05/05/paul-garner-people-who-have-a-more-protracted-illness-need-help-to-understand-and-cope-with-the-constantly-shifting-bizarre-symptoms.

22. Covid-19: What do we know about “long covid”? BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2815 (Published 14 July 2020)





Appendix 1

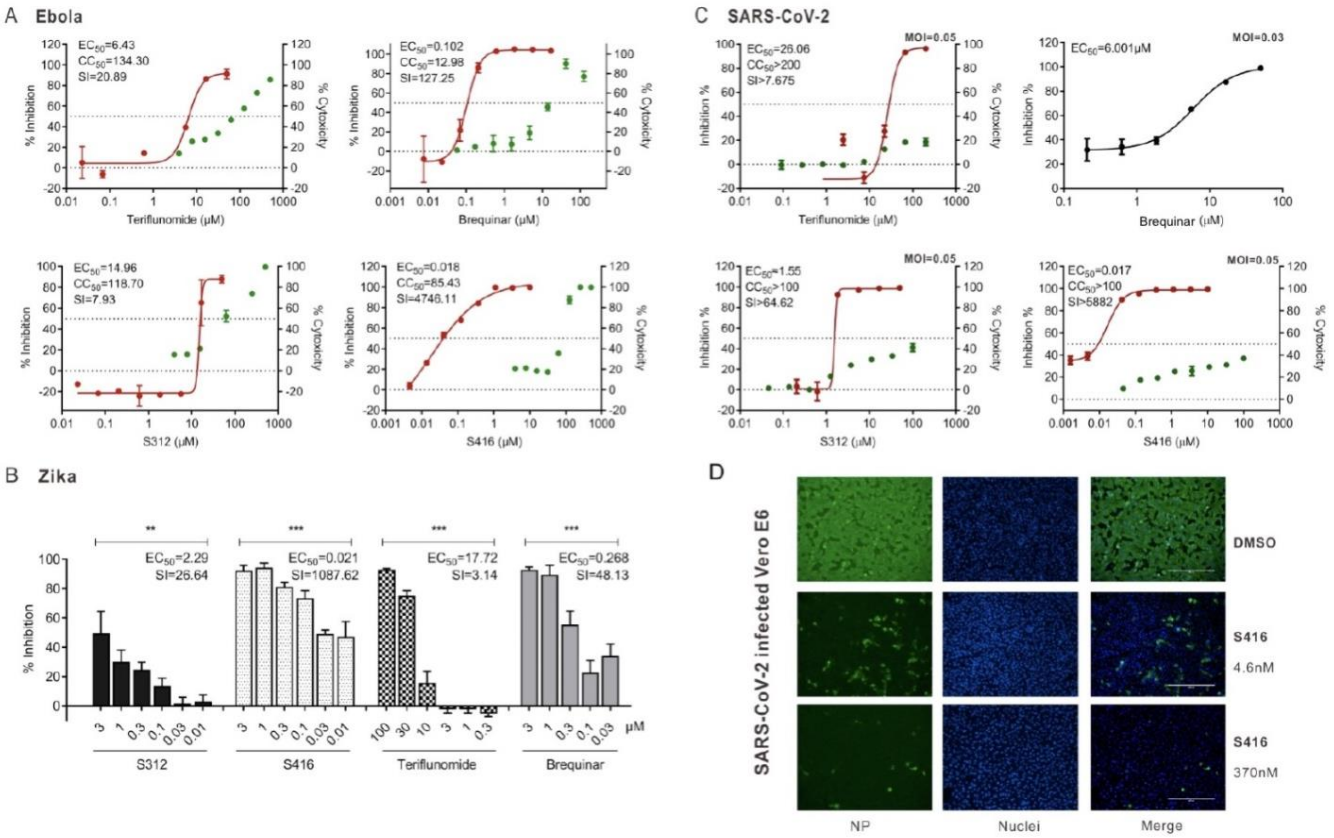
Table 1: Broad-spectrum antiviral efficacies of DHODH inhibitors (from Xiong et al. [2020](8)

IC_{50} (μM) (SI*)	Virus type				
	H1N1[a]	**H3N2[b]**	**H9N2[c]**	**Zika virus**	**Ebola-replicon**
S312	2.36 (25)	8.43 (7)	13.2 (4)	2.29 (26)	15.0 (7.9)
S416	0.0161 (27)	0.013 (126)	0.020 (82)	0.021 (1090)	0.018 (4750)
Teriflunomide	29.3 (6)	2.73 (32)	3.36 (26)	17.7 (3)	6.43 (32)
Leflunomide	>25.0 (<2.7)	NT	NT	NT	NT
Oseltamivir	7.68 (680)	NT	NT	NT	NT
Brequinar	0.240 (11.9)	0.022 (130)	0.060 (48)	0.268 (48)	0.102 (127)

SI* value was equal to CC_{50}/IC_{50}; values were rounded for significant figures from Xiong et al. 2020(8)

[a]A/WSN/33; [b]A/DongHu/06; [c]A/GuangZhou/99 NT (not tested)

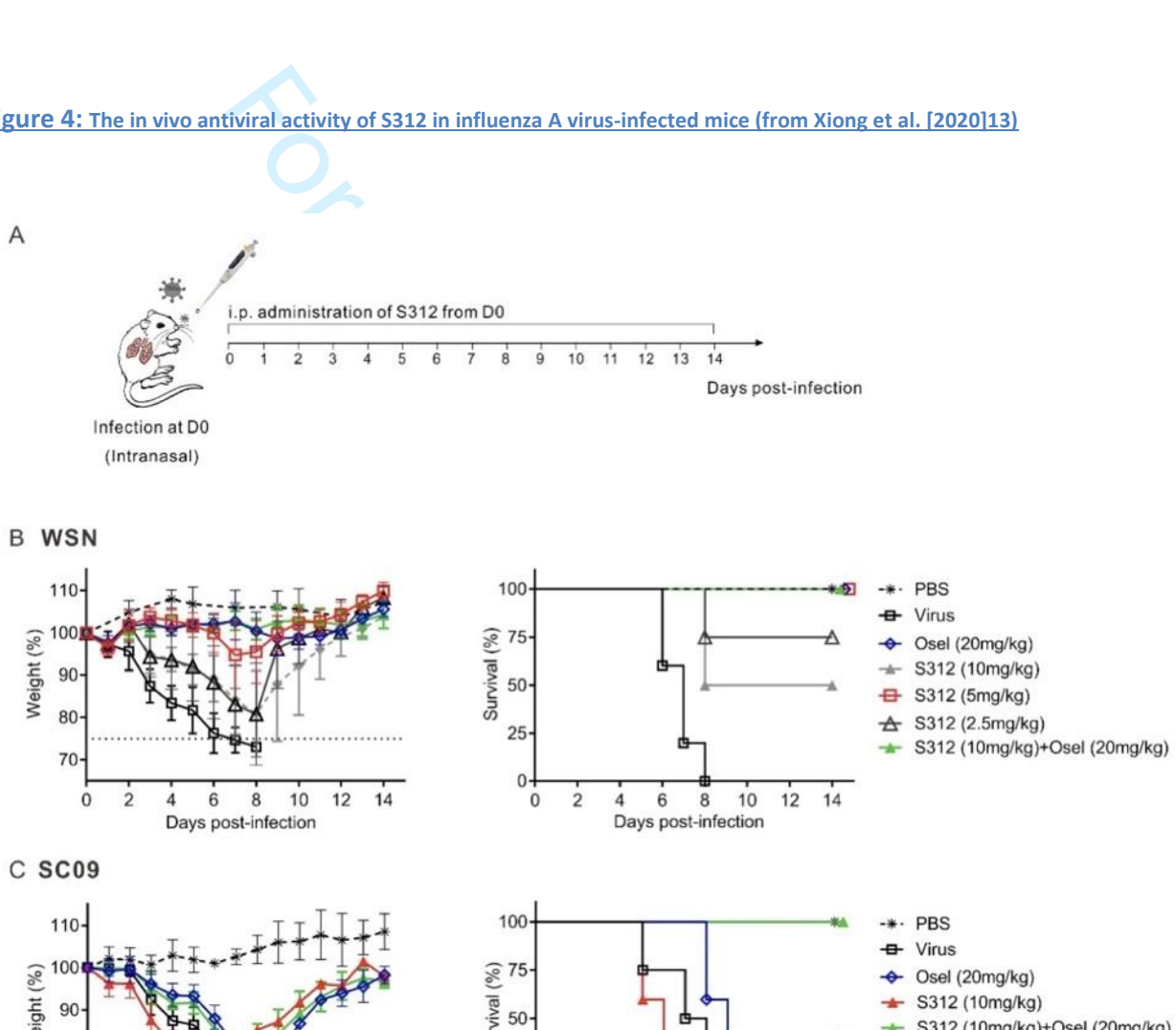
Figure 3: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]13)



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.

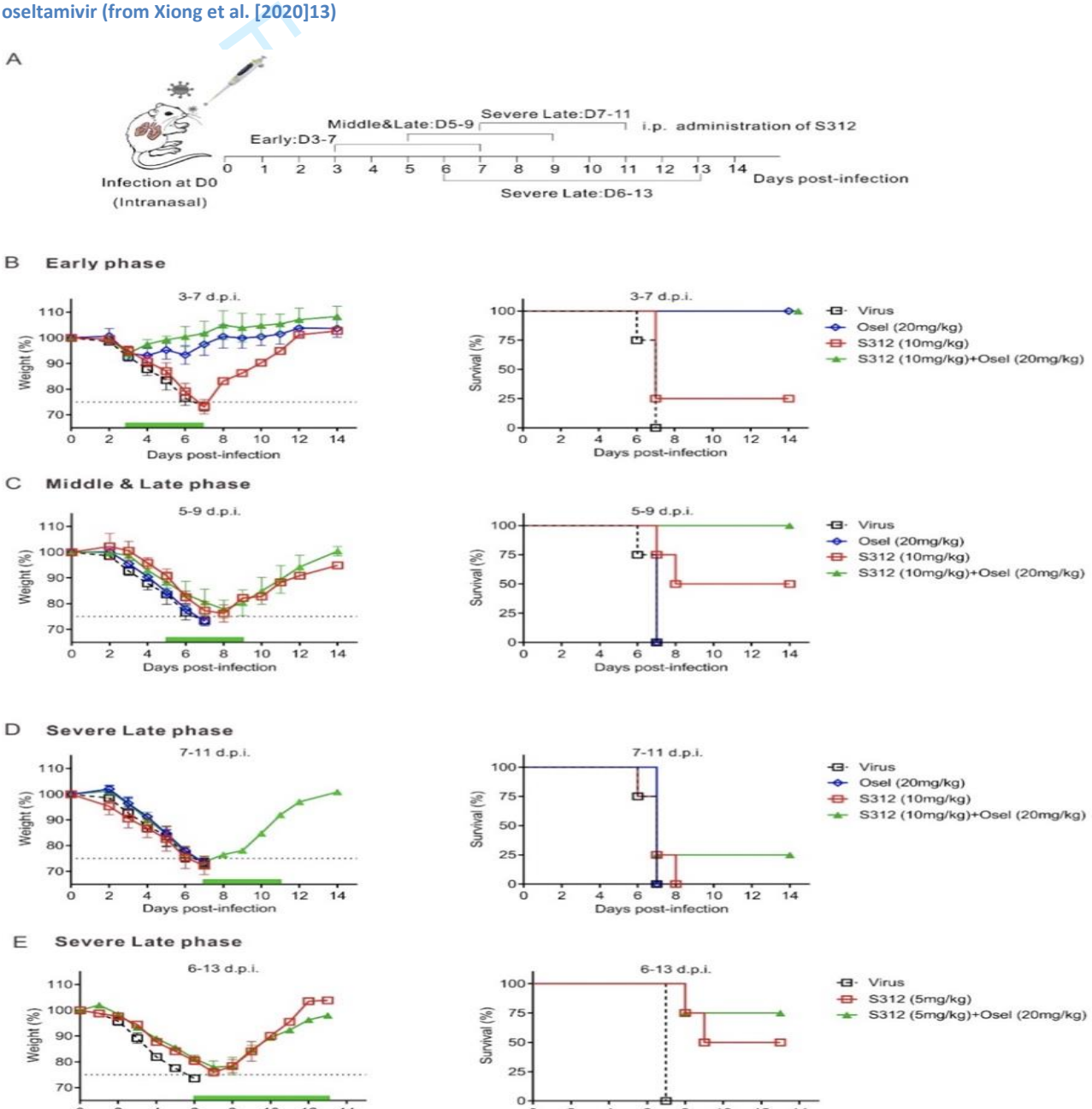
Figure 4: The in vivo antiviral activity of S312 in influenza A virus-infected mice (from Xiong et al. [2020]13)



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

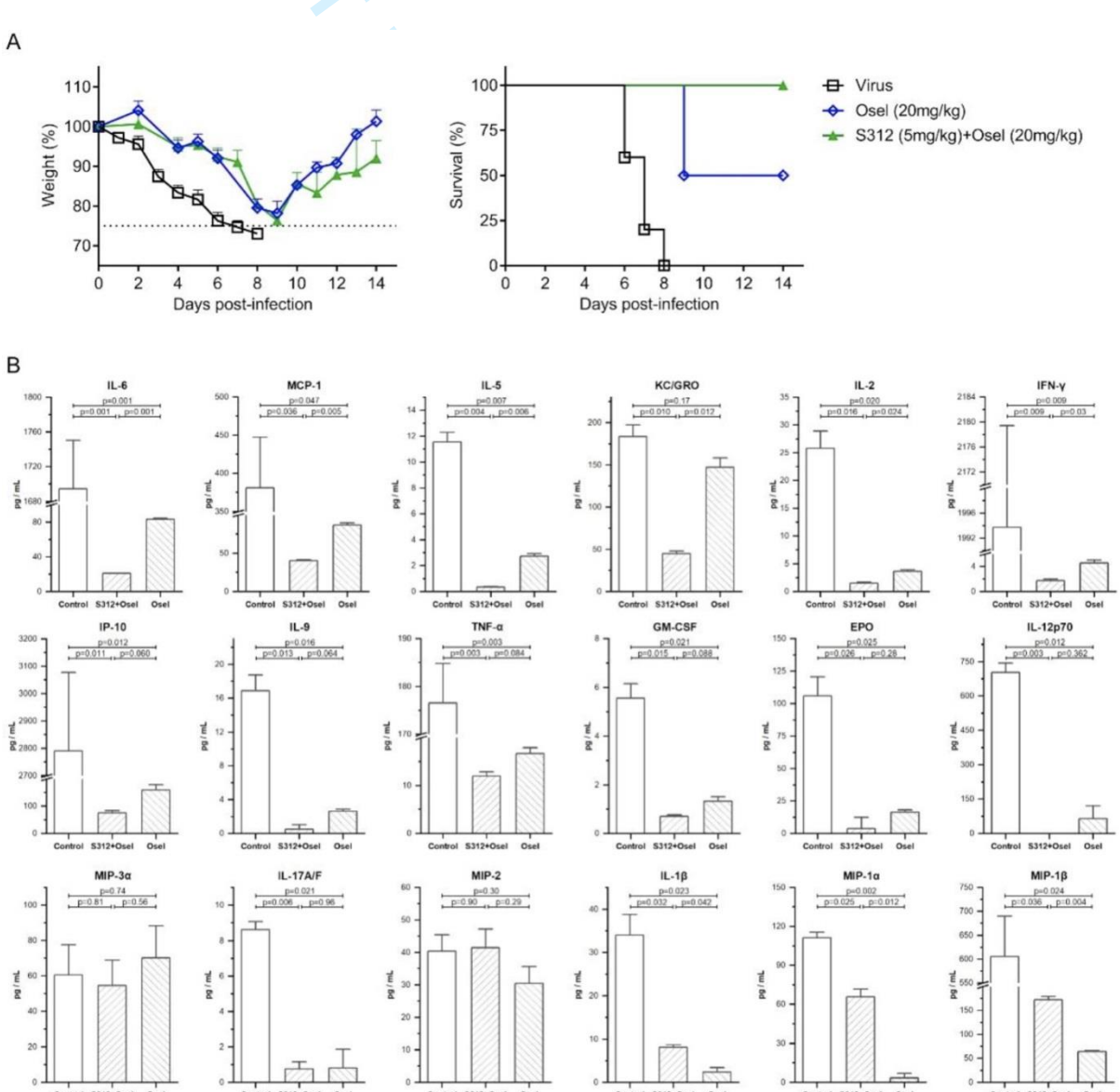
respectively. The body weight and survival were monitored for 14 days or until body weight reduced to 75% (n = 4 mice per group). (C) Mice were inoculated intranasally with 600 PFU of A/SC/09 (H1N1) and then i.p. with S312 (10mg/kg), Oseltamivir (20mg/kg) and S312+Oseltamivir (10mg/kg+20mg/kg) once per 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 5: S312 is more effective at the late and severe infection phase as compared to the direct-acting antiviral drug oseltamivir (from Xiong et al. [2020]13)



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 6: Cytokine and chemokine measurements following antiviral therapy (from Xiong et al. [2020]13)



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

Ordinal Scale for Clinical Improvement

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

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, sorafinib, 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 of investigational medicial 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 progestrogen 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 2: Recommended dosing for Oseltamivir

GFR	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	75 mg twice daily
> 10 to 30 (ml/min)	75 mg once daily
≤ 10 (ml/min)	75mg as single dose *

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 patent 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.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

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Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3,19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3,19
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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
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BMJ Open

Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Effectiveness and Safety of IMU-838, in Combination with Oseltamivir, in Adults with Coronavirus-19 – The IONIC Trial Protocol

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Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Effectiveness and Safety of IMU-838, in Combination with oseltamivir, in Adults with Coronavirus-19 – The **IONIC Trial Protocol**

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Key words: COVID-19, IMU-838, Vidofludimus calcium, oseltamivir,

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 COVID 19 patients to curb the pandemic. IMU-838 is a dihydroorotate dehydrogenase (DHODH) 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.[13] The IONIC trial is a randomized control trial that will investigate whether time to clinical improvement in COVID 19 patients 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 control arm (oseltamivir only). The primary outcome is 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). The study is sponsored by UHCW 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.

Trial Registration: The trial was registered with EudraCT (2020-001805-21) on 09.04.2020 and ISRCTN on 23.09.2020 (ISRCTN53038326) and Clinicaltrials.gov on 17.08.2020 (NCT04516915)

Strengths and Limitations:

- It is the only trial exploring the effectiveness of IMU-838 and the effect of 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

Table 1: Administrative details and Trial Summary

Short study title		**I**MU-838 and **oseltamivir** (Tamiflu®) in the treatment of **N**ovel **C**oronovirus: **The IONIC Trial**	
Primary Registration		Clinicaltrials.gov NCT04516915	
Date of Registry in primary registration		18th Aug 2020	
Secondary identifiers		ISRCTN: ISRCTN53038326, EudraCT: 2020-001805-21	
Sponsor		University Hospitals Coventry & Warwickshire NHS Trust	
Funder		Life Arc & Immunic Therapeutics, Germany	
Ethics/REC Comitte		Wales.REC1	
REC & HRA Approval date		15.05.2020	
MHRA Approval date		15.05.2020	
Version & Date		4.0_11.01.2021	
Amendment Number	**Protocol Version**	**Date of Amendment**	**Date of Approval**
Substantial Amendment (SA) 1.0	2.0	01.06.2020	09.06.2020
SA 2.0	3.0	15.07.2020	23/07/2020
SA 3.0	4.0	23.11.2020	26.01.2021
Contact for public queries		Kavi Sharma Email: kavi.sharma@uhcw.nhs.uk Contact number: 024769 26197	
Contact for scientific queries		Professor Ramesh Arasaradnam, Email: ramesh.arasaradnam@uhcw.nhs.uk	
Countries of recruitment		United Kingdom (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		**Inclusion:** 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.	

	Exclusion criteria: Allergic or hypersensitivity to the IMU-838, oseltamivir, or any of the ingredients, Pregnant or breastfeeding or with intention to become pregnant during the study, medical or concomitant disease history preventing participation	
Interventions	**Control Group:** oseltamivir (75mg BID) plus standard care **Interventional Group:** Loading dose of 45mg IMU-838 followed by 22.5mg BID plus oseltamivir (75mg BID) and standard care ***(IONIC Intervention)***	
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	10.07.2020	
Recruitment Status	Recruiting	
	Objectives	**Outcome Measures**
Primary	To evaluate whether clinical time-to-improvement is significantly better in IMU-838 plus oseltamivir *(IONIC Intervention)* and standard care vs. 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)
Key Secondary Outcome	• To evaluate safety and tolerability of *IONIC intervention* vs. oseltamivir in adult subjects with COVID-19. • To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale	• Incidence of Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities • Proportion of patients with two-point change on WHO ordinal scale at Day 7 and 28
Investigational Medicinal Product(s)	I. IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase (DHODH). II. oseltamivir is an influenza neuraminidase inhibitor (NAI)	

1. Background

1.1 Background and Justification

The World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus (SARS-CoV-2) infections (causing coronavirus disease 2019 [COVID-19]) a pandemic on March 11, 2020. Main clinical symptoms include fever, cough, myalgia or fatigue, expectoration, and dyspnoea[1]. While a majority of patients do not experience severe symptoms, one early meta-analysis found that approximately 18% of cases were severe[2] with a fatality rates estimated to be ~4-7% at this time[2,3]. A more recent meta-analysis suggests fatality rates of COVID 19 are around 0.68%[4].

At the time of study conception, there were no known treatments for COVID-19. Whilst 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[5].

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 hospitalised adult patients receiving usual standard of care.

1.2 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 (INNM: vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

1.3 Safety of IMU-838

To date, 351 individuals have been exposed to vidofludimus (not including the ongoing and still blinded Phase 2 trial in 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 during Phase 1 with IMU-838.

The most frequent adverse events for IMU-838 during Phase 1 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 of adverse reactions compared with placebo, and no increased infection rate.

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

IMU-838 selectively inhibits pyrimidine synthesis via inhibition of DHODH, which may be promising approach to treat COVID-19. Inhibition of de novo pyrimidine biosynthesis is a well-recognized mechanism of action associated with antiviral effects against respiratory viruses[6–10]. 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[7,9]. 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 Appendix 1.

1.5 IMU-838 and oseltamivir (Tamiflu®)

The data described by Xiong et al. [9] 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 figure 1).

While there is 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 co-infection with SARS-CoV-2 [11,12]. Hence it would seem prudent to protect patients in both arms including the 'control arm' of this possibility. In fact Ding et al.[11] reported use of oseltamivir in addition to standard care in patients with SARS-CoV-2 co-infected with Influenza. Of note, oseltamivir is usually given early in a viral infection. Xiong et al. [9] data shows that IMU-838 re-sensitizes 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 COVID-19 patients in a trial in China[13]. Moreover, the recent report by Costanzo et al.[14] 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[15] and a systematic review of oseltamivir (in Influenza) has shown reduction in the proportion with diarrhoea[16]. 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 to other anti-virals as oseltamivir is cheap and is easily available. We did explore other anti-viral 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. 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 available evidence. It is for the above reasons we have chosen to add oseltamivir within the control arm.

2. Methodology

2.1. 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 twice daily [45 mg/day]) plus oseltamivir (75mg twice daily [150mg/day]) (IONIC Intervention) in comparison with oseltamivir alone (75mg twice daily) for 14 days in hospitalised patients with COVID-19. Figure 2 illustrates the design of the trial.

The IONIC trial comprises of a screening period, a 14-day treatment period, a 14-day follow-up period, and a long term follow up to one year evaluating the effectiveness of IONIC intervention in comparison to oseltamivir alone. All participants will receive standard care as necessary (e.g., 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.

2.2. Screening and Consent

All patients admitted and hospitalised at UHCW with a confirmed or suspected case of COVID 19, that 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 patient 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.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[4], patients who lack capacity to consent due to severe disease (e.g. needs 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.

2.3. 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 category 3-5 on the 9-point clinical status category scale proposed by WHO master protocol:

I. Category 3: hospitalized, no oxygen therapy
II. Category 4: hospitalized, oxygen by mask or nasal prongs
III. Category 5: hospitalized, 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, breastfeeding or with the intention to become pregnant during the study, or participants who cannot take the trial 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 (Appendix 2).

2.4. Objectives and Outcome Measures/Endpoints

Primary objective

(i) To evaluate the effectiveness of IONIC Intervention (IMU-838 plus oseltamivir and standard care) vs. 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 (Appendix 3).

Secondary objectives

(i) To evaluate safety and tolerability of *IONIC intervention* vs. oseltamivir in adult subjects with COVID-19.

(ii) To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale

(iii) To assess the effects of IONIC Intervention vs. oseltamivir on the need for invasive ventilation, renal replacement therapy or Extracorporeal membrane oxygenation (ECMO)

(iv) To assess the effects of IONIC Intervention vs. oseltamivir on the length of hospital and intensive care unit (ICU) stays

(v) To assess the effects of (IONIC Intervention) vs. oseltamivir on the time from treatment initiation to death.

Primary endpoints

(i) 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 twenty-eight, hospital discharge, or death (whichever occurs sooner), with the worst score for that day recorded.

Secondary endpoints

(i) Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities

(ii) Proportion of patients with two-point change on WHO ordinal scale at Day 7, 14 and 28 (± 2 days)

(iii) Proportion of patients free of invasive ventilation, renal replacement therapy or ECMO at Day 7 and 14

(iv) Hospital length of stay and Length of stay in Intensive care

(v) Mortality at Day 28

(vi) Time from treatment initiation to death (days)

2.5. 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 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.

2.6. 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 (±24 hours) to monitor adverse events and drug compliance by a delegated research team member.

2.6.1 Long Term Follow-up

There is 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'[17–19]. 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 3 time points i.e., 3 months (±2 weeks), 6 months (±2 weeks) and 12 months (±2 weeks). Each follow-up will record the participants WHO

clinical status, health related quality of life questionnaire (EQ-5D-5L)[20,21] 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 1.

2.7. 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; adverse event which, in the opinion of the investigator, may jeopardize the patient's health or may compromise the trial objectives; relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize 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 IMP and supplies. Patients who discontinue therapy with IMP will be encouraged to continue with trial-related assessments (including EoS visit) until their trial completion.

2.8 End of study definition (EOS)

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

Table 2: Schedule of events

	PHASE I							PHASE II (Long term Follow-up)		
	Screening/Baseline	Treatment Period[1]					End of Trial/ Early Withdrawal	3 months	6 Months	12 Months
Evaluation	Day -4 to 0[5]	Day 1[5]	Day 2 to 6	Day 7	Day 8 to 14	Day 15 (EoT)	Days 15-28 or up to 14 days after last assessment (Discharge/Withdrawal)			
Assessments										
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[2]			
Laboratory assessments										
Screening labs (incl. pregnancy test)[3]	X[3]									
Routine Blood tests – U&E (sodium, potassium, urea and creatinine), GFR, Glucose, and HbA1c[1]	X[3]	X[1]	X[1]	X[3]	X[1]	X[3]				
Liver Function test (LFT) [3]	X[3]	X[1]	X[1]	X[3]	X[1]	X[3]				
RBC urine (dipstick) [3]		X[1]	X[1]	X[3]	X[1]	X[3]				
Viral Load[4]	X[4]	X[1]	X[1]	X[4]	X[1]	X[4]	X[4]			
Safety assessments										
AEs and SAE assessment			X[2]	X[2]	X[2]	X[2]	X[2]			
IMP										
IMP administration		X (IMU-838 loading dose /oseltamivir single dose pm)	X (twice daily)	X (twice daily)	X (twice daily)	X (oseltamivir single dose AM)				
Long Term follow Up										
HRQOL EQ-5D									X[2]	X[2]

Clinical Status		X[2]	X[2]	X[2]
All-cause Mortality & Morbidity		X[2]	X[2]	X[2]

Note: Glomerular Filtration Rate (GFR), Glycated hemoglobin (HBA1c), Red Blood Cell (RBC), Adverse events (AE), Serious Adverse Events (SAE), Investigational Medicinal Product (IMP), health related quality of life (HRQOL)

Standard Treatment pathway: Assessments/Laboratory Assessments/Investigations (e.g., 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

[2]**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.

[3]**Research activity:** Conducted if not assessed as part of standard care for participants in intervention arm. No further laboratory assessments are required following discharge.

[4]**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

[5]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 IMU-838 / single dose for Oseltaimivir) on Day 1.

3. TRIAL TREATMENTS

3.1 IMU-838 (Vidofludimus calcium)

IMU 838 will be supplied by Immunic AG and will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines and local requirements. IMU-838 will be administered twice daily as oral tablets starting with a loading dose of 45mg on the first day (Day 1, Table 3).

Day 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 litres per day throughout the trial).

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

	Day 1		Day 2-13		Day 14	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		2	1	1	1	1
Dose of IMU-838		45 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg
		α	β	β	β	β

α Day1: loading dose of 45mg IMU-838 once daily given on the evening of Day 1
β Day 2-14: dosing 22.g mg of IMU-838 BID

3.2 Oseltamivir

oseltamivir will be taken from commercially available stock with a UK Marketing Authorisation. 28 doses of oseltamivir 75mg will be administered over 15 days as defined in the table below. Dose adjustments for renal impairment are outlined in (Appendix 4).

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

	Day 1		Day 2-14		Day 15	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		1	1	1	1	
Dose of oseltamivir		75 mg	75 mg	75 mg	75 mg	
		α	β		¥	

α Day1: Single dose 75mg on the evening of Day 1
β Day 2-14: dosing 75 mg of BID of oseltamivir
¥ Day 15**:** Single dose 75mg on the morning of Day 15

4. STATISTICS AND DATA ANALYSIS

4.1 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 (i.e., a clinically significant improvement). 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 a hazard ratio of 2[22]. Using the standard formula for sample sizes of time-to-event outcomes suggests that fifty-two patients are required in each arm of the study to detect a hazard ratio 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.

4.2 Statistical analysis plan

The primary analysis will be on an intention-to-treat basis (i.e., 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-days period will be right-censored. We will report hazard ratios and their 95% confidence intervals, 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 standard deviation 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 (i.e., 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 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 summarized. All analyses will be undertaken in R4.0.0.

4.3 Interim Analysis

We will conduct key event analysis after data are available on 30 participants (15 in each arm) participants. This will allow the independent Data Monitoring Committee (DMEC) 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.

4.4 DATA MANAGEMENT

Trial data will be collected on CRFs and validated questionnaires, either on paper or electronically. An online validated, GCP compliant, Electronic Data Capture 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.

5. Declarations

5.1 DISSEMINATION POLICY

All data arising from the conduct of this study will remain the property of University Hospitals Coventry and Warwickshire 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 healthcare commissioning groups.

5.2 MONITORING, AUDIT & INSPECTION

The study will be monitored by the Research & 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.

5.3 Ethics approval

This study has been independently reviewed and approved by Wales Research Ethics Committee – (Ref No: 20/WA/0146); Health Research Authority (HRA) Approval was granted on 15/05/2020. In addition, required regulatory approvals were received from Medicines and Healthcare products Regulatory Agency (MHRA).

5.4 Consent for publication

Not applicable

5.5 Availability of data and materials

Data from this study will be made available to researchers who provide a methodologically sound proposal in writing to the Sponsor, following the publication of the main study paper. Anonymised, individual participant data, data dictionary, study protocol and statistical analysis plan will be accessible upon application.

5.6 Competing interests

The authors declare that they have no competing interests

5.7 Funding

The main phase of the study has received funding from LifeArc organisation. Immunic Therapeutics the manufacturer of IMU-838 has provided the funding for the trial drug used for this trial. The

funding source had no role in the design of this study and will not have any role during its execution, analysis, interpretation of the data, or decision to submit results

5.8 Public and Patient Involvement

14 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 co-applicant on the funding application and continues to be part of the research team as a co-investigator, 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.

5.9 Author contributions

AA and KS conceived of 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. TM has led the research delivery team and assisted in recruitment. All authors discussed the results and contributed to the final manuscript.

5.10 Acknowledgements:

Mr John Todd[2]
Dr Neerja Bhala[3,]
Dr Ravi Gowda, Prof Luca Frullon, Dr Mounia Hocine[4]
National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility[5]
The clinical research delivery team
Research participants

[2] Patient and public representative
[3] Independent chair IONIC Data monitoring Committee / Trial Steering Committee
[4] Independent Members IONIC Data monitoring Committee / Trial Steering Committee
[5] This publication presents independent research funded by LifeArc and carried out with the support of the National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of LifeArc, the NHS, the NIHR or the Department of Health

Figure 1: Pharmacokinetic profile for 22.5 mg BD of IMU-838 over a 14 day treatment period

Figure 2: Flow of participants in trial

REFERENCES

1 Li L-Q, Huang T, Wang Y-Q, *et al.* COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020;**92**:577–83. doi:10.1002/jmv.25757

2 Sun P, Qie S, Liu Z, *et al.* Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection. *Journal of medical virology* Published Online First: 28 February 2020. doi:10.1002/jmv.25735

3 Research AA for C. Nucleotide Stress Controls Transcriptional Regulation through HEXIM1. *Cancer Discov* 2016;**6**:OF17–OF17. doi:10.1158/2159-8290.CD-RW2016-072

4 Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis* 2020;**101**:138–48. doi:10.1016/j.ijid.2020.09.1464

5 Cooper I, Mondal A, Antonopoulos CG. A SIR model assumption for the spread of COVID-19 in different communities. *Chaos Solitons Fractals* 2020;**139**:110057. doi:10.1016/j.chaos.2020.110057

6 Cheung NN, Lai KK, Dai J, *et al.* Broad-spectrum inhibition of common respiratory RNA viruses by a pyrimidine synthesis inhibitor with involvement of the host antiviral response. *J Gen Virol* 2017;**98**:946–54. doi:10.1099/jgv.0.000758

7 Lucas-Hourani M, Dauzonne D, Jorda P, *et al.* Inhibition of Pyrimidine Biosynthesis Pathway Suppresses Viral Growth through Innate Immunity. *PLoS Pathog* 2013;**9**:e1003678. doi:10.1371/journal.ppat.1003678

8 Luthra P, Naidoo J, Pietzsch CA, *et al.* Inhibiting pyrimidine biosynthesis impairs Ebola virus replication through depletion of nucleoside pools and activation of innate immune responses. *Antiviral Res* 2018;**158**:288–302. doi:10.1016/j.antiviral.2018.08.012

9 Xiong R, Zhang L, Li S, *et al.* Novel and potent inhibitors targeting DHODH, a rate-limiting enzyme in de novo pyrimidine biosynthesis, are broad-spectrum antiviral against RNA viruses including newly emerged coronavirus SARS-CoV-2. 2020. doi:10.1101/2020.03.11.983056

10 Wang M, Cao R, Zhang L, *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;**30**:269–71. doi:10.1038/s41422-020-0282-0

11 Ding Q, Lu P, Fan Y, *et al.* The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *Journal of Medical Virology* 2020;**92**:1549–55. doi:10.1002/jmv.25781

12 Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of Coronavirus Disease 2019 and Influenza A: A Report from Iran. *Arch Iran Med* 2020;**23**:239–43. doi:10.34172/aim.2020.04

13 Cai Q, Yang M, Liu D, *et al.* Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering* 2020;**6**:1192–8. doi:10.1016/j.eng.2020.03.007

14 Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and other Drugs for the Treatment of the New Coronavirus. *Current Medicinal Chemistry* 2020;**27**:4536–41. doi:10.2174/0929867327666200416131117

15 Lin L, Jiang X, Zhang Z, *et al.* Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020;**69**:997–1001. doi:10.1136/gutjnl-2020-321013

16 Jefferson T, Jones M, Doshi P, *et al.* Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;**348**:g2545. doi:10.1136/bmj.g2545

17 Mahase E. Covid-19: What do we know about “long covid”? *BMJ* 2020;**370**:m2815. doi:10.1136/bmj.m2815

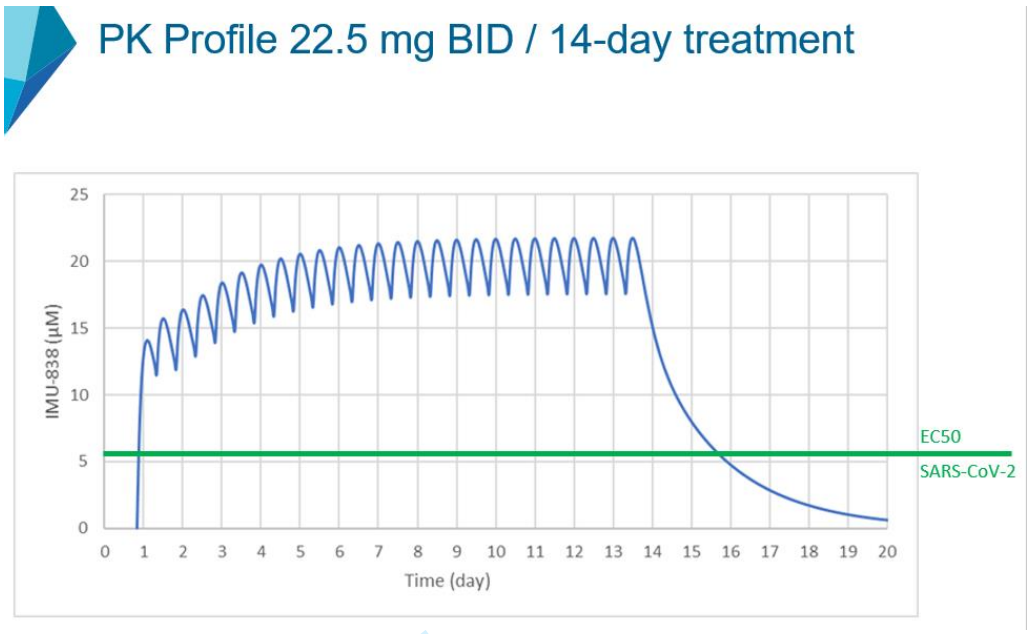
18 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open* 2021;**4**:e2111417. doi:10.1001/jamanetworkopen.2021.11417

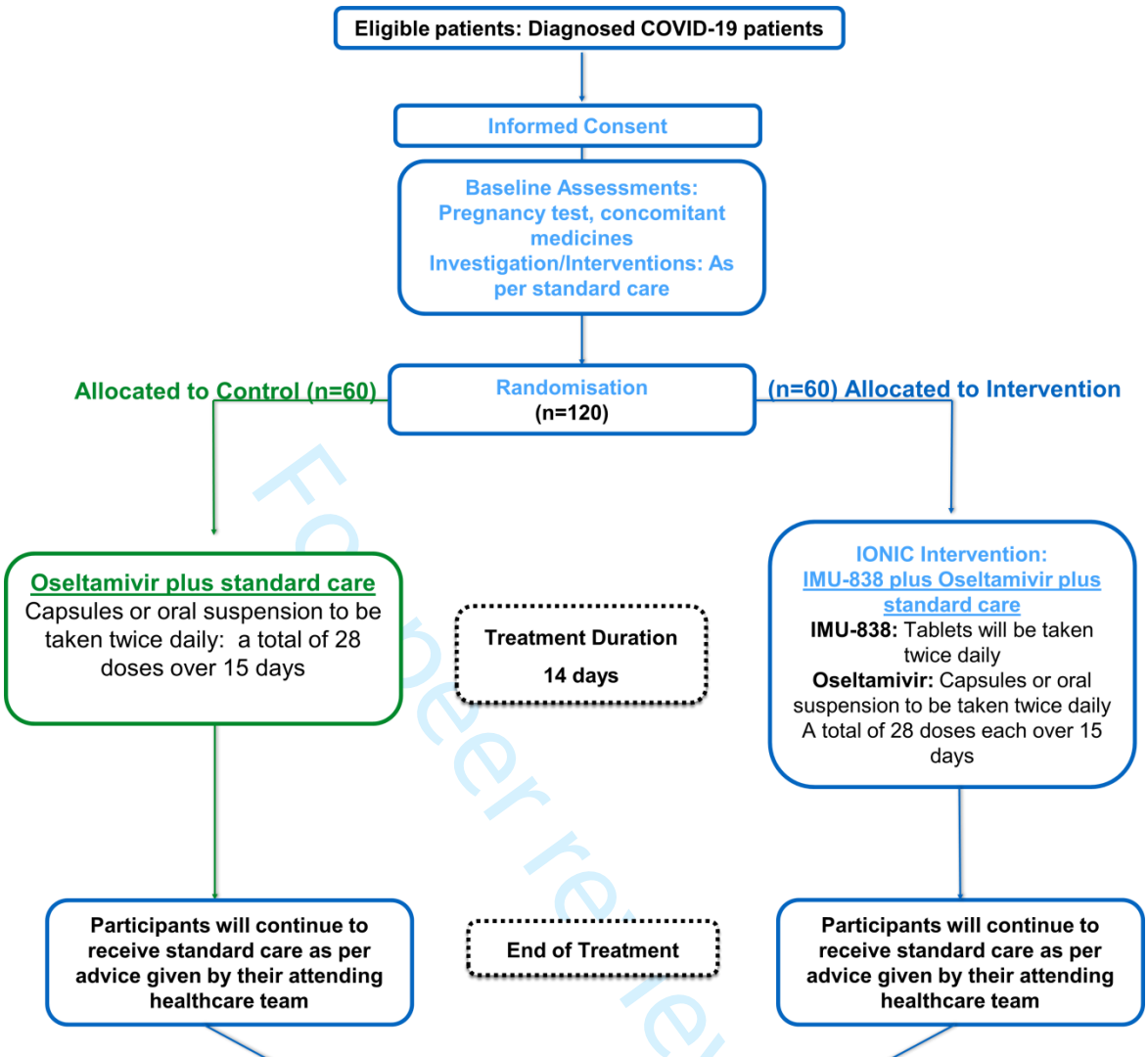
19 Taquet M, Dercon Q, Luciano S, *et al.* Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021;**18**:e1003773. doi:10.1371/journal.pmed.1003773

20 Poudel AN, Zhu S, Cooper N, *et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021;**16**:e0259164. doi:10.1371/journal.pone.0259164

21 Lam CLK, Tse ETY, Wong CKH, *et al.* A pilot study on the validity and psychometric properties of the electronic EQ-5D-5L in routine clinical practice. *Health Qual Life Outcomes* 2021;**19**:266. doi:10.1186/s12955-021-01898-3

22 Van Houwelingen H. Modelling Survival Data in Medical Research. D. Collett, Chapman & Hall, London, 1994. No of pages: XVII + 347. Price: E19.99. ISBN 0-41 2-44890-4. *Statistics in Medicine* 1995;**14**:1147–8. doi:10.1002/sim.4780140936





The IONIC Trial

CONSENT FORM

Study title: **IMU-838 and Oseltamivir in treatment of Novel Coronavirus (COVID-19)**

Name of Researcher: **Professor Ramesh Arasaradnam**

IRAS ID:282532 Participant ID:

No.	Statement	Please initial box
1	I confirm that I have read (or had read to me) and understood the information sheet dated 01.06.2020 (v2.0) for the above study. If I am unable to read or sign the consent I understand a witness was available to certify the accurate reading. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from UHCW NHS Trust or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4	I give consent for the information collected about me by the doctors, nurses and hospitals that provide me with care can be used to support other research in the future, and can be shared anonymously with other researchers for up to *25* years following my completion of the above study.	
5	I agree to provide the blood and urine samples and understand that these may be stored and utilised in future research as specified in the Information Sheet dated (v2.0_01.06.2020) for the above study.	
6	Should I choose to withdraw consent, I agree that information obtained from me in this study up to that point may still be used.	
7	I understand that the information held and maintained by UHCW NHS Trust will be recorded on a computer database and that this data will be stored on computers supervised by UHCW. This data may be used to help contact me or provide information about my health status.	
8	I agree to be contacted by telephone following discharge from hospital to collect follow-up information.	
9	I agree to take part in the above study.	

Name of Participant	Signature	Date
Name of Person receiving consent	Signature	Date

When completed: 1 copy for the participant; 1 in their medical notes, and keep the original in the study site file.

University Hospitals Coventry and Warwickshire NHS Trust

The IONIC Trial

WITNESS CONSENT FORM

Study title: **IMU-838 and Oseltamivir in treatment of Novel Coronavirus (COVID-19)**

Name of Researcher: **Professor Ramesh Arasaradnam**

Participant ID:

If participant is unable to read the text and/or sign for themselves but has capacity to give consent.

I witnessed the accurate reading of the consent form to the potential participant, who could ask any questions and got satisfactory replies.

I confirm that they gave their consent freely.

Name of Witness	Signature	Date
Name of Person receiving consent	Signature	Date

If consent is recorded over the phone.

I witnessed the accurate reading of the consent form to the potential participant, who could ask any questions and got satisfactory replies.

I confirm they gave their consent freely.

Name of Witness	Signature	Date
Name of Person receiving consent	Signature	Date

When completed: 1 copy for the participant; 1 in their medical notes, and keep the original in the study site file.

Appendix 1

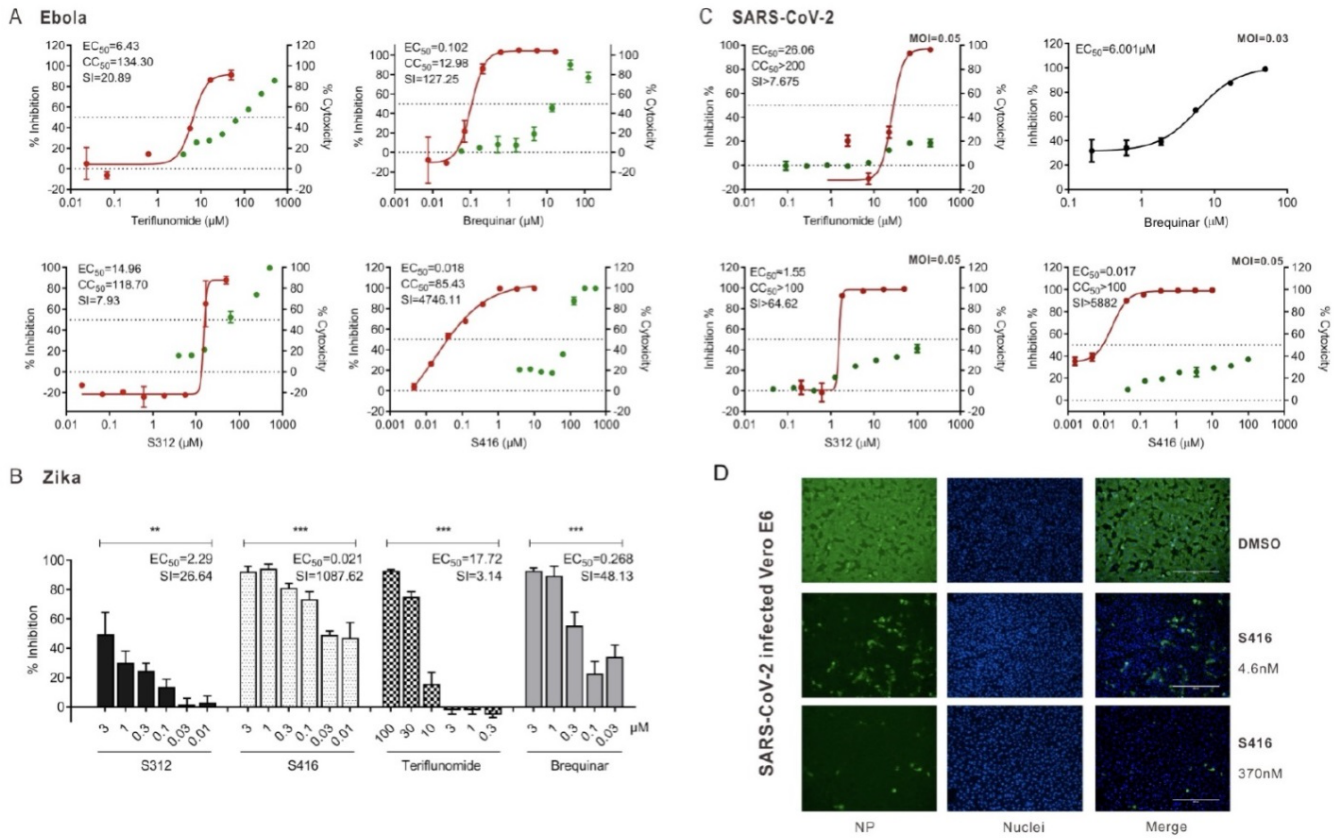
Table 1: Broad-spectrum antiviral efficacies of DHODH inhibitors (from Xiong et al. [2020](8)

IC_{50} (μM) (SI*)	Virus type				
	H1N1[a]	**H3N2[b]**	**H9N2[c]**	**Zika virus**	**Ebola-replicon**
S312	2.36 (25)	8.43 (7)	13.2 (4)	2.29 (26)	15.0 (7.9)
S416	0.0161 (27)	0.013 (126)	0.020 (82)	0.021 (1090)	0.018 (4750)
Teriflunomide	29.3 (6)	2.73 (32)	3.36 (26)	17.7 (3)	6.43 (32)
Leflunomide	>25.0 (<2.7)	NT	NT	NT	NT
Oseltamivir	7.68 (680)	NT	NT	NT	NT
Brequinar	0.240 (11.9)	0.022 (130)	0.060 (48)	0.268 (48)	0.102 (127)

SI* value was equal to CC_{50}/IC_{50}; values were rounded for significant figures from Xiong et al. 2020(8)

[a]A/WSN/33; [b]A/DongHu/06; [c]A/GuangZhou/99 NT (not tested)

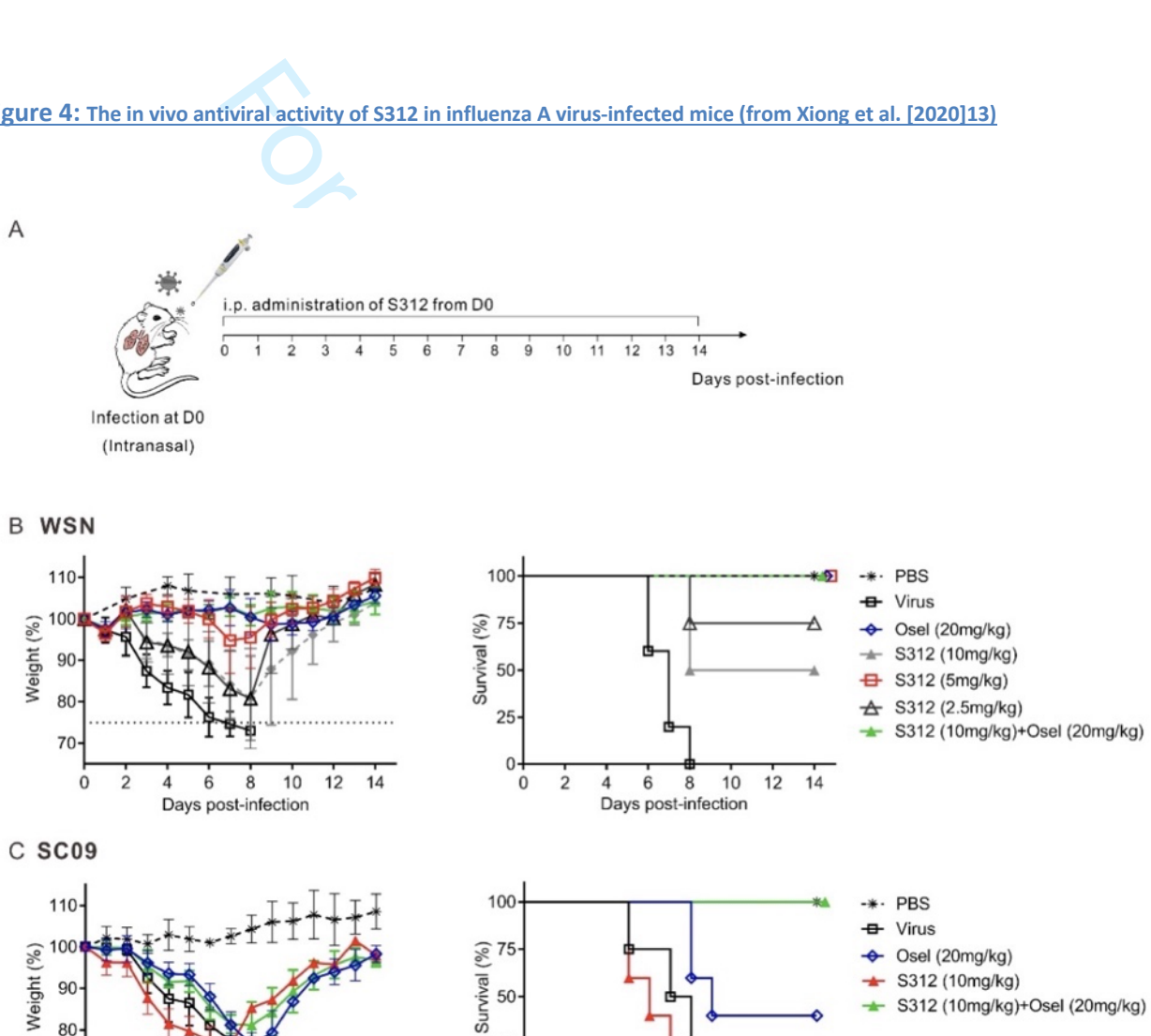
Figure 3: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]13)



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.

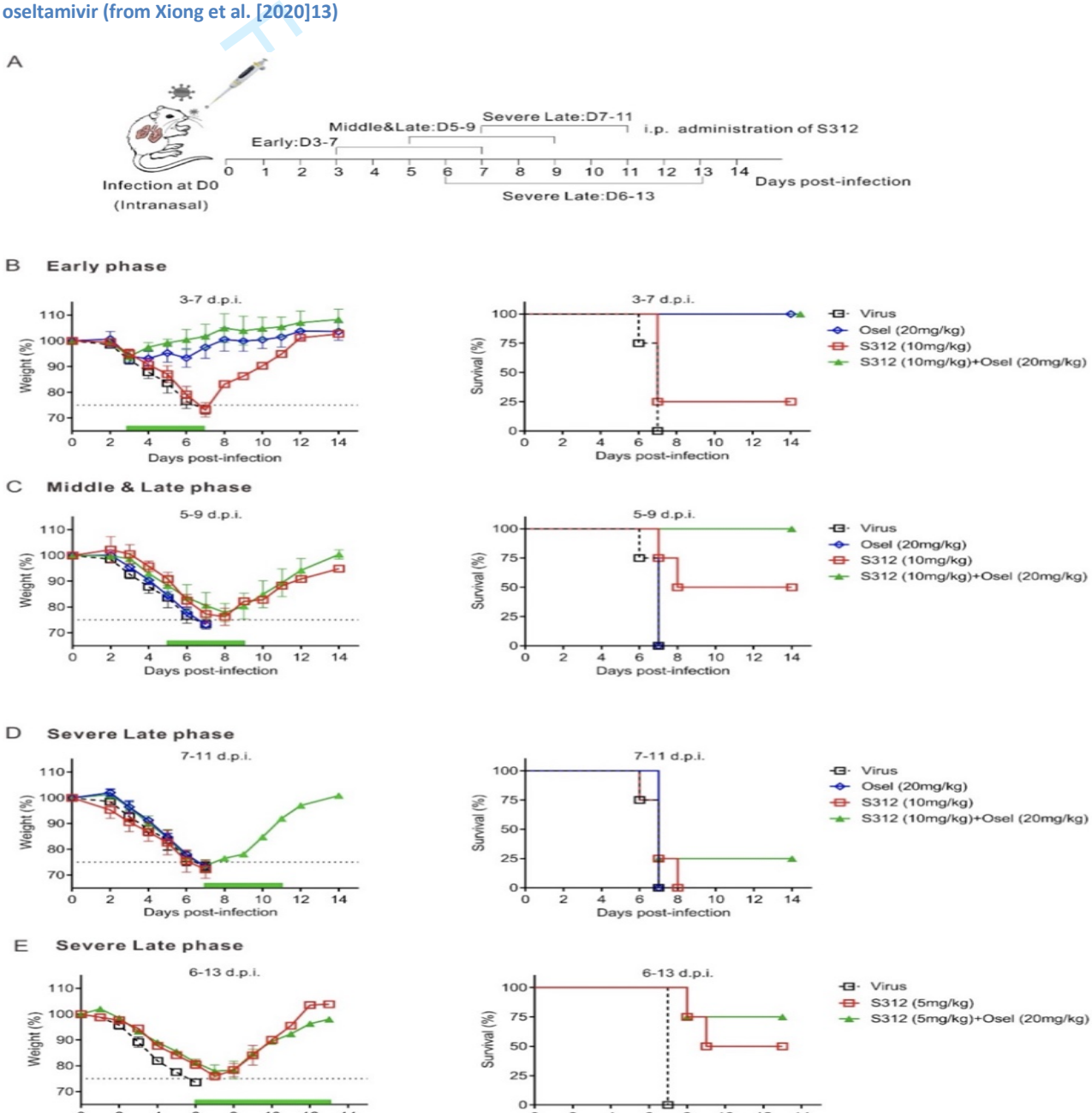
Figure 4: The in vivo antiviral activity of S312 in influenza A virus-infected mice (from Xiong et al. [2020]13)



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

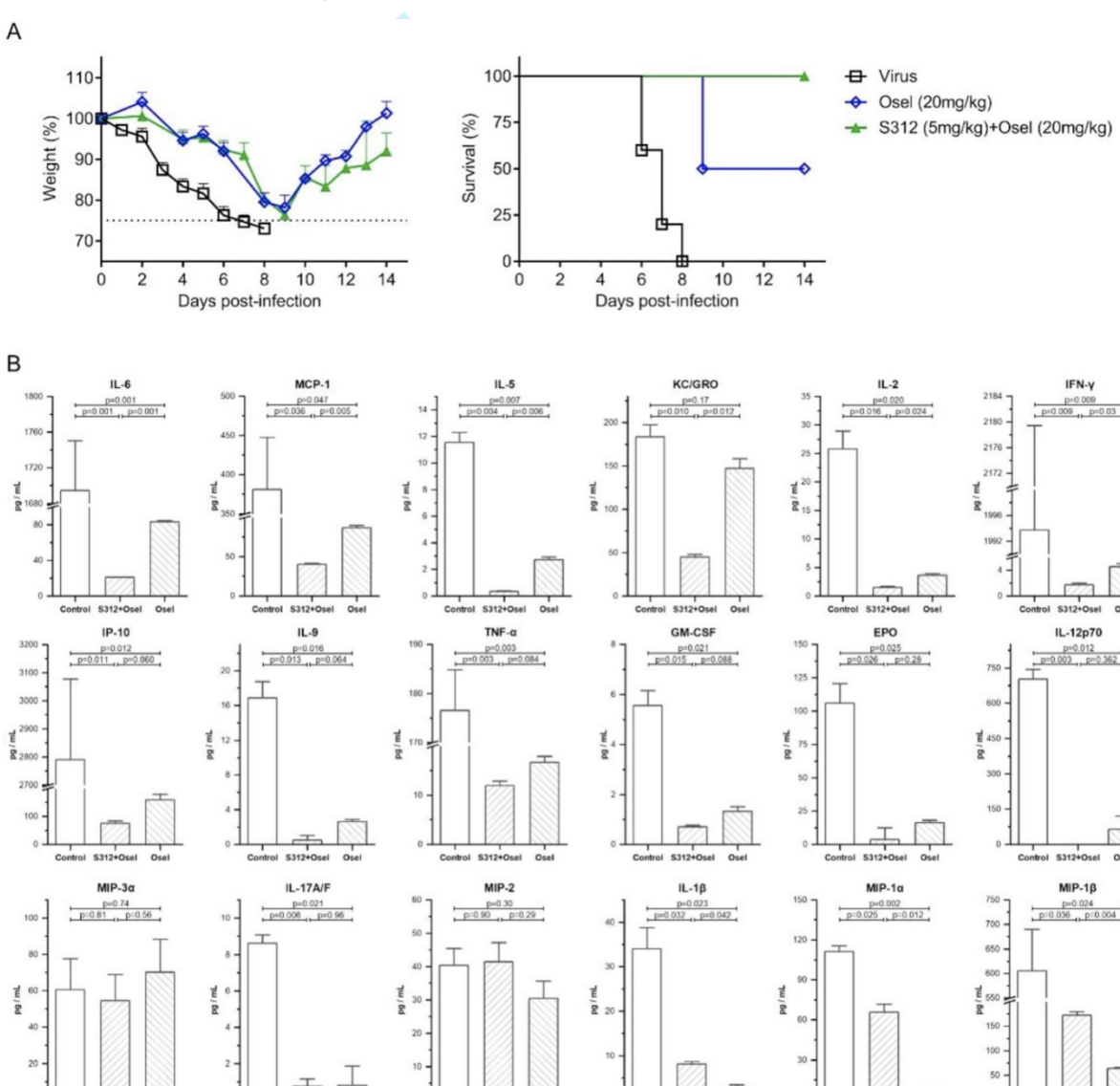
respectively. The body weight and survival were monitored for 14 days or until body weight reduced to 75% (n = 4 mice per group). (C) Mice were inoculated intranasally with 600 PFU of A/SC/09 (H1N1) and then i.p. with S312 (10mg/kg), Oseltamivir (20mg/kg) and S312+Oseltamivir (10mg/kg+20mg/kg) once per 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 5: S312 is more effective at the late and severe infection phase as compared to the direct-acting antiviral drug oseltamivir (from Xiong et al. [2020]13)



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 6: Cytokine and chemokine measurements following antiviral therapy (from Xiong et al. [2020]13)



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

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, sorafinib, 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 of investigational medicial 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 progestrogen 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 3

WHO Ordinal Scale for Clinical Improvement

Ordinal Scale for Clinical Improvement

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

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:

GFR	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	75 mg twice daily
> 10 to 30 (ml/min)	75 mg once daily
≤ 10 (ml/min)	75mg as single dose*

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 patent 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.

Appendix 5

Consent Form

NHS
University Hospitals
Coventry and Warwickshire
NHS Trust

The IONIC Trial

CONSENT FORM

Study title: **IMU-838 and Oseltamivir in treatment of Novel Coronavirus (COVID-19)**

Name of Researcher: **Professor Ramesh Arasaradnam**

IRAS ID:282532 Participant ID:

No.	Statement	Please initial box
1	I confirm that I have read (or had read to me) and understood the information sheet dated 01.06.2020 (v2.0) for the above study. If I am unable to read or sign the consent I understand a witness was available to certify the accurate reading. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from UHCW NHS Trust or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4	I give consent for the information collected about me by the doctors, nurses and hospitals that provide me with care can be used to support other research in the future, and can be shared anonymously with other researchers for up to *25* years following my completion of the above study.	
5	I agree to provide the blood and urine samples and understand that these may be stored and utilised in future research as specified in the Information Sheet dated (v2.0_01.06.2020) for the above study.	
6	Should I choose to withdraw consent, I agree that information obtained from me in this study up to that point may still be used.	
7	I understand that the information held and maintained by UHCW NHS Trust will be recorded on a computer database and that this data will be stored on computers supervised by UHCW. This data may be used to help contact me or provide information about my health status.	
8	I agree to be contacted by telephone following discharge from hospital to collect follow-up information.	
9	I agree to take part in the above study.	

Name of Participant	Signature	Date
Name of Person receiving consent	Signature	Date

When completed: 1 copy for the participant; 1 in their medical notes, and keep the original in the study site file.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3,19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3,19
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18,19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	9,10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	9

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16-17
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	30-35
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	30
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13,14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16,17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18, 19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	3
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19,20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	36
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18

BMJ Open

Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Effectiveness and Safety of IMU-838, in Combination with Oseltamivir, in Adults with Coronavirus-19 – The IONIC Trial Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-055205.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Jul-2022
Complete List of Authors:	Sharma, Kavi; Ultromics Limited, R&D; Brighton and Sussex Medical School Berry, Lisa; University Hospitals Coventry and Warwickshire NHS Trust Vryonis, Evangelos; University Hospitals Coventry and Warwickshire NHS Trust Ali, Asad; University Hospitals Coventry and Warwickshire NHS Trust Lara, Beatriz; University Hospitals Coventry and Warwickshire NHS Trust, Department of Cardiology and Respiratory Noufaily, Angela; University of Warwick Warwick Medical School, Statistics and Epidemiology Parsons, Nicholas; University of Warwick, Warwick Medical School Bradley, Christopher; University Hospitals Coventry and Warwickshire NHS Trust Haley, Becky; University Hospitals Coventry and Warwickshire NHS Trust Tabuso, Maria; University Hospitals Coventry and Warwickshire NHS Trust Arasaradnam, Ramesh; University Hospitals Coventry and Warwickshire NHS Trust, Gastroenterology; University of Warwick
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Intensive care, Global health, Gastroenterology and hepatology
Keywords:	INFECTIOUS DISEASES, IMMUNOLOGY, PUBLIC HEALTH, COVID-19

Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Effectiveness and Safety of IMU-838, in Combination with oseltamivir, in Adults with Coronavirus-19 – The **IONIC Trial Protocol**

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Word Count:

Title: 25

Abstract: 299

Body of Text: 4020

References: 700

Table: 624

Appendices: 2528

Key words: COVID-19, IMU-838, Vidofludimus calcium, oseltamivir,

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 COVID 19 patients to curb the pandemic. IMU-838 is a dihydroorotate dehydrogenase (DHODH) 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.[13] The IONIC trial is a randomized control trial that will investigate whether time to clinical improvement in COVID 19 patients 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 control arm (oseltamivir only). The primary outcome is 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). The study is sponsored by UHCW 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.

Trial Registration: The trial was registered with EudraCT (2020-001805-21) on 09.04.2020 and ISRCTN on 23.09.2020 (ISRCTN53038326) and Clinicaltrials.gov on 17.08.2020 (NCT04516915)

Strengths and Limitations:

- 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

Table 1: Administrative details and Trial Summary

Short study title		**I**MU-838 and **oseltamivir** (Tamiflu®) in the treatment of **N**ovel **C**oronovirus: **The IONIC Trial**	
Primary Registration		Clinicaltrials.gov NCT04516915	
Date of Registry in primary registration		18th Aug 2020	
Secondary identifiers		ISRCTN: ISRCTN53038326, EudraCT: 2020-001805-21	
Sponsor		University Hospitals Coventry & Warwickshire NHS Trust	
Funder		Life Arc & Immunic Therapeutics, Germany	
Ethics/REC Comitte		Wales.REC1	
REC & HRA Approval date		15.05.2020	
MHRA Approval date		15.05.2020	
Version & Date		4.0_11.01.2021	
Amendment Number	**Protocol Version**	**Date of Amendment**	**Date of Approval**
Substantial Amendment (SA) 1.0	2.0	01.06.2020	09.06.2020
SA 2.0	3.0	15.07.2020	23/07/2020
SA 3.0	4.0	23.11.2020	26.01.2021
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Contact for scientific queries		Professor Ramesh Arasaradnam, Email: ramesh.arasaradnam@uhcw.nhs.uk	
Countries of recruitment		United Kingdom (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		**Inclusion:** 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.	

	Exclusion criteria: Allergic or hypersensitivity to the IMU-838, oseltamivir, or any of the ingredients, Pregnant or breastfeeding or with intention to become pregnant during the study, medical or concomitant disease history preventing participation	
Interventions	**Control Group:** oseltamivir (75mg BID) plus standard care **Interventional Group:** Loading dose of 45mg IMU-838 followed by 22.5mg BID plus oseltamivir (75mg BID) and standard care ***(IONIC Intervention)***	
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	10.07.2020	
Recruitment Status	Recruiting	
	Objectives	**Outcome Measures**
Primary	To evaluate whether clinical time-to-improvement is significantly better in IMU-838 plus oseltamivir *(IONIC Intervention)* and standard care vs. 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)
Key Secondary Outcome	• To evaluate safety and tolerability of *IONIC intervention* vs. oseltamivir in adult subjects with COVID-19. • To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale	• Incidence of Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities • Proportion of patients with two-point change on WHO ordinal scale at Day 7 and 28
Investigational Medicinal Product(s)	I. IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase (DHODH). II. oseltamivir is an influenza neuraminidase inhibitor (NAI)	

1. Background

1.1 Background and Justification

The World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus (SARS-CoV-2) infections (causing coronavirus disease 2019 [COVID-19]) a pandemic on March 11, 2020. Main clinical symptoms include fever, cough, myalgia or fatigue, expectoration, and dyspnoea[1]. While a majority of patients do not experience severe symptoms, one early meta-analysis found that approximately 18% of cases were severe[2] with a fatality rates estimated to be ~4-7% at this time[2,3]. A more recent meta-analysis suggests fatality rates of COVID 19 are around 0.68%[4].

At the time of study conception, there were no known treatments for COVID-19. Whilst 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[5].

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 hospitalised adult patients receiving usual standard of care.

1.2 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 (INNM: vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

1.3 Safety of IMU-838

To date, 351 individuals have been exposed to vidofludimus (not including the ongoing and still blinded Phase 2 trial in 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 during Phase 1 with IMU-838.

The most frequent adverse events for IMU-838 during Phase 1 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 of adverse reactions compared with placebo, and no increased infection rate.

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

IMU-838 selectively inhibits pyrimidine synthesis via inhibition of DHODH, which may be promising approach to treat COVID-19. Inhibition of de novo pyrimidine biosynthesis is a well-recognized mechanism of action associated with antiviral effects against respiratory viruses[6–10]. 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[7,11]. 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 Appendix 1 (Table 1 and Figure 1-4).

1.5 IMU-838 and oseltamivir (Tamiflu®)

The data described by Xiong et al. [11] 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 figure 1).

While there is 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 co-infection with SARS-CoV-2 [12,13]. Hence it would seem prudent to protect patients in both arms including the 'control arm' of this possibility. In fact Ding et al.[12] reported use of oseltamivir in addition to standard care in patients with SARS-CoV-2 co-infected with Influenza. Of note, oseltamivir is usually given early in a viral infection[11] data shows that IMU-838 re-sensitizes 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 COVID-19 patients in a trial in China[14]. Moreover, the recent report by Costanzo et al.[15] 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[16] and a systematic review of oseltamivir (in Influenza) has shown reduction in the proportion with diarrhoea[17]. 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 to other anti-virals as oseltamivir is cheap and is easily available. We did explore other anti-viral 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.[11] 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 available evidence. It is for the above reasons we have chosen to add oseltamivir within the control arm.

2. Methodology

2.1. 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 twice daily [45 mg/day]) plus oseltamivir (75mg twice daily [150mg/day]) (IONIC Intervention) in comparison with oseltamivir alone (75mg twice daily) for 14 days in hospitalised patients with COVID-19. Figure 2 illustrates the design of the trial.

The IONIC trial comprises of a screening period, a 14-day treatment period, a 14-day follow-up period, and a long term follow up to one year evaluating the effectiveness of IONIC intervention in comparison to oseltamivir alone. All participants will receive standard care as necessary (e.g., 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.

2.2. Screening and Consent

All patients admitted and hospitalised at UHCW with a confirmed or suspected case of COVID 19, that 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 patient 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.

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort[4], patients who lack capacity to consent due to severe disease (e.g. needs 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.

2.3. 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 category 3-5 on the 9-point clinical status category scale proposed by WHO master protocol:

I. Category 3: hospitalized, no oxygen therapy
II. Category 4: hospitalized, oxygen by mask or nasal prongs
III. Category 5: hospitalized, 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, breastfeeding or with the intention to become pregnant during the study, or participants who cannot take the trial 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 (Appendix 2).

2.4. Objectives and Outcome Measures/Endpoints

Primary objective

(i) To evaluate the effectiveness of IONIC Intervention (IMU-838 plus oseltamivir and standard care) vs. 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 (Appendix 3).

Secondary objectives

(i) To evaluate safety and tolerability of *IONIC intervention* vs. oseltamivir in adult subjects with COVID-19.

(ii) To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale

(iii) To assess the effects of IONIC Intervention vs. oseltamivir on the need for invasive ventilation, renal replacement therapy or Extracorporeal membrane oxygenation (ECMO)

(iv) To assess the effects of IONIC Intervention vs. oseltamivir on the length of hospital and intensive care unit (ICU) stays

(v) To assess the effects of (IONIC Intervention) vs. oseltamivir on the time from treatment initiation to death.

Primary endpoints

(i) 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 twenty-eight, hospital discharge, or death (whichever occurs sooner), with the worst score for that day recorded.

Secondary endpoints

(i) Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities

(ii) Proportion of patients with two-point change on WHO ordinal scale at Day 7, 14 and 28 (± 2 days)

(iii) Proportion of patients free of invasive ventilation, renal replacement therapy or ECMO at Day 7 and 14

(iv) Hospital length of stay and Length of stay in Intensive care

(v) Mortality at Day 28

(vi) Time from treatment initiation to death (days)

2.5. 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 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.

2.6. 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 (±24 hours) to monitor adverse events and drug compliance by a delegated research team member.

2.6.1 Long Term Follow-up

There is 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'[18–20]. 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 3 time points i.e., 3 months (±2 weeks), 6 months (±2 weeks) and 12 months (±2 weeks). Each follow-up will record the participants WHO

clinical status, health related quality of life questionnaire (EQ-5D-5L)[21,22] 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.

2.7. 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; adverse event which, in the opinion of the investigator, may jeopardize the patient's health or may compromise the trial objectives; relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize 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 IMP and supplies. Patients who discontinue therapy with IMP will be encouraged to continue with trial-related assessments (including EoS visit) until their trial completion.

2.8 End of study definition (EOS)

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

Table 2: Schedule of events

	PHASE I							PHASE II (Long term Follow-up)		
	Screening/Baseline	Treatment Period[1]					End of Trial/ Early Withdrawal	3 months	6 Months	12 Months
Evaluation	Day -4 to 0[5]	Day 1[5]	Day 2 to 6	Day 7	Day 8 to 14	Day 15 (EoT)	Days 15-28 or up to 14 days after last assessment (Discharge/Withdrawal)			
Assessments										
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[2]			
Laboratory assessments										
Screening labs (incl. pregnancy test)[3]	X[3]									
Routine Blood tests – U&E (sodium, potassium, urea and creatinine), GFR, Glucose, and HbA1c[1]	X[3]	X[1]	X[1]	X[3]	X[1]	X[3]				
Liver Function test (LFT) [3]	X[3]	X[1]	X[1]	X[3]	X[1]	X[3]				
RBC urine (dipstick) [3]		X[1]	X[1]	X[3]	X[1]	X[3]				
Viral Load[4]	X[4]	X[1]	X[1]	X[4]	X[1]	X[4]	X[4]			
Safety assessments										
AEs and SAE assessment			X[2]	X[2]	X[2]	X[2]	X[2]			
IMP										
IMP administration		X (IMU-838 loading dose /oseltamivir single dose pm)	X (twice daily)	X (twice daily)	X (twice daily)	X (oseltamivir single dose AM)				
Long Term follow Up										
HRQOL EQ-5D									X[2]	X[2]

Clinical Status		X[2]	X[2]	X[2]
All-cause Mortality & Morbidity		X[2]	X[2]	X[2]

Note: Glomerular Filtration Rate (GFR), Glycated hemoglobin (HBA1c), Red Blood Cell (RBC), Adverse events (AE), Serious Adverse Events (SAE), Investigational Medicinal Product (IMP), health related quality of life (HRQOL)

Standard Treatment pathway: Assessments/Laboratory Assessments/Investigations (e.g., 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

[2]**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.

[3]**Research activity:** Conducted if not assessed as part of standard care for participants in intervention arm. No further laboratory assessments are required following discharge.

[4]**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

[5]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 IMU-838 / single dose for Oseltaimivir) on Day 1.

3. TRIAL TREATMENTS

3.1 IMU-838 (Vidofludimus calcium)

IMU 838 will be supplied by Immunic AG and will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines and local requirements. IMU-838 will be administered twice daily as oral tablets starting with a loading dose of 45mg on the first day (Day 1, Table 3).

Day 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 litres per day throughout the trial).

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

	Day 1		Day 2-13		Day 14	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		2	1	1	1	1
Dose of IMU-838		45 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg
		α	β	β	β	β

α Day1: loading dose of 45mg IMU-838 once daily given on the evening of Day 1
β Day 2-14: dosing 22.g mg of IMU-838 BID

3.2 Oseltamivir

oseltamivir will be taken from commercially available stock with a UK Marketing Authorisation. 28 doses of oseltamivir 75mg will be administered over 15 days as defined in the table 4 below. Dose adjustments for renal impairment are outlined in (Appendix 4).

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

	Day 1		Day 2-14		Day 15	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		1	1	1	1	
Dose of oseltamivir		75 mg	75 mg	75 mg	75 mg	
		α	β		¥	

α Day1: Single dose 75mg on the evening of Day 1
β Day 2-14: dosing 75 mg of BID of oseltamivir
¥ Day 15**:** Single dose 75mg on the morning of Day 15

4. STATISTICS AND DATA ANALYSIS

4.1 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 (i.e., a clinically significant improvement). 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 a hazard ratio of 2[23]. Using the standard formula for sample sizes of time-to-event outcomes suggests that fifty-two patients are required in each arm of the study to detect a hazard ratio 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.

4.2 Statistical analysis plan

The primary analysis will be on an intention-to-treat basis (i.e., 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-days period will be right-censored. We will report hazard ratios and their 95% confidence intervals, 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 standard deviation 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 (i.e., 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 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 summarized. All analyses will be undertaken in R4.0.0.

4.3 Interim Analysis

We will conduct key event analysis after data are available on 30 participants (15 in each arm) participants. This will allow the independent Data Monitoring Committee (DMEC) 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.

4.4 DATA MANAGEMENT

Trial data will be collected on CRFs and validated questionnaires, either on paper or electronically. An online validated, GCP compliant, Electronic Data Capture 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.

5. Declarations

5.1 DISSEMINATION POLICY

All data arising from the conduct of this study will remain the property of University Hospitals Coventry and Warwickshire 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 healthcare commissioning groups.

5.2 MONITORING, AUDIT & INSPECTION

The study will be monitored by the Research & 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.

5.3 Ethics approval

This study has been independently reviewed and approved by Wales Research Ethics Committee – (Ref No: 20/WA/0146); Health Research Authority (HRA) Approval was granted on 15/05/2020. In addition, required regulatory approvals were received from Medicines and Healthcare products Regulatory Agency (MHRA).

5.4 Consent for publication

Not applicable

5.5 Availability of data and materials

Data from this study will be made available to researchers who provide a methodologically sound proposal in writing to the Sponsor, following the publication of the main study paper. Anonymised, individual participant data, data dictionary, study protocol and statistical analysis plan will be accessible upon application.

5.6 Competing interests

The authors declare that they have no competing interests

5.7 Funding

The main phase of the study has received funding from LifeArc organisation. Immunic Therapeutics the manufacturer of IMU-838 has provided the funding for the trial drug used for this trial. The

funding source had no role in the design of this study and will not have any role during its execution, analysis, interpretation of the data, or decision to submit results

5.8 Public and Patient Involvement

14 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 co-applicant on the funding application and continues to be part of the research team as a co-investigator, 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.

5.9 Author contributions

AA and KS conceived of 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. TM has led the research delivery team and assisted in recruitment. All authors discussed the results and contributed to the final manuscript.

5.10 Acknowledgements:

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Dr Neerja Bhala[3,]
Dr Ravi Gowda, Prof Luca Frullon, Dr Mounia Hocine[4]
National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility[5]
The clinical research delivery team
Research participants

[2] Patient and public representative
[3] Independent chair IONIC Data monitoring Committee / Trial Steering Committee
[4] Independent Members IONIC Data monitoring Committee / Trial Steering Committee
[5] This publication presents independent research funded by LifeArc and carried out with the support of the National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of LifeArc, the NHS, the NIHR or the Department of Health

Figure 1: Pharmacokinetic profile for 22.5 mg BD of IMU-838 over a 14 day treatment period

Figure 2: Flow of participants in trial

Appendices Figure 1: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]11)

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

Appendices 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)

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

REFERENCES

1 Li L-Q, Huang T, Wang Y-Q, *et al.* COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020;**92**:577–83. doi:10.1002/jmv.25757

2 Sun P, Qie S, Liu Z, *et al.* Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection. *Journal of medical virology* Published Online First: 28 February 2020. doi:10.1002/jmv.25735

3 Research AA for C. Nucleotide Stress Controls Transcriptional Regulation through HEXIM1. *Cancer Discov* 2016;**6**:OF17–OF17. doi:10.1158/2159-8290.CD-RW2016-072

4 Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis* 2020;**101**:138–48. doi:10.1016/j.ijid.2020.09.1464

5 Cooper I, Mondal A, Antonopoulos CG. A SIR model assumption for the spread of COVID-19 in different communities. *Chaos Solitons Fractals* 2020;**139**:110057. doi:10.1016/j.chaos.2020.110057

6 Cheung NN, Lai KK, Dai J, *et al.* Broad-spectrum inhibition of common respiratory RNA viruses by a pyrimidine synthesis inhibitor with involvement of the host antiviral response. *J Gen Virol* 2017;**98**:946–54. doi:10.1099/jgv.0.000758

7 Lucas-Hourani M, Dauzonne D, Jorda P, *et al.* Inhibition of Pyrimidine Biosynthesis Pathway Suppresses Viral Growth through Innate Immunity. *PLoS Pathog* 2013;**9**:e1003678. doi:10.1371/journal.ppat.1003678

8 Luthra P, Naidoo J, Pietzsch CA, *et al.* Inhibiting pyrimidine biosynthesis impairs Ebola virus replication through depletion of nucleoside pools and activation of innate immune responses. *Antiviral Res* 2018;**158**:288–302. doi:10.1016/j.antiviral.2018.08.012

9 Xiong R, Zhang L, Li S, *et al.* Novel and potent inhibitors targeting DHODH, a rate-limiting enzyme in de novo pyrimidine biosynthesis, are broad-spectrum antiviral against RNA viruses including newly emerged coronavirus SARS-CoV-2. 2020. doi:10.1101/2020.03.11.983056

10 Wang M, Cao R, Zhang L, *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;**30**:269–71. doi:10.1038/s41422-020-0282-0

11 Xiong R, Zhang L, Li S, *et al.* Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. *Protein Cell* 2020;**11**:723–39. doi:10.1007/s13238-020-00768-w

12 Ding Q, Lu P, Fan Y, *et al.* The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *Journal of Medical Virology* 2020;**92**:1549–55. doi:10.1002/jmv.25781

13 Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of Coronavirus Disease 2019 and Influenza A: A Report from Iran. *Arch Iran Med* 2020;**23**:239–43. doi:10.34172/aim.2020.04

14 Cai Q, Yang M, Liu D, *et al.* Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering* 2020;**6**:1192–8. doi:10.1016/j.eng.2020.03.007

15 Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and other Drugs for the Treatment of the New Coronavirus. *Current Medicinal Chemistry* 2020;**27**:4536–41. doi:10.2174/0929867327666200416131117

16 Lin L, Jiang X, Zhang Z, *et al.* Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020;**69**:997–1001. doi:10.1136/gutjnl-2020-321013

17 Jefferson T, Jones M, Doshi P, *et al.* Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;**348**:g2545. doi:10.1136/bmj.g2545

18 Mahase E. Covid-19: What do we know about “long covid”? *BMJ* 2020;**370**:m2815. doi:10.1136/bmj.m2815

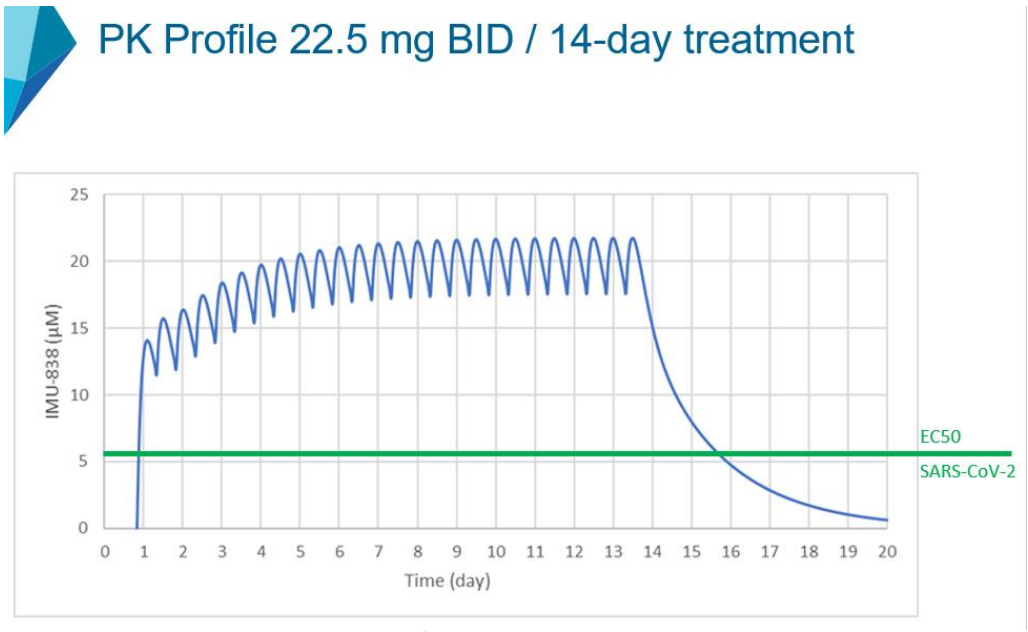
19 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open* 2021;**4**:e2111417. doi:10.1001/jamanetworkopen.2021.11417

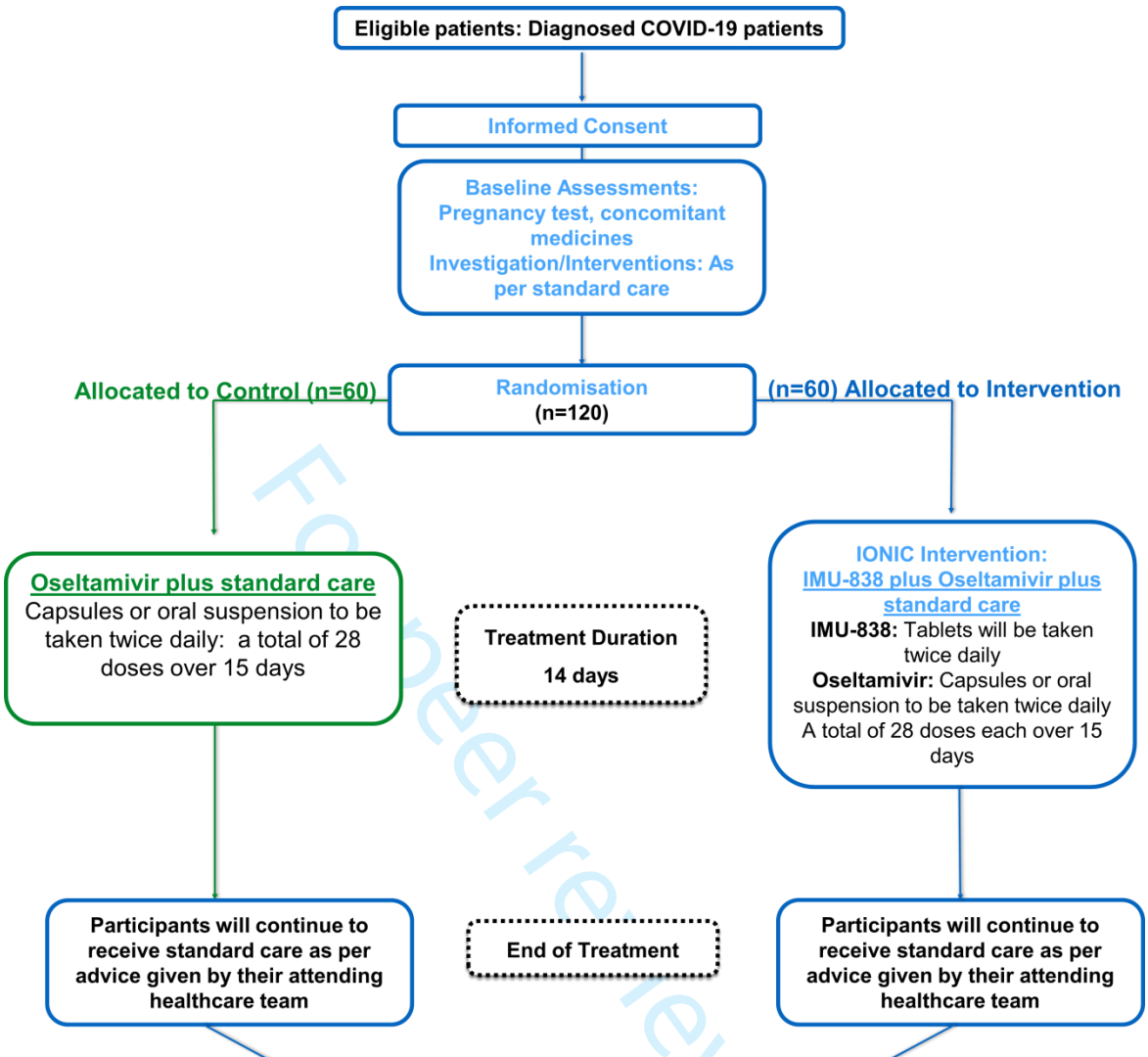
20 Taquet M, Dercon Q, Luciano S, *et al.* Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021;**18**:e1003773. doi:10.1371/journal.pmed.1003773

21 Poudel AN, Zhu S, Cooper N, *et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021;**16**:e0259164. doi:10.1371/journal.pone.0259164

22 Lam CLK, Tse ETY, Wong CKH, *et al.* A pilot study on the validity and psychometric properties of the electronic EQ-5D-5L in routine clinical practice. *Health Qual Life Outcomes* 2021;**19**:266. doi:10.1186/s12955-021-01898-3

23 Van Houwelingen H. Modelling Survival Data in Medical Research. D. Collett, Chapman & Hall, London, 1994. No of pages: XVII + 347. Price: E19.99. ISBN 0-41 2-44890-4. *Statistics in Medicine* 1995;**14**:1147–8. doi:10.1002/sim.4780140936





Appendix 1

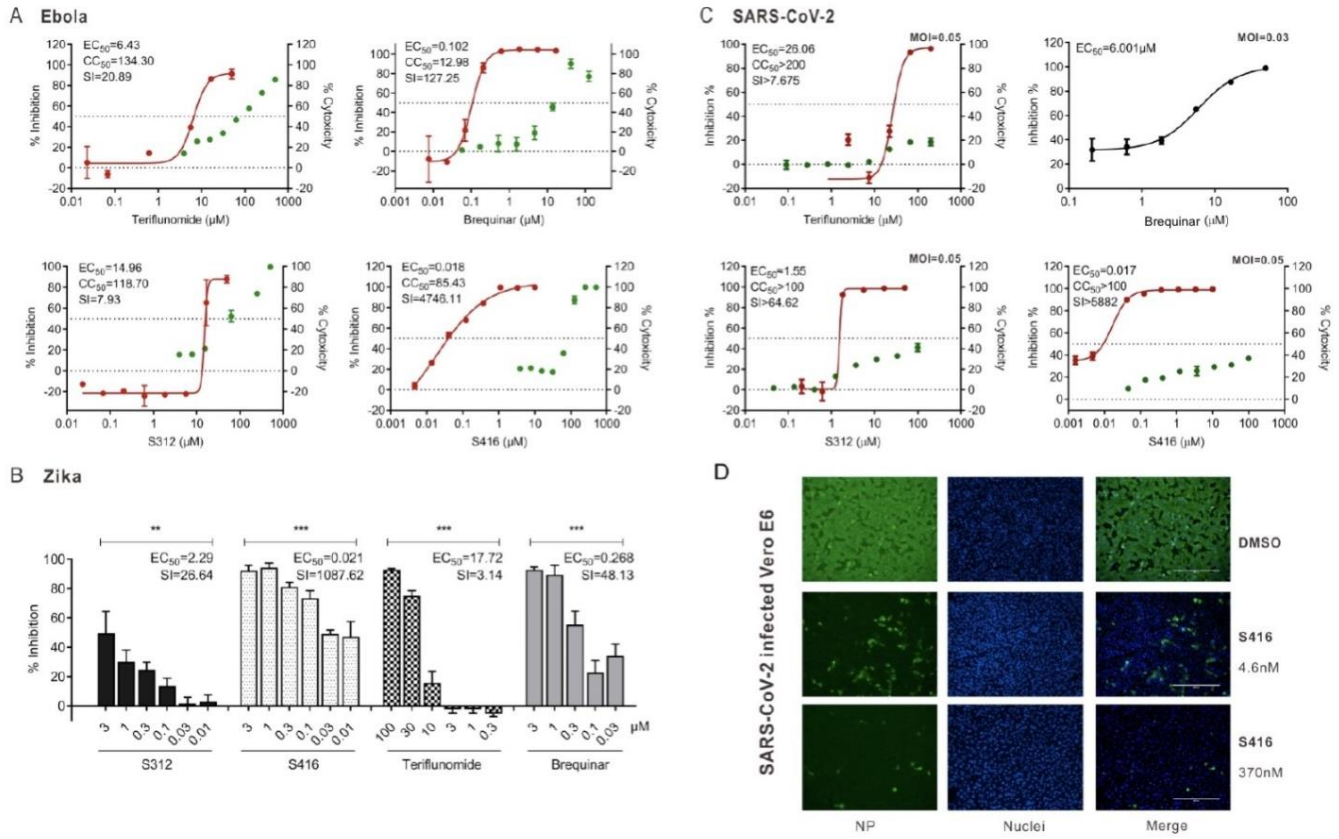
Table 1: Broad-spectrum antiviral efficacies of DHODH inhibitors (from Xiong et al. [2020](11))

IC_{50} (μM) (SI*)	Virus type				
	H1N1[a]	**H3N2[b]**	**H9N2[c]**	**Zika virus**	**Ebola-replicon**
S312	2.36 (25)	8.43 (7)	13.2 (4)	2.29 (26)	15.0 (7.9)
S416	0.0161 (27)	0.013 (126)	0.020 (82)	0.021 (1090)	0.018 (4750)
Teriflunomide	29.3 (6)	2.73 (32)	3.36 (26)	17.7 (3)	6.43 (32)
Leflunomide	>25.0 (<2.7)	NT	NT	NT	NT
Oseltamivir	7.68 (680)	NT	NT	NT	NT
Brequinar	0.240 (11.9)	0.022 (130)	0.060 (48)	0.268 (48)	0.102 (127)

SI* value was equal to CC_{50}/IC_{50}; values were rounded for significant figures from Xiong et al. 2020[1]

[a]A/WSN/33; [b]A/DongHu/06; [c]A/GuangZhou/99 NT (not tested)

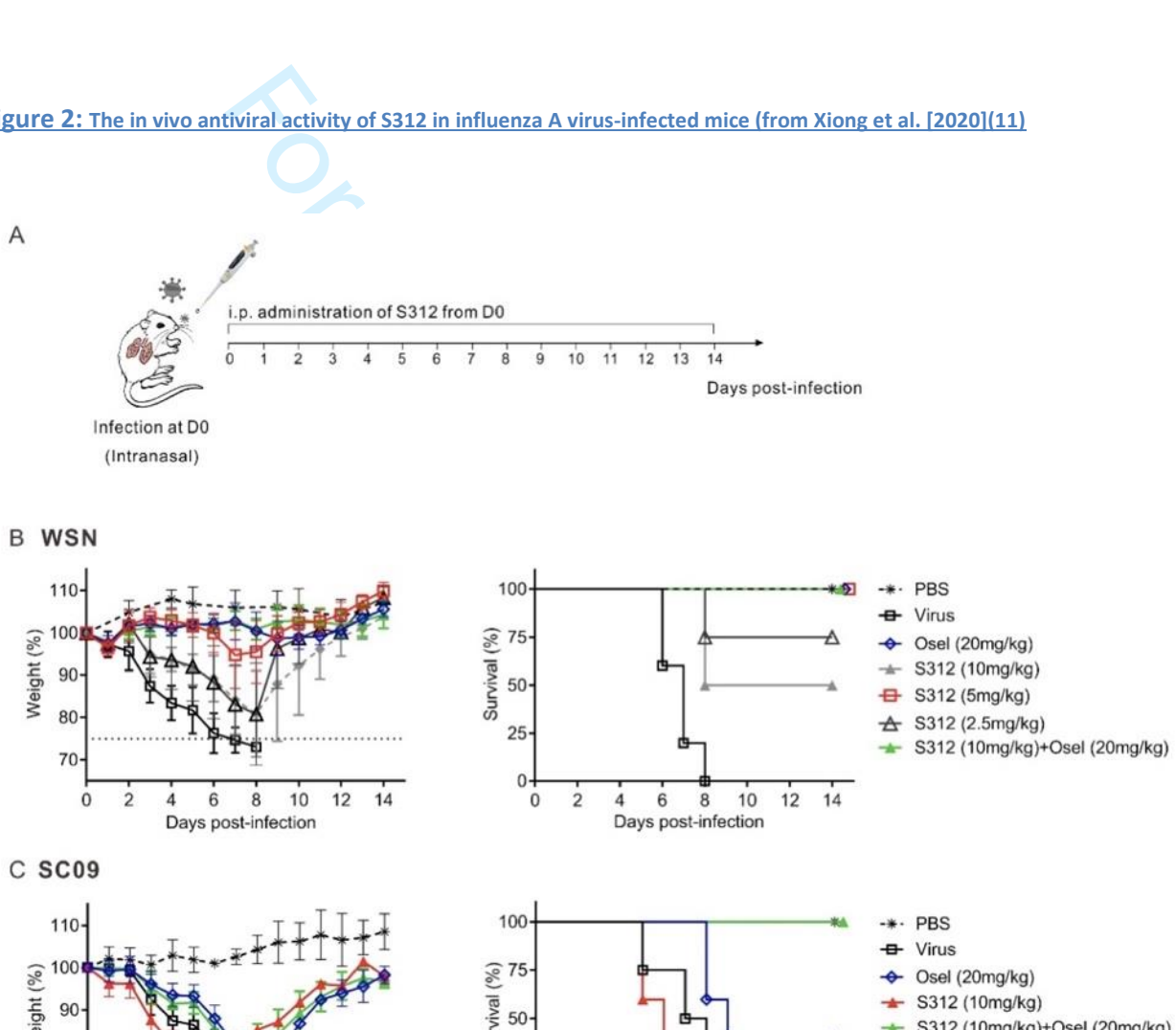
Figure 1: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]11)



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.

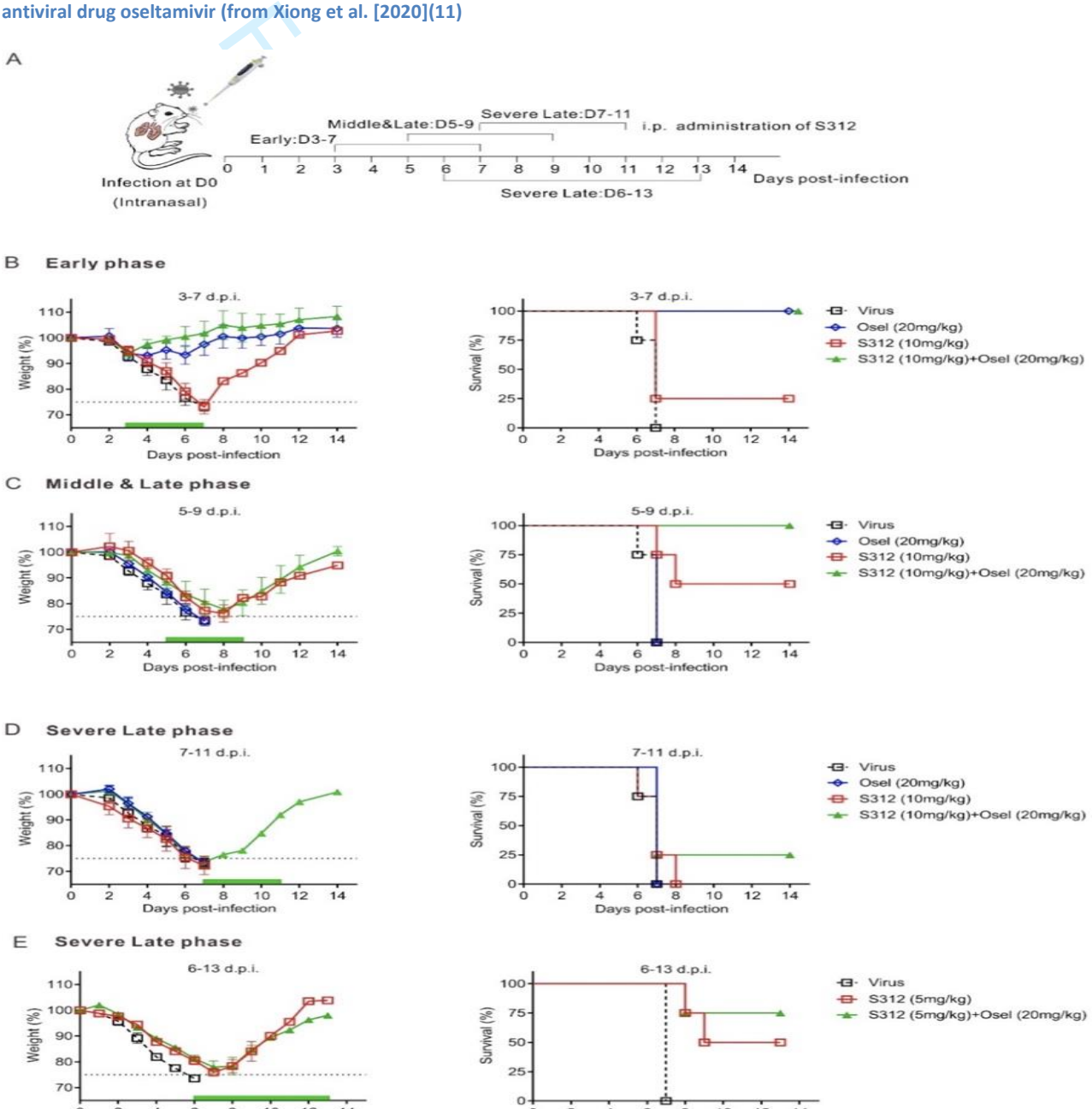
Figure 2: The in vivo antiviral activity of S312 in influenza A virus-infected mice (from Xiong et al. [2020](11)



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

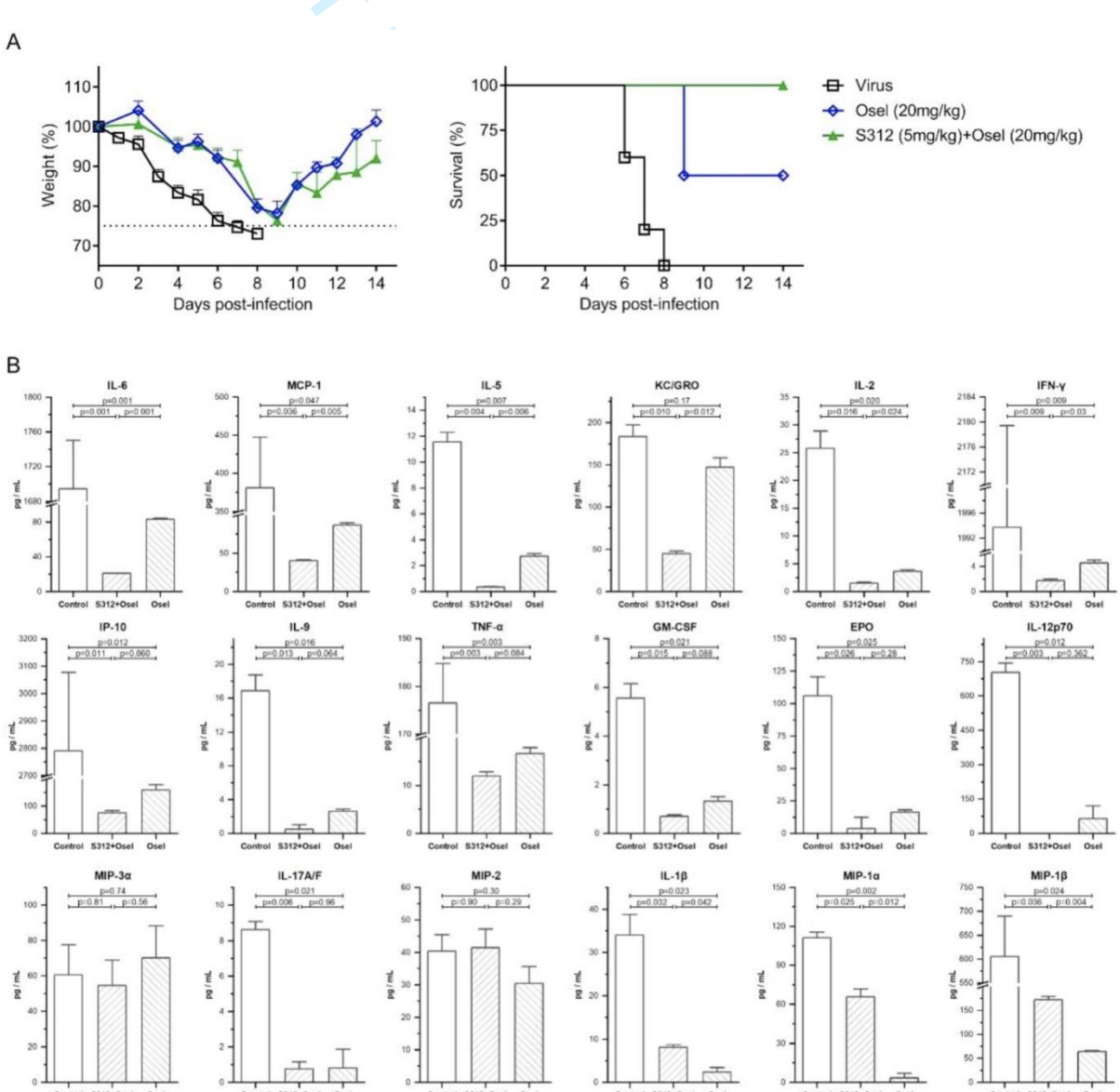
respectively. The body weight and survival were monitored for 14 days or until body weight reduced to 75% (n = 4 mice per group). (C) Mice were inoculated intranasally with 600 PFU of A/SC/09 (H1N1) and then i.p. with S312 (10mg/kg), Oseltamivir (20mg/kg) and S312+Oseltamivir (10mg/kg+20mg/kg) once per 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)



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))



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

Ordinal Scale for Clinical Improvement

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

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, sorafinib, 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 of investigational medicial 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 progestrogen 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:

GFR	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	75 mg twice daily
> 10 to 30 (ml/min)	75 mg once daily
≤ 10 (ml/min)	75mg as single dose*

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 patent 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.

The IONIC Trial

CONSENT FORM

Study title: **IMU-838 and Oseltamivir in treatment of Novel Coronavirus (COVID-19)**

Name of Researcher: **Professor Ramesh Arasaradnam**

IRAS ID: 282532 Participant ID:

No.	Statement	Please initial box
1	I confirm that I have read (or had read to me) and understood the information sheet dated 01.06.2020 (v2.0) for the above study. If I am unable to read or sign the consent I understand a witness was available to certify the accurate reading. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorised individuals from UHCW NHS Trust or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4	I give consent for the information collected about me by the doctors, nurses and hospitals that provide me with care can be used to support other research in the future, and can be shared anonymously with other researchers for up to *25* years following my completion of the above study.	
5	I agree to provide the blood and urine samples and understand that these may be stored and utilised in future research as specified in the Information Sheet dated (v2.0_01.06.2020) for the above study.	
6	Should I choose to withdraw consent, I agree that information obtained from me in this study up to that point may still be used.	
7	I understand that the information held and maintained by UHCW NHS Trust will be recorded on a computer database and that this data will be stored on computers supervised by UHCW. This data may be used to help contact me or provide information about my health status.	
8	I agree to be contacted by telephone following discharge from hospital to collect follow-up information.	
9	I agree to take part in the above study.	

Name of Participant	Signature	Date
Name of Person receiving consent	Signature	Date

When completed: 1 copy for the participant; 1 in their medical notes, and keep the original in the study site file.

University Hospitals Coventry and Warwickshire NHS Trust

The IONIC Trial

WITNESS CONSENT FORM

Study title: **IMU-838 and Oseltamivir in treatment of Novel Coronavirus (COVID-19)**

Name of Researcher: **Professor Ramesh Arasaradnam**

Participant ID:

If participant is unable to read the text and/or sign for themselves but has capacity to give consent.

I witnessed the accurate reading of the consent form to the potential participant, who could ask any questions and got satisfactory replies.

I confirm that they gave their consent freely.

Name of Witness	Signature	Date
Name of Person receiving consent	Signature	Date

If consent is recorded over the phone.

I witnessed the accurate reading of the consent form to the potential participant, who could ask any questions and got satisfactory replies.

I confirm they gave their consent freely.

Name of Witness	Signature	Date
Name of Person receiving consent	Signature	Date

When completed: 1 copy for the participant; 1 in their medical notes, and keep the original in the study site file.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3,19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3,19
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18,19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	9,10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	9

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16-17
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	30-35
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	30
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13,14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16,17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18, 19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	3
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19,20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	36
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18

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Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Effectiveness and Safety of IMU-838, in Combination with Oseltamivir, in Adults with Coronavirus-19 – The IONIC Trial Protocol

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Primary Subject Heading:	Infectious diseases
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Prospective, Randomized, Parallel-Group, Open-Label Study to Evaluate the Effectiveness and Safety of IMU-838, in Combination with oseltamivir, in Adults with Coronavirus-19 – The **IONIC Trial Protocol**

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Key words: COVID-19, IMU-838, Vidofludimus calcium, oseltamivir,

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 COVID 19 patients to curb the pandemic. IMU-838 is a dihydroorotate dehydrogenase (DHODH) 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.[13] The IONIC trial is a randomized control trial that will investigate whether time to clinical improvement in COVID 19 patients 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 control arm (oseltamivir only). The primary outcome is 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). The study is sponsored by UHCW 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, dissemination and Trial Registration: 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 (MHRA). The trial was registered with EudraCT (2020-001805-21) on 09.04.2020 and ISRCTN on 23.09.2020 (ISRCTN53038326) and Clinicaltrials.gov on 17.08.2020 (NCT04516915)

Strengths and Limitations:

- 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

Table 1: Administrative details and Trial Summary

Short study title		**I**MU-838 and **oseltamivir** (Tamiflu®) in the treatment of **N**ovel **C**oronovirus: **The IONIC Trial**	
Primary Registration		Clinicaltrials.gov NCT04516915	
Date of Registry in primary registration		18th Aug 2020	
Secondary identifiers		ISRCTN: ISRCTN53038326, EudraCT: 2020-001805-21	
Sponsor		University Hospitals Coventry & Warwickshire NHS Trust	
Funder		Life Arc (COVID-19 Call) & Immunic Therapeutics, Germany (No award number)	
Ethics/REC Comitte		Wales.REC1	
REC & HRA Approval date		15.05.2020	
MHRA Approval date		15.05.2020	
Version & Date		4.0_11.01.2021	
Amendment Number	**Protocol Version**	**Date of Amendment**	**Date of Approval**
Substantial Amendment (SA) 1.0	2.0	01.06.2020	09.06.2020
SA 2.0	3.0	15.07.2020	23/07/2020
SA 3.0	4.0	23.11.2020	26.01.2021
Contact for public queries		Kavi Sharma Email: kavi.sharma@uhcw.nhs.uk Contact number: 024769 26197	
Contact for scientific queries		Professor Ramesh Arasaradnam, Email: ramesh.arasaradnam@uhcw.nhs.uk	
Countries of recruitment		United Kingdom (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		**Inclusion:** 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. **Exclusion criteria:** Allergic or hypersensitivity to the IMU-838, oseltamivir, or any of the ingredients, Pregnant or breastfeeding or with intention to	

	become pregnant during the study, medical or concomitant disease history preventing participation	
Interventions	**Control Group:** oseltamivir (75mg BID) plus standard care **Interventional Group:** Loading dose of 45mg IMU-838 followed by 22.5mg BID plus oseltamivir (75mg BID) and standard care ***(IONIC Intervention)***	
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	10.07.2020	
Recruitment Status	Recruiting	
	Objectives	**Outcome Measures**
Primary	To evaluate whether clinical time-to-improvement is significantly better in IMU-838 plus oseltamivir *(IONIC Intervention)* and standard care vs. 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)
Key Secondary Outcome	• To evaluate safety and tolerability of *IONIC intervention* vs. oseltamivir in adult subjects with COVID-19. • To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale	• Incidence of Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities • Proportion of patients with two-point change on WHO ordinal scale at Day 7 and 28
Investigational Medicinal Product(s)	I. IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase (DHODH). II. oseltamivir is an influenza neuraminidase inhibitor (NAI)	

1. Background

1.1 Background and Justification

The World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus (SARS-CoV-2) infections (causing coronavirus disease 2019 [COVID-19]) a pandemic on March 11, 2020. Main clinical symptoms include fever, cough, myalgia or fatigue, expectoration, and dyspnoea[1]. 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 rates estimated to be ~4-7% at this time[2]. A more recent meta-analysis suggests fatality rates of COVID 19 are around 0.68%[3].

At the time of study conception, there were no known treatments for COVID-19. Whilst 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[4].

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 hospitalised adult patients receiving usual standard of care (Table 1).

1.2 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 (INNM: vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

1.3 Safety of IMU-838

To date, 351 individuals have been exposed to vidofludimus (not including the ongoing and still blinded Phase 2 trial in 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 during Phase 1 with IMU-838.

The most frequent adverse events for IMU-838 during Phase 1 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 of adverse reactions compared with placebo, and no increased infection rate.

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

IMU-838 selectively inhibits pyrimidine synthesis via inhibition of DHODH, which may be promising approach to treat COVID-19. Inhibition of de novo pyrimidine biosynthesis is a well-recognized mechanism of action associated with antiviral effects against respiratory viruses[5–7]. 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[6,8]. 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 Appendix 1 (Appendices Table 1 & Figure 1-4).

1.5 IMU-838 and oseltamivir (Tamiflu®)

The data described by Xiong et al. [8] 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 figure 1- Appendix 1).

While there is 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 co-infection with SARS-CoV-2 [9,10]. Hence it would seem prudent to protect patients in both arms including the 'control arm' of this possibility. In fact Ding et al.[9] reported use of oseltamivir in addition to standard care in patients with SARS-CoV-2 co-infected with Influenza. Of note, oseltamivir is usually given early in a viral infection[8] data shows that IMU-838 re-sensitizes 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 COVID-19 patients in a trial in China[11]. Moreover, the recent report by Costanzo et al.[12] 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[13] and a systematic review of oseltamivir (in Influenza) has shown reduction in the proportion with diarrhoea[14]. 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 to other anti-virals as oseltamivir is cheap and is easily available. We did explore other anti-viral 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.[8] 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 available evidence. It is for the above reasons we have chosen to add oseltamivir within the control arm.

2. Methodology

2.1. 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 twice daily [45 mg/day]) plus oseltamivir (75mg twice daily [150mg/day]) (IONIC Intervention) in comparison with oseltamivir alone (75mg twice daily) for 14 days in hospitalised patients with COVID-19. Figure 1 illustrates the design of the trial.

The IONIC trial comprises of a screening period, a 14-day treatment period, a 14-day follow-up period, and a long term follow up to one year evaluating the effectiveness of IONIC intervention in comparison to oseltamivir alone. All participants will receive standard care as necessary (e.g., 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.

2.2. Screening and Consent

All patients admitted and hospitalised at UHCW with a confirmed or suspected case of COVID 19, that 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 patient 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 supplemental material).

Due to the poor outcomes in COVID-19 patients who require ventilation (>90% mortality in one cohort*[3]*, patients who lack capacity to consent due to severe disease (e.g. needs 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.

2.3. 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 category 3-5 on the 9-point clinical status category scale proposed by WHO master protocol:

I. Category 3: hospitalized, no oxygen therapy
II. Category 4: hospitalized, oxygen by mask or nasal prongs
III. Category 5: hospitalized, 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, breastfeeding or with the intention to become pregnant during the study, or participants who cannot take the trial 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 (Appendix 2).

2.4. Objectives and Outcome Measures/Endpoints

Primary objective

(i) To evaluate the effectiveness of IONIC Intervention (IMU-838 plus oseltamivir and standard care) vs. 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 (Appendix 3).

Secondary objectives

(i) To evaluate safety and tolerability of *IONIC intervention* vs. oseltamivir in adult subjects with COVID-19.

(ii) To determine the effects of *IONIC Intervention* on improvement of at least two points in clinical status scale

(iii) To assess the effects of IONIC Intervention vs. oseltamivir on the need for invasive ventilation, renal replacement therapy or Extracorporeal membrane oxygenation (ECMO)

(iv) To assess the effects of IONIC Intervention vs. oseltamivir on the length of hospital and intensive care unit (ICU) stays

(v) To assess the effects of (IONIC Intervention) vs. oseltamivir on the time from treatment initiation to death.

Primary endpoints

(i) 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 twenty-eight, hospital discharge, or death (whichever occurs sooner), with the worst score for that day recorded.

Secondary endpoints

(i) Adverse events (AEs) and serious adverse events (SAEs), including COVID-19 worsening and incidence of laboratory abnormalities

(ii) Proportion of patients with two-point change on WHO ordinal scale at Day 7, 14 and 28 (± 2 days)

(iii) Proportion of patients free of invasive ventilation, renal replacement therapy or ECMO at Day 7 and 14

(iv) Hospital length of stay and Length of stay in Intensive care

(v) Mortality at Day 28

(vi) Time from treatment initiation to death (days)

2.5. 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 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.

2.6. 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 (±24 hours) to monitor adverse events and drug compliance by a delegated research team member.

2.6.1 Long Term Follow-up

There is 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'[15–17]. 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 3 time points i.e., 3 months (±2 weeks), 6 months (±2 weeks) and 12 months (±2 weeks). Each follow-up will record the participants WHO

clinical status, health related quality of life questionnaire (EQ-5D-5L)[18,19] 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.

2.7. 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; adverse event which, in the opinion of the investigator, may jeopardize the patient's health or may compromise the trial objectives; relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize 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 IMP and supplies. Patients who discontinue therapy with IMP will be encouraged to continue with trial-related assessments (including EoS visit) until their trial completion.

2.8 End of study definition (EOS)

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

Table 2: Schedule of events

	PHASE I							PHASE II (Long term Follow-up)		
	Screening/Baseline	Treatment Period[1]					End of Trial/ Early Withdrawal	3 months	6 Months	12 Months
Evaluation	Day -4 to 0[5]	Day 1[5]	Day 2 to 6	Day 7	Day 8 to 14	Day 15 (EoT)	Days 15-28 or up to 14 days after last assessment (Discharge/Withdrawal)			
Assessments										
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[2]			
Laboratory assessments										
Screening labs (incl. pregnancy test)[3]	X[3]									
Routine Blood tests – U&E (sodium, potassium, urea and creatinine), GFR, Glucose, and HbA1c[1]	X[3]	X[1]	X[1]	X[3]	X[1]	X[3]				
Liver Function test (LFT) [3]	X[3]	X[1]	X[1]	X[3]	X[1]	X[3]				
RBC urine (dipstick) [3]		X[1]	X[1]	X[3]	X[1]	X[3]				
Viral Load[4]	X[4]	X[1]	X[1]	X[4]	X[1]	X[4]	X[4]			
Safety assessments										
AEs and SAE assessment			X[2]	X[2]	X[2]	X[2]	X[2]			
IMP										
IMP administration		X (IMU-838 loading dose /oseltamivir single dose pm)	X (twice daily)	X (twice daily)	X (twice daily)	X (oseltamivir single dose AM)				
Long Term follow Up										
HRQOL EQ-5D									X[2]	X[2]

Clinical Status		X[2]	X[2]	X[2]
All-cause Mortality & Morbidity		X[2]	X[2]	X[2]

Note: Glomerular Filtration Rate (GFR), Glycated hemoglobin (HBA1c), Red Blood Cell (RBC), Adverse events (AE), Serious Adverse Events (SAE), Investigational Medicinal Product (IMP), health related quality of life (HRQOL)

Standard Treatment pathway: Assessments/Laboratory Assessments/Investigations (e.g., 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

[2]**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.

[3]**Research activity:** Conducted if not assessed as part of standard care for participants in intervention arm. No further laboratory assessments are required following discharge.

[4]**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

[5]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 IMU-838 / single dose for Oseltaimivir) on Day 1.

3. TRIAL TREATMENTS

3.1 IMU-838 (Vidofludimus calcium)

IMU 838 will be supplied by Immunic AG and will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines and local requirements. IMU-838 will be administered twice daily as oral tablets starting with a loading dose of 45mg 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 RBC in urine. An elimination half-life of 30-40 hours allows a once daily administration with minimal accumulation (see Figure 2)

Day 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 litres per day throughout the trial).

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

	Day 1		Day 2-13		Day 14	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		2	1	1	1	1
Dose of IMU-838		45 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg
		α	β	β	β	β

α Day1: loading dose of 45mg IMU-838 once daily given on the evening of Day 1
β Day 2-14: dosing 22.g mg of IMU-838 BID

3.2 Oseltamivir

oseltamivir will be taken from commercially available stock with a UK Marketing Authorisation. 28 doses of oseltamivir 75mg will be administered over 15 days as defined in the table 4 below. Dose adjustments for renal impairment are outlined in (Appendix 4).

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

	Day 1		Day 2-14		Day 15	
Time	AM	PM	AM	PM	AM	PM
Number of Tablets		1	1	1	1	
Dose of oseltamivir		75 mg	75 mg	75 mg	75 mg	
		α	β		¥	

α Day1: Single dose 75mg on the evening of Day 1
β Day 2-14: dosing 75 mg of BID of oseltamivir
¥ Day 15**:** Single dose 75mg on the morning of Day 15

4. STATISTICS AND DATA ANALYSIS

4.1 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 (i.e., a clinically significant improvement). 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 a hazard ratio of 2[20]. Using the standard formula for sample sizes of time-to-event outcomes suggests that fifty-two patients are required in each arm of the study to detect a hazard ratio 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.

4.2 Statistical analysis plan

The primary analysis will be on an intention-to-treat basis (i.e., 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-days period will be right-censored. We will report hazard ratios and their 95% confidence intervals, 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 standard deviation 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 (i.e., 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 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 summarized. All analyses will be undertaken in R4.0.0.

4.3 Interim Analysis

We will conduct key event analysis after data are available on 30 participants (15 in each arm) participants. This will allow the independent Data Monitoring Committee (DMEC) 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.

4.4 DATA MANAGEMENT

Trial data will be collected on CRFs and validated questionnaires, either on paper or electronically. An online validated, GCP compliant, Electronic Data Capture 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.

5 Public and Patient Involvement

14 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 co-applicant on the funding application and continues to be part of the research team as a co-investigator, 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.

6. Ethics and Dissemination

6.1 DISSEMINATION POLICY

All data arising from the conduct of this study will remain the property of University Hospitals Coventry and Warwickshire 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 healthcare commissioning groups.

6.2 MONITORING, AUDIT & INSPECTION

The study will be monitored by the Research & 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.

6.3 Ethics approval

This study has been independently reviewed and approved by Wales Research Ethics Committee – (Ref No: 20/WA/0146); Health Research Authority (HRA) Approval was granted on 15/05/2020. In addition, required regulatory approvals were received from Medicines and Healthcare products Regulatory Agency (MHRA).

6.4 Consent for publication

Not applicable

6.5 Availability of data and materials

Data from this study will be made available to researchers who provide a methodologically sound proposal in writing to the Sponsor, following the publication of the main study paper. Anonymised, individual participant data, data dictionary, study protocol and statistical analysis plan will be accessible upon application.

6.6 Competing interests

The authors declare that they have no competing interests

6.7 Funding

The main phase of the study has received funding from LifeArc organisation (grant-COVID-19 call/no award number). Immunic Therapeutics the manufacturer of IMU-838 has provided the funding for the trial drug used for this trial. The funding source had no role in the design of this study and will not have any role during its execution, analysis, interpretation of the data, or decision to submit results

6.9 Author contributions

AA and KS conceived of 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. TM 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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Mr John Todd[2]
Dr Neerja Bhala[3,]
Dr Ravi Gowda, Prof Luca Frullon, Dr Mounia Hocine[4]
National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility[5]
The clinical research delivery team
Research participants

[2] Patient and public representative
[3] Independent chair IONIC Data monitoring Committee / Trial Steering Committee
[4] Independent Members IONIC Data monitoring Committee / Trial Steering Committee
[5] This publication presents independent research funded by LifeArc and carried out with the support of the National Institute of Health Research (NIHR) Coventry and Warwickshire Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of LifeArc, the NHS, the NIHR or the Department of Health

Figure 1: Flow of participants in trial

Figure 2: Pharmacokinetic profile for 22.5 mg BD of IMU-838 over a 14 day treatment period

Appendices Figure 1: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]11)

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

Appendices 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)

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

REFERENCES

1 Li L-Q, Huang T, Wang Y-Q, *et al.* COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol* 2020;**92**:577–83. doi:10.1002/jmv.25757

2 Sun P, Qie S, Liu Z, *et al.* Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection. *Journal of medical virology* Published Online First: 28 February 2020. doi:10.1002/jmv.25735

3 Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis* 2020;**101**:138–48. doi:10.1016/j.ijid.2020.09.1464

4 Cooper I, Mondal A, Antonopoulos CG. A SIR model assumption for the spread of COVID-19 in different communities. *Chaos Solitons Fractals* 2020;**139**:110057. doi:10.1016/j.chaos.2020.110057

5 Cheung NN, Lai KK, Dai J, *et al.* Broad-spectrum inhibition of common respiratory RNA viruses by a pyrimidine synthesis inhibitor with involvement of the host antiviral response. *J Gen Virol* 2017;**98**:946–54. doi:10.1099/jgv.0.000758

6 Lucas-Hourani M, Dauzonne D, Jorda P, *et al.* Inhibition of Pyrimidine Biosynthesis Pathway Suppresses Viral Growth through Innate Immunity. *PLoS Pathog* 2013;**9**:e1003678. doi:10.1371/journal.ppat.1003678

7 Luthra P, Naidoo J, Pietzsch CA, *et al.* Inhibiting pyrimidine biosynthesis impairs Ebola virus replication through depletion of nucleoside pools and activation of innate immune responses. *Antiviral Res* 2018;**158**:288–302. doi:10.1016/j.antiviral.2018.08.012

8 Xiong R, Zhang L, Li S, *et al.* Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. *Protein Cell* 2020;**11**:723–39. doi:10.1007/s13238-020-00768-w

9 Ding Q, Lu P, Fan Y, *et al.* The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *Journal of Medical Virology* 2020;**92**:1549–55. doi:10.1002/jmv.25781

10 Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of Coronavirus Disease 2019 and Influenza A: A Report from Iran. *Arch Iran Med* 2020;**23**:239–43. doi:10.34172/aim.2020.04

11 Cai Q, Yang M, Liu D, *et al.* Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering* 2020;**6**:1192–8. doi:10.1016/j.eng.2020.03.007

12 Costanzo M, De Giglio MAR, Roviello GN. SARS-CoV-2: Recent Reports on Antiviral Therapies Based on Lopinavir/Ritonavir, Darunavir/Umifenovir, Hydroxychloroquine, Remdesivir, Favipiravir and other Drugs for the Treatment of the New Coronavirus. *Current Medicinal Chemistry* 2020;**27**:4536–41. doi:10.2174/0929867327666200416131117

13 Lin L, Jiang X, Zhang Z, *et al.* Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. *Gut* 2020;**69**:997–1001. doi:10.1136/gutjnl-2020-321013

14 Jefferson T, Jones M, Doshi P, *et al.* Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;**348**:g2545. doi:10.1136/bmj.g2545

15 Mahase E. Covid-19: What do we know about “long covid”? *BMJ* 2020;**370**:m2815. doi:10.1136/bmj.m2815

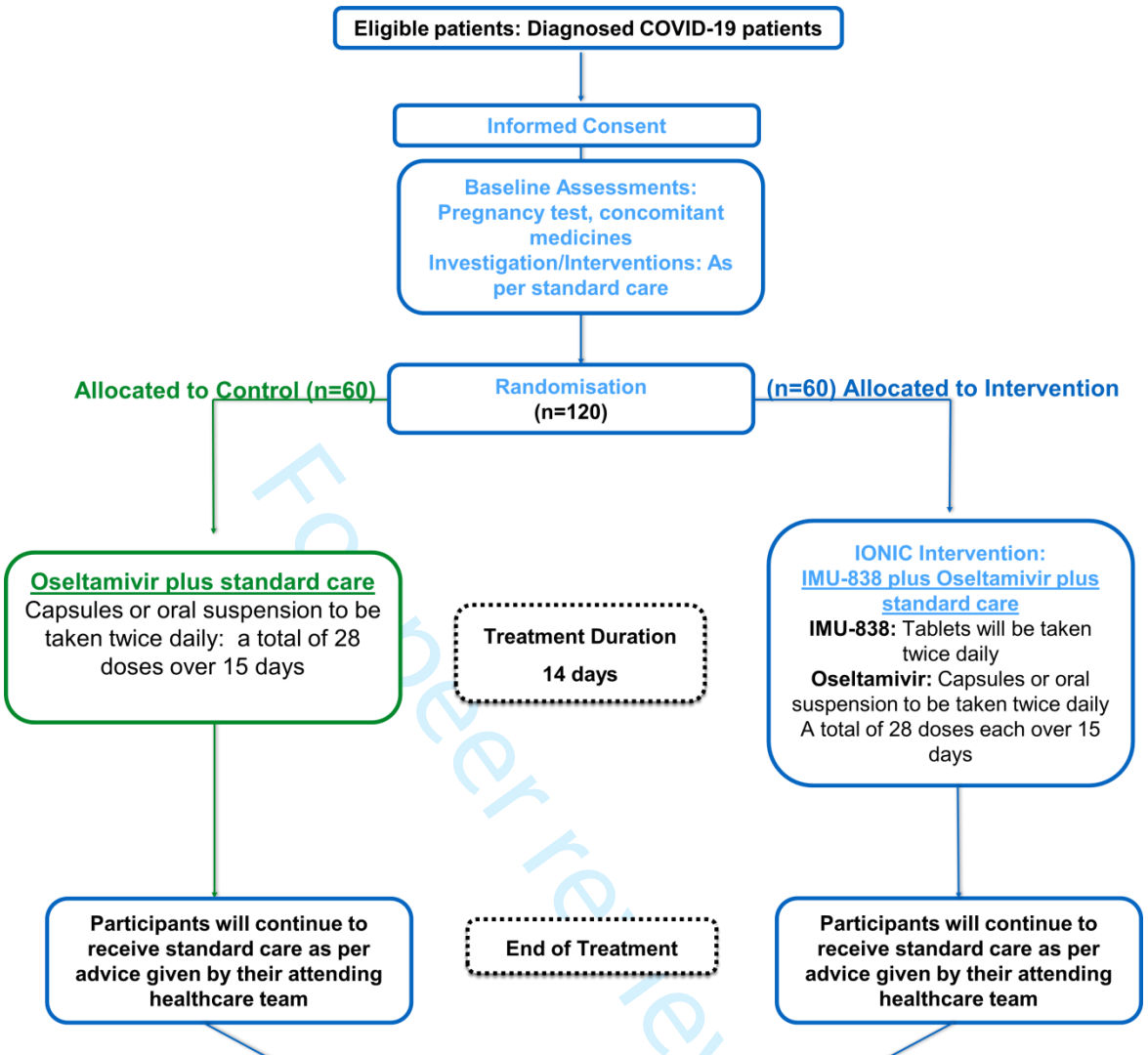
16 Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. *JAMA Netw Open* 2021;**4**:e2111417. doi:10.1001/jamanetworkopen.2021.11417

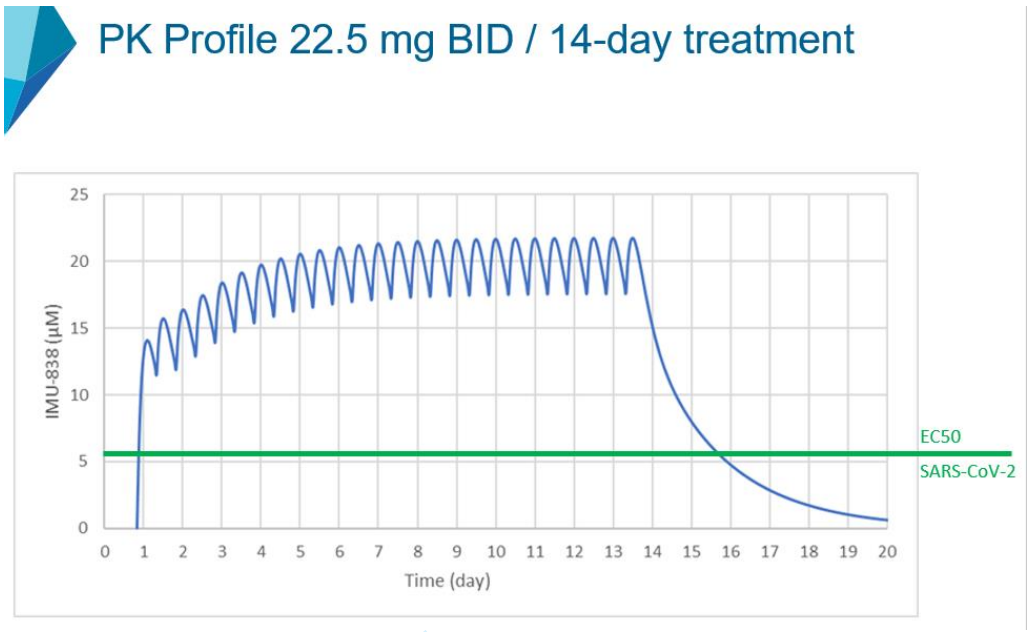
17 Taquet M, Dercon Q, Luciano S, *et al.* Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021;**18**:e1003773. doi:10.1371/journal.pmed.1003773

18 Poudel AN, Zhu S, Cooper N, *et al.* Impact of Covid-19 on health-related quality of life of patients: A structured review. *PLoS One* 2021;**16**:e0259164. doi:10.1371/journal.pone.0259164

19 Lam CLK, Tse ETY, Wong CKH, *et al.* A pilot study on the validity and psychometric properties of the electronic EQ-5D-5L in routine clinical practice. *Health Qual Life Outcomes* 2021;**19**:266. doi:10.1186/s12955-021-01898-3

20 Van Houwelingen H. Modelling Survival Data in Medical Research. D. Collett, Chapman & Hall, London, 1994. No of pages: XVII + 347. Price: E19.99. ISBN 0-41 2-44890-4. *Statistics in Medicine* 1995;**14**:1147–8. doi:10.1002/sim.4780140936





Appendix 1

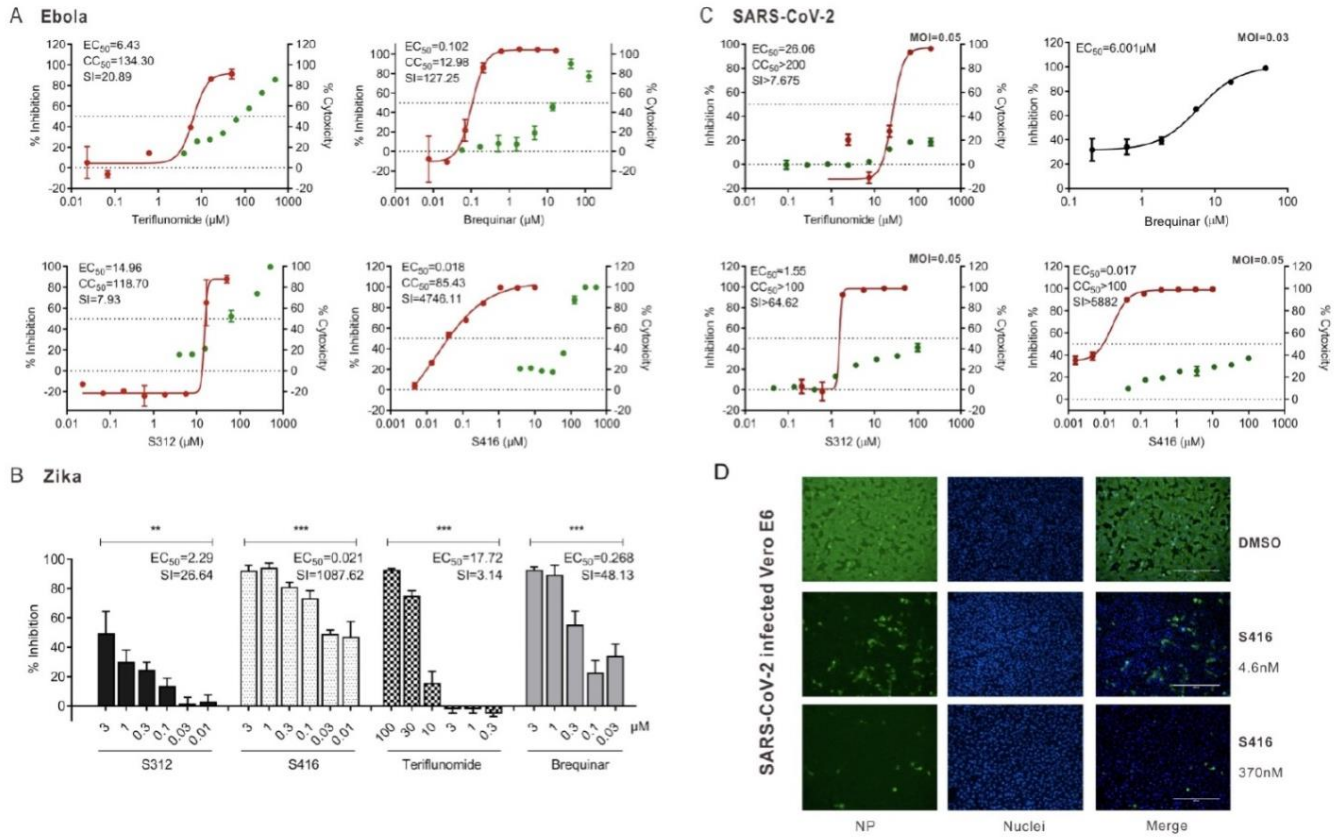
Table 1: Broad-spectrum antiviral efficacies of DHODH inhibitors (from Xiong et al. [2020](11))

IC_{50} (μM) (SI*)	Virus type				
	H1N1[a]	**H3N2[b]**	**H9N2[c]**	**Zika virus**	**Ebola-replicon**
S312	2.36 (25)	8.43 (7)	13.2 (4)	2.29 (26)	15.0 (7.9)
S416	0.0161 (27)	0.013 (126)	0.020 (82)	0.021 (1090)	0.018 (4750)
Teriflunomide	29.3 (6)	2.73 (32)	3.36 (26)	17.7 (3)	6.43 (32)
Leflunomide	>25.0 (<2.7)	NT	NT	NT	NT
Oseltamivir	7.68 (680)	NT	NT	NT	NT
Brequinar	0.240 (11.9)	0.022 (130)	0.060 (48)	0.268 (48)	0.102 (127)

SI* value was equal to CC_{50}/IC_{50}; values were rounded for significant figures from Xiong et al. 2020[1]

[a]A/WSN/33; [b]A/DongHu/06; [c]A/GuangZhou/99 NT (not tested)

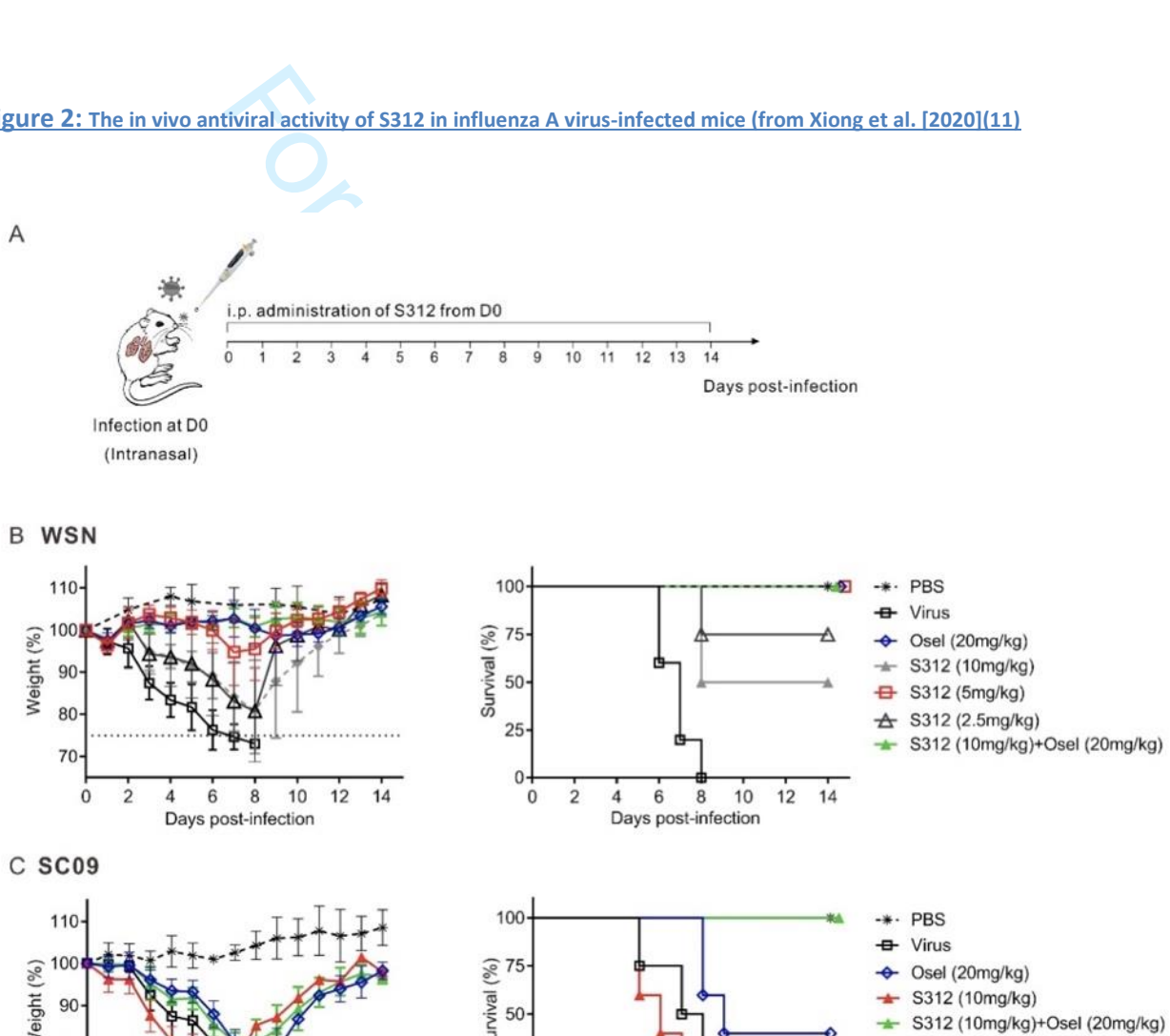
Figure 1: Antiviral activity of DHODH inhibitors (from Xiong et al. [2020]11)



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.

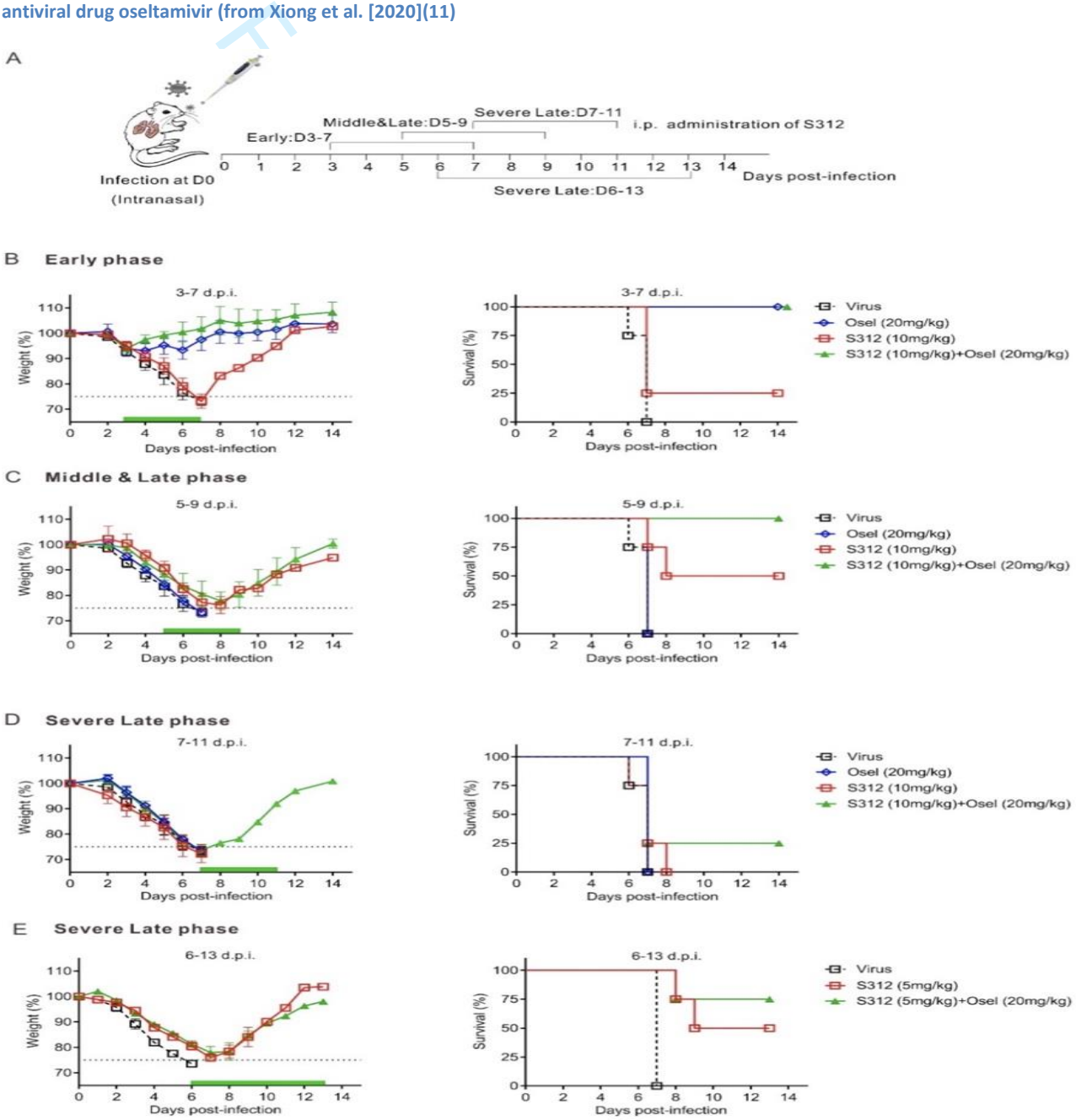
Figure 2: The in vivo antiviral activity of S312 in influenza A virus-infected mice (from Xiong et al. [2020](11)



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

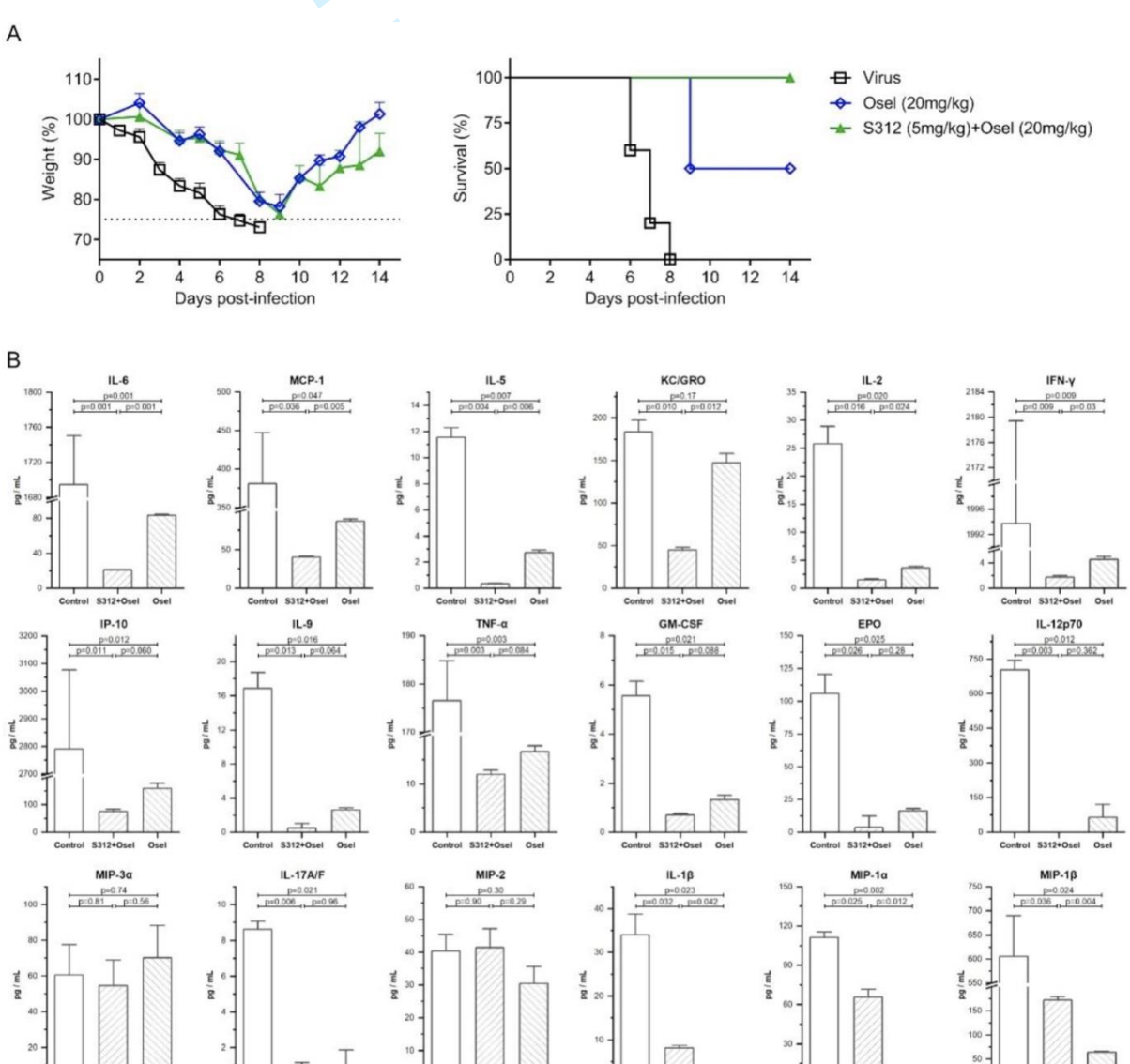
respectively. The body weight and survival were monitored for 14 days or until body weight reduced to 75% (n = 4 mice per group). (C) Mice were inoculated intranasally with 600 PFU of A/SC/09 (H1N1) and then i.p. with S312 (10mg/kg), Oseltamivir (20mg/kg) and S312+Oseltamivir (10mg/kg+20mg/kg) once per 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)



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))



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

Ordinal Scale for Clinical Improvement

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

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, sorafinib, 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 of investigational medicial 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 progestrogen 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:

GFR	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	75 mg twice daily
> 10 to 30 (ml/min)	75 mg once daily
≤ 10 (ml/min)	75mg as single dose*

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 patent 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.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	3,19

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3,19
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18,19
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	9,10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	9

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16-17
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	30-35
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	19
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	30
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13,14
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16,17
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18, 19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	3
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19,20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	36
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	18