CLINICAL TRIAL PROTOCOL

A Prospective, Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Study to Evaluate the Efficacy, Safety and Tolerability of IMU-838 as Addition to Investigator's Choice of Standard of Care Therapy, in Patients with Coronavirus Disease 19

(CALVID-1)

IND:	149,167
EudraCT No:	2020-001264-28
Protocol no.:	P2-IMU-838-COV
Sponsor:	Immunic AG Lochhamer Schlag 21 82166 Graefelfing, Germany
Coordinating investigator:	Prof. Neera Ahuja, Stanford University School of Medicine
Protocol version and date:	Final 3.0, 04-Sep-2020
Previous protocol versions and date:	Final 2.1 (USA), 29-May-2020 *(valid only in US)* Final 2.1 (BG), 20-May-2020 *(valid only in BG)* Final 2.1 (DE), 05-May-2020 *(valid only in DE)* Final 2.0, 30-Apr-2020 Final 1.0, 21-Apr-2020

REVISION CHRONOLOGY

- Original version: Version 1.0, dated 21-Apr-2020
- Version 2.0, dated 30-Apr-2020

  The following changes were included in Version 2.0 compared with Version 1.0:

  - Section 1 and Section 9.3 (Exclusion Criterion 11), Section 11.2.1, and Section 11.2.2:

    Included that Chloroquine and Hydroxychloroquine are prohibited for all centers in all countries unless already taken for indicated use before entering the trial (in Version 1.0 it was only prohibited for all centers in Germany and allowed with special recommendations in other countries)
  - Section 1, Section 9.3 (Exclusion Criterion 11), and Section 11.2.2:
    - Included that use of other DHODH inhibitors, including teriflunomide or leflunomide is prohibited
    - Orafenib was replaced by sorafenib (spelling mistake)
  - Section 1 and Section 7:

    Under Secondary endpoints

    Clinical patient status on the 9-category WHO ordinal scale[1] on Days 6, 14, and 28

    Changed to

    Change in daily clinical patient status on the WHO 9-category ordinal scale[1]
  - Appendix 1:

    Urine uric acid deleted in Lab Kit A as this was added there in error instead of blood serum-based uric acid

    Clarified that estimated glomerular filtration rate (eGFR) will be calculated according to the Schwartz bedside equation for children and adolescents and not according to the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) equation that will be used for adults. Respective references were added.
  - Editorial changes.
- Version 3.0, dated 04-Sep-2020

  ➢ **The following changes were included in Version 3.0 compared with Version 2.0, 2.1(DE), 2.1 (BG), and 2.1 (USA) as indicated**

  Protocol P2-IMU-838.COV was primarily amended to specify that Part 1 and Part 2 of the trial will now be handled and analyzed completely independent of each other. The primary objective of Part 1 is to show proof-of-activity. If activity of IMU-838 can be

demonstrated during the main analysis of Part 1 (MA1), Part 2 will be initiated. Sample size estimations for Part 2 will be done based on the MA1 results. Further, endpoints and other trial features will be re-evaluated and adjusted if deemed necessary.

Changes based on this modification of trial design and further changes are outlined below. Country-specific changes are indicated in *italics.*

If changes are indicated old replaced text is ~~struck through~~ and newly added text written in **bold**.

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
Title Page and Section 2	Address of Sponsor changed	✓	✓	✓	✓
Revision Chronology	Under 'changes included in Protocol Version 2.0 compared with Version 1.0', explained why urine uric acid was deleted from Lab Kit A (see above Appendix 1)	✓			
1 (below Table 1), 4	Deleted that in case of inconsistencies between text in the protocol and the schedule of assessments, the schedule of assessment (Table 1) will predominate'.	✓	✓		✓
1, Table 1, 8.1, 12.6	Included safety follow up to be performed after D28/EOS examination until Day 60. Sections updated accordingly and new Section 12.6 ‚Safety follow up' added.	✓	✓	✓ (+Sec. 12.1)	
1	• The SFU added to trial periods	✓	✓	✓	✓
	• Statistical methods shortened and adjusted to describe modifications as outlined below for Section 16.3.2	✓	✓	✓	✓
1, Table 1, 8.1, 11.1.3, 11.1.5, 12.3, 12.5 (only valid in BG)	*Following a request from the Bulgarian Drug Agency, patients randomized into the trial in Bulgaria must be kept hospitalized for the entire 14-day treatment period (Day 0 to Day 14). Sections updated accordingly*	✓	✓		✓
1, 6	Participating countries updated, number of centers updated	✓	✓	✓	✓
1, 7	Under secondary efficacy endpoints the specification that some endpoints maybe evaluated for a subset of only surviving patients deleted as this will be specified in the SAP	✓	✓	✓	✓
	Under pharmacokinetic endpoints: indicated that morning plasma trough values of IMU-838 will be measured at Days 0, 1 through 6, 14, and 28 (instead of Days 0, 1, 2, 3, 6, 14 and 28) to be consistent with Table 1	✓	✓		
	'Proportion of patients surviving without respiratory failure' added as key secondary endpoint and respective objective	✓	✓	✓	✓

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
1, 7 *(continued)*	Following secondary endpoint changed as indicated: 'Cumulative dose of vasoactive therapies **(daily until Day 14)** and days with vasoactive therapies (~~daily~~ until Day 14)'	✓	✓	✓	✓
	Following secondary endpoint corrected as indicated: 'Proportion of patients with clinical improvement, defined as ~~the time from first dose of IMP to~~ ~~an~~ improvement of at least 2 points on the WHO 9-category ordinal scale….'',	✓	✓	✓	✓
	For the secondary endpoint 'Proportion of patients with auxiliary therapy, indicated that the need of auxiliary oxygen therapy is sufficient for this endpoint and clarified that this proportion will be assessed not on but until Days 6, 14, and 28	✓	✓	✓	✓
	For the secondary endpoint 'Rate of IC admission' clarified that this proportion will be assessed not on but until Days 6, 14, and 28	✓	✓	✓	✓
1, 8.1	*Clarified that early safety analysis will be performed after 30 patients have completed Day 28. For US centers only, enrollment will be paused in the US at this time until after the IDMC has reviewed trial safety stopping criteria for the trial.*	✓	✓	✓	
	Safety follow-up added	✓	✓	✓	
	For consistency reasons 'early interims safety analysis' replaced by 'early safety analysis'	✓	✓	✓	✓
1, 8.1, 9.1, 16.1, 16.3.1, 16.4	Sections updated to reflect the following as applicable:				
	• Specified that Part 1 and Part 2 will be handled as independent parts and respective changes in analysis, sample size and trial conduct described	✓	✓	✓	✓
	• Alpha level for Part 2 changed from 0.05 to 0.025 (1-sided); information rate from 20% (α<0.0001) to 50% (α=0.0026)	✓	✓	✓	✓
	• Sample size calculation adjusted	✓	✓	✓	✓
1, 9.2 (Inclusion Criterion 1)	Included that the potential extension of the trial to include children after the MA1 will only be implemented after the approval of a respective protocol amendment	✓			
1, 9.3	The following exclusion criteria were added				
	• Patients with clinically relevant conditions leading to hyperuricemia (Exclusion Criterion 12)	✓			

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
1, 9.3 (continued)	The following exclusion criteria were added • Patients with known Gilbert syndrome (unless their indirect [unconjugated] bilirubin level is confirmed to be <1.2 x ULN, i.e. <1.1 mg/dL) (Exclusion Criterion 16)	✓			
	• Patients with known acute or clinically relevant chronic renal failure, patients currently on dialysis, as well as patients with an estimated glomerular filtration rate value <30 mL/min/1.73 m² body surface area according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults (or the Schwartz bedside equation for children and adolescents, if applicable) (Exclusion Criterion 17)	✓			
1, 9.3	Previous Exclusion Criterion 14 now Exclusion Criterion 15 was modified to include in addition to patients with Child Pugh C liver impairment also patients with Child Pugh B liver impairment	✓			
1, 23	Start and end of trial updated	✓	✓	✓	✓
Table 1	Status hospitalization/status ICU, SARS-CoV-2 viral load, SARS-CoV-2 status, and Serology: SARS-CoV-2 antibodies added for USV(SFU)	✓	✓	✓ (+Sec. 12.1)	✓
	SARS-CoV-2 viral load and SARS-CoV-2 status assessments changed from a daily to a 2-daily assessment	✓	✓	✓ (+Sec. 12.1)	✓
	Indicated that use of RRT and ECMO at SFU must not be noted if performed as telephone visit				✓
	Indicated that score assessment (9-point WHO scale), documentation of ECMO use, RRT use, vasopressor dose, and O_2 supplementation must be performed also on Day 28 (needed for respective endpoints) (only Table 1)	✓			
Table 1, Section 15.3	Clarified that height and weight are only to be measured at D0, pre-dose	✓	✓	✓ (+Sec. 12.1)	✓
Table 1, Appendix 1	Clarified which samples must be sent to the central safety laboratory and which to the central virology laboratory	✓	✓		
Table 1, Appendix 2,	A list of required local laboratory tests was included; Appendix 2 newly added, previous Appendix 2 now Appendix 3	✓	✓	✓ (+Sec. 12.1)	✓

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
Table 1, 14.3, Appendix 1	Included that nasopharyngeal swab and spontaneous sputum samples must be stored at at least -20°C (-4°F) on site, and shipped to the laboratory on dry ice within 7 days (instead of storing at ambient temperature and shipment on day of sampling)	✓			
	Clarified that the qualitative SARS-CoV-2 status assessment will be based on the viral load test.	✓			
Table 1, 14.3, Appendix 1 (continued)	Further clarified that qualitative SARS-CoV-2 status assessment may be evaluated as absence or presence of virus in the quantitative SARS-CoV-2 RT-PCR assessments	✓	✓	✓ (+Sec. 12.1)	✓
Table 1, 13.3	Specified that any new viral or non-viral infection as well as site of infection and source of culture will be documented if assessed during routine clinical practice.	✓	✓	✓ (+Sec. 12.1)	✓
Table 1, 14.3,19.3	*Sections updated to reflect the following as applicable: Additional blood collection to evaluate immune cells and immune reactions in future research studies added (at Days 0, 6, 14, and 28), only valid for centers in the USA and optional for patients consenting to these additional blood collections.*	✓	✓	✓ (+Sec. 12.1)	✓
Table 1, 14.1, 14.2, 14.3, 15.2.2, Appendix 1	Clarified to store laboratory samples at at least -20°C (-4°F)	✓	✓		
Figure 1	SFU added	✓	✓	✓	✓
2, 6	Central virology laboratory added	✓	✓	Only US lab	Only EU lab
10.1	The following was added: For the MA1 the IDMC and Sponsor will be unblinded, the blind will, however, be kept for patients and investigators until FA1.	✓	✓	✓	✓
11.2.2	Specified that CYP2C8 metabolized drugs, potent CYP2C8 inhibitors and strong and moderate CYP2C8 inducers should be used with caution	✓	✓	✓	✓
12	Schedule of assessment (Table 3) included; new subheading i.e., 12.1 Schedule of assessment included; heading numbering of remaining section headings adjusted	✓	✓		✓
14	Indicated that samples must be prepared according to the respective laboratory manuals	✓	✓		

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
15.1.3	AE reporting indicated as follows to be consistent with Table 3: All AEs occurring between the time written informed consent was obtained and ~~14 days after the patient's last IMP intake~~ **until the end of the safety follow-up period** (**safety** observation period) ~~or until EoS, whatever occurs later,~~ must be recorded. All AEs that occur during the **safety** observation period…	✓	✓	✓	✓
15.1.6	Was modified to indicate that also COVID-19 related symptoms with clinically unusual worsening during the trial must now be reported as AEs as follows: Typical COVID-19-related symptoms **present at Baseline** (examples such as fever, dyspnea, viral pneumonia, or hypoxia) **and continuing during the trial without clinically unusual worsening*** are considered anticipated clinical events of the underlying condition and will not be collected as AEs~~, and disease-related symptoms such as temperature, blood oxygen saturation, respiratory rate and presence of viral pneumonia and bacterial superinfections are collected separately as efficacy measures.~~ In addition, disease characteristics and severity will be regularly captured within the scope of the clinical status assessment ~~and complete physical examinations will be recorded multiple times.~~ Death, ~~or~~ hospitalization, **and use of ventilation, ECMO, or dialysis** due to COVID-19 or its complications **(which all are recorded as clinical endpoints for this trial) are** ~~is~~ not considered ~~an~~ AE**s** (see Section 15.1.2) and **should not be considered medically significant events by itself for the assessment of SAEs.** ~~are recorded as clinical endpoints for this trial.~~ Any **clinically unusual** worsening* of COVID-19-related disease symptoms present at trial inclusion **and any clinically relevant changes in clinical laboratory parameters, vital signs or other findings during physical examination which are considered unusual for COVID-19 disease and where a relationship to drug treatment cannot be excluded** should ~~only~~ be recorded as ~~an~~ AE**s** ~~if their course is abnormally severe, significant or unexpected~~. *** "Unusual worsening" means that, in terms of type or severity of symptoms, time frame or symptom fluctuations, the** course **of the disease progression is different from that in most patients with the same general conditions (disease status, age, health status, concurrent diseases).**	✓			

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
15.1.6 (continued)	Typical COVID-19-related symptoms present at Baseline (examples such as fever, dyspnea, viral pneumonia, or hypoxia) and continuing during the trial without clinically **unusual** ~~relevant~~ worsening* are considered anticipated clinical events of the underlying condition and will not be collected as AEs. In addition, disease characteristics and severity will be regularly captured within the scope of the clinical status assessment. Death, ~~or~~ hospitalization **and use of ventilation, ECMO, or dialysis** due to COVID-19 or its complications **(which all are recorded as clinical endpoints for this trial) are** ~~is~~ not considered ~~an~~ AE**s** (see Section 15.1.2) and **should not be considered medically significant events by itself for the assessment of SAEs.** ~~are recorded as clinical endpoints for this trial.~~ Any clinically ~~relevant~~ **unusual** worsening* of COVID-19-related disease symptoms present at trial inclusion, and any clinically relevant changes in clinical laboratory parameters, vital signs or other findings during physical examination **which are considered unusual for COVID-19 disease and** where a relationship to drug treatment cannot be excluded should be recorded as ~~an~~ AE**s**. ***"Unusual worsening" means that, in terms of type or severity of symptoms, time frame or symptom fluctuations, the course of the disease progression is different from that in most patients with the same general conditions (disease status, age, health status, concurrent diseases).**		✓	✓	
15.2	Section renamed to 'Safety laboratory investigations'	✓	✓		✓
	Clarified that clinically significantly abnormal values must be reported as AE, if not already clinically significantly abnormal at Baseline **or if there are known circumstances unrelated to a disease or the medication (such as patient activities or sample handling) that are a likely explanation for the abnormal value**	✓	✓	✓	✓
	Clarified that clinical **safety** laboratory tests are to be performed at the indicated times	✓	✓		✓
16.3.2	Section updated to reflect the following: • Included that patients who are lost to follow-up or discontinue the trial on or before Day 13 (last treatment day) due to any reason other than death, and who discontinue with a last observed WHO clinical status no lower than that at Screening are considered treatment failures for the primary endpoint.	✓	✓	✓	✓

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
16.3.2 *(continued)*	Section updated to reflect the following: • New sensitivity analysis for the primary endpoint specified for patients who discontinued before EoS, using the available information on INV until EoS.	✓	✓	✓	✓
	• Analysis of the new key secondary endpoint 'proportion of patients surviving without respiratory failure' added; sensitivity analysis specified	✓	✓	✓	✓
	• Center as covariate excluded in the logistic regression analyses (Part 2)	✓	✓	✓	✓
	• Rules for imputation of missing ICU data specified	✓	✓	✓	✓
	• Corrected that patients who discontinued the trial before Day 28 due to any other reason than death will be considered as **deaths** ~~survived~~, unless survival status can be obtained through other means	✓	✓	✓	✓
	• Sensitivity analysis for all-cause mortality specified	✓	✓	✓	✓
	• Analyses applicable for Part 1 and Part 2 described separately; clarified that Part 1 will only be done exploratory, while Part 2will include confirmatory tests	✓	✓	✓	✓
16.4	Completely rewritten and adjusted to the new trial design; new heading, procedures and criteria for Part 1 to Part 2 transition described	✓	✓	✓	✓
17.1	For the purpose of patient discontinuation for safety text changed as follows: Any SAE of Grade 3 or 4~~, that in the opinion of the investigator, (1) is likely related to IMP and (2)~~ when in the investigator's opinion the benefits do not outweigh the risk for continuing in the trial	✓	✓	✓	
18	The following changes to IDMC meetings and enrollment stop were made: • … • Meeting for **MA~~IA~~1** • …	✓	✓	✓	✓
	'If at ~~any interim analysis~~ the **IA2** the IMU-838 therapy arm proves to be statistically significantly more beneficial..'	✓	✓	✓	✓
19.3	*Included that patients from whom additional blood samples will be collected to immune cell subtyping for further research studies will have to provide their consent to that optional additional procedure in the ICF (only applicable for the US)*	✓	✓	✓	✓

Sections affected	Change	Applicable for Version			
		2.0	2.1 (DE)	2.1 (BG)	2.1 (USA)
20	Section 20.1 Trial safety stopping criteria newly introduced, numbering of subsequent sections adapted	✓	✓	✓	
	Clarified that the trial will be stopped during **the early and potential additional** ~~any interim~~ safety **analyses** ~~analysis~~ when the stopping criteria are fulfilled: …	✓	✓	✓	✓
	Section 20.2 (previous Section 20.1) renamed in '**Other** criteria for halting or terminating the trial'	✓	✓	✓	
22.6	Specified that the results of Part 1 and Part 2 of the trial will be each summarized in a clinical trial report according to the ICH E3	✓	✓	✓	✓
	Clarified that conclusions of early safety analysis, **MA1** ~~IA1~~ and IA2 will be submitted as appropriate.	✓	✓	✓	✓
1, 2, 6, 7, 9.2 (Inclusion Criteria 2 + 4), 19.1, 19.3, 22.6	Information applicable for centers in the USA included			✓	
Table 1, 8.1, 11.1.3, 11.1.5, 12.1, 12.3	Procedures to be performed in case of hospital discharge before Day 14 included (not applicable in BG)			✓	
	Editorial changes	✓	✓	✓	✓

1 Summary and flow chart

Trial code
P2-IMU-838-COV

Title of the trial
A Prospective, Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Study to Evaluate the Efficacy, Safety and Tolerability of IMU-838 as Addition to Investigator's Choice of Standard of Care Therapy, in Patients with Coronavirus Disease 19

Short title
CALVID-1

Principal investigators and trial centers
Planned: about 10 to 45 centers in the European Union, Bosnia and Herzegovina, Moldova, North Macedonia, Russia, Ukraine, and USA (and as back up countries: Croatia and Serbia)

Coordinating investigator: Prof. Neera Ahuja, Stanford University, School of Medicine

Clinical phase: Phase 2 (Part 1), Phase 3 (optional Part 2)

Phase 2 (Proof-of-Activity Phase, Part 1):

Estimated start (first patient in):	May 2020 (actual 12-Jun-2020)
Estimated recruitment period:	4 months
Estimated end of trial (last patient out):	Nov 2020

Optional Phase 3 (Part 2):
Depending on the outcome of the main analysis of Part 1 (MA1), this optional trial expansion will be started which will then be considered a Phase 3 trial.

Trial periods
The trial consists of screening, a 14-day blinded treatment (BT) period, a 14-day follow-up (FU) period, and a 32-day safety FU (SFU).

Trial objectives and endpoints

Objective	Endpoint
Primary	
• To evaluate the efficacy of IMU-838 plus investigator's choice of standard of care therapy (SoC) vs placebo plus SoC in the treatment of coronavirus disease 2019 (COVID-19) based on the need for invasive ventilation (INV) up to 28 days	• Proportion of patients without any need* for INV until end-of-study (EoS)

Trial objectives and endpoints *(continued)*

Key secondary	
• To evaluate the efficacy of IMU-838 (+SoC) vs placebo (+SoC) in the treatment of COVID-19 based on survival without respiratory failure, the duration of hospitalization in intensive care unit (ICU) and all-cause mortality up to 28 days	• Proportion of patients surviving without respiratory failure (defined as any need of ICU, INV, high-flow oxygen or extracorporeal membrane oxygenation [ECMO*] until EoS) • Duration of ICU treatment until EoS • 28-day all-cause mortality
Secondary	
Efficacy	

• To evaluate the efficacy of IMU-838 (+SoC) vs placebo (+SoC) in the treatment of COVID-19 based on a variety of further variables and time points (e.g., clinical status, renal impairment, oxygenation, hospitalization, concomitant vasoactive treatments, clinical recovery)	• Time to clinical improvement, defined as the time from first dose of investigational medicinal product (IMP) to an improvement of at least 2 points on the WHO 9-category ordinal scale[1], or live discharge from hospital without oxygen supplementation, whichever comes first
	• Duration of hospitalization (*for US sites only*: *or treatment in special outpatient setting in lieu of hospitalization due to resource restraints*)
	• Proportion of patients
	  • free of renal-replacement therapy (RRT)* until EoS
	  • free of ECMO* until EoS

[1] WHO. WHO R&D: Blueprint Novel Coronavirus COVID-19 Therapeutic Trial Synopsis [Online] 2020. Available from: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary *(continued)*	

Efficacy *(continued)*	• Proportion of patients
	  • free of INV until Days 6 and 14*
	  • free of RRT until Days 6 and 14*
	  • free of ECMO until Days 6 and 14*
	  • with improvement of at least 2 points (from randomization) on the 9-category WHO ordinal scale[1] on Days 6, 14, and 28
	  • with auxiliary oxygen therapy* (including all types of oxygen therapy) until Days 6, 14, and 28
	  • with clinical recovery defined as
	  • Axillary temperature ≤36.6 °C, or oral temperature ≤37.2 °C, or rectal or tympanic temperature ≤37.8 °C; and
	  • Respiratory frequency ≤24 times/min without oxygen inhalation; and
	  • Oxygen saturation ≥98% without oxygen inhalation
	  • With clinical improvement, defined as an improvement of at least 2 points on the WHO 9-category ordinal scale, or live discharge from hospital without oxygen supplementation, whichever comes first
	• Change in daily clinical patient status on the WHO 9-category ordinal scale[1]
	• Duration of INV
	• Duration of ECMO
	• Duration of RRT

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary *(continued)*	
Efficacy *(continued)*	• Duration of auxiliary oxygen therapy (including all types of oxygen therapy) • Duration of hospitalization for survivors • Rate of ICU* admission until Days 6, 14, and 28 • Hospital-free days • Time from IMP treatment initiation to death • Time to first prescription of INV • Time to first prescription of RRT • Time to first prescription of ECMO • Time to first prescription of INV, RRT, and ECMO • Time to ICU admission • Cumulative dose of vasoactive therapies (daily until Day 14) and days with vasoactive therapies (until Day 14) • Time to clinical recovery
Pharmacokinetics	
To evaluate trough plasma levels of IMU-838	• Morning trough plasma levels of IMU-838 on Days 0, 1 through 6, 14, and 28 • Correlation of trough levels (quartiles) to selected clinical outcomes
Safety	
To evaluate safety and tolerability of IMU-838	• Adverse events (AEs) and serious AEs • Vital signs • Clinical laboratory parameters (blood chemistry, hematology, and urinalysis) • Electrocardiogram (ECG) parameters • Temperature

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary *(continued)*	
Disease markers	
To explore blood levels of disease markers	• D-dimer • Lactate dehydrogenase (LDH) • C-reactive protein • Troponin I • Procalcitonin • Correlation of disease markers to selected clinical outcomes The analysis for all endpoints includes absolute values and absolute change from Baseline over time; for LDH log transformed values will be used.
Virologic markers, biomarkers, and serologic markers	***Virologic markers***

To explore viral titers, measures of viral virulence and inflammatory markers	• Severe Acute Respiratory Syndrome Coronavirus Virus (SARS-CoV-2) mean viral load - log10 copies in spontaneous sputum and nasopharyngeal swab samples
	  • Decrease of SARS-CoV-2 viral load
	  • Time course of SARS-CoV-2 viral load
	• Qualitative virologic clearance in spontaneous sputum and nasopharyngeal swab samples (= 2 consecutive negative SARS-CoV-2 reverse transcriptase polymerase chain reaction tests at least 24 hours apart)
	• Rate of conversion to a negative SARS-CoV-2 (qualitative) test on Days 6, 14 and 28
	• Time to conversion to a negative SARS-CoV-2 (qualitative) test

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary ***(continued)***	

Virologic markers, biomarkers, and serologic markers (continued)	***Biomarkers***
	• Interleukin (IL)-17, IL-1ß, IL-6, interferon gamma (IFNγ), tumor necrosis factor alpha
	Serologic markers
	• Immunoglobulin (Ig)A and IgG antibodies against SARS-CoV-2
	  • Time to appearance of IgA and/or IgG antibodies
	  • Proportion of patients with IgA and/or IgG antibodies on Days 6, 14, and 28
	
	The analysis for all endpoints includes absolute values, relative and absolute change from Baseline over time, if applicable.

* Patients who are assessed by the investigator to have a medical need of the respective treatment (i.e., INV, ECMO, RRT, ICU, hospitalization) but do not receive these treatments for other reasons will be counted for this endpoint.

Methodology

The trial consists of 2 independent parts: a Phase 2 proof-of-activity phase (Part 1) with the option to continue enrollment (without interruption) to a confirmatory Phase 3 part (Expansion Phase, Part 2). Part 2 will only be started after results from the main analysis of Part 1 (MA1) have been analyzed and results indicate activity of IMU-838 in COVID-19.

Both parts follow a multicenter, double-blind, placebo-controlled, randomized, parallel-group design evaluating the safety and efficacy of IMU-838 as addition to investigator's choice of SoC treatment in patients with COVID-19. Eligible patients will be centrally randomized 1:1 to twice-daily (BID) oral 22.5 mg IMU-838 (45 mg/day + SoC) or placebo (+ SoC). Randomization will be stratified by age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals).

Part 1 and Part 2 will be analyzed independently from each other.

The unblinded main analysis of Part 1 (MA1) will be performed after approximately 200 patients have completed Day 28/EoS, either as scheduled or prematurely, while enrollment continues. Based on the MA1 results the trial may be expanded into Part 2, if activity of IMU-838 is observed, or stopped, if no activity of IMU-838 is observed. A further approximately 30 patients are expected

to be enrolled and treated in a double-blind manner until the results of the MA1 are available (when no activity of IMU-838 was found) or until the enrollment in Part 2 has commenced (if MA1 indicated proof-of-activity). A final analysis of Part 1 (FA1) will be performed after completion of Part 1 using all enrolled patients, i.e. approximately 230 patients.

In addition, an early safety analysis will be performed and evaluated by an Independent Data Monitoring Committee (IDMC) after 30 patients in Part 1 have completed Day 28 to assess unblinded safety data.

For US centers only: Enrollment into the trial will be paused after these 30 patients have reached Day 28 until the IDMC has evaluated safety stopping criteria. If the trial safety stopping criteria are not fulfilled, the enrollment in the trial will be resumed and the IDMC will continue with a full review of the available safety data.

Further safety analyses can be initiated at any time by the IDMC or Sponsor when new safety signals are identified within this or other trials of IMU-838.

Apart from assessing the IMU-838 activity, the MA1 will also be used to establish the sample size, endpoint selection as well as possible other trial adjustments (e.g. changes for study conduct due to safety or changes in the study population) for Part 2. The IDMC will also review MA1 results and act in a consultative capacity to assist the Sponsor in sample size calculations, endpoint selection and other adjustments for Part 2. The final design of Part 2 will be submitted as protocol amendment to regulatory authorities, and enrollment in Part 2 will only start after approval of the amended Part 2 protocol.

Part 2 of the trial, if performed, will use an adaptive sequential design with the IDMC reviewing unblinded data in an interim analysis during Part 2 (IA2) and providing the Sponsor with recommendations regarding modifications of sample size and trial conduct. The IA2 will be performed after approximately 50% of patients of the Part 2 sample size have been enrolled to adjust sample size and other trial features if needed. The final analysis of Part 2 (FA2) will be done after all patients have completed Part 2.

Screening

Patients can be screened for a maximum of 2 days (from Day -2 to Day 0) and eligible patients will be randomized on Day 0 and treated with IMP + SoC for 14 days. It is encouraged to screen potential participants immediately at the day of hospitalization (including informed consent, assessment of inclusion/exclusion criteria, screening laboratory tests all done locally, assessment of clinical and blood gas criteria) and randomize patients on the same day (Day 0). To assess eligibility criteria, existing local laboratory values obtained within 48 hours of randomization can also be used, except for testing of positive status of SARS-CoV-2 infection where a 4-day window is allowed.

IMP administration should start as quickly as possible after randomization and first IMP dose intended to be given in the evening of the screening day (Day 0).

Blinded Treatment period (Day 0 to Day 13) and Day 14 (end-of-treatment)

The first dose of IMP (2 tablets) should always be given on Day 0 (allowed range for first dose: 12:00 noon on Day 0 to 02:00 a.m.). All further IMP doses are 1 tablet each in the morning and evening. For details of IMP administration see section Test product. Information about the status and patient care are continuously obtained and documented once or twice daily (see Table 1). Further examinations and tests, laboratory parameters, biomarkers, disease markers, and virologic parameters are to be assessed as outlined in Table 1.

After the last IMP dose in the evening of Day 13, the end-of-treatment (EoT) assessments will be done on Day 14 (see Table 1). Blood sampling for IMU-838 trough values must be performed in the morning around the time the morning dose was usually taken by the respective patient. Patients may then continue to receive SoC without any further restrictions on concomitant medications as during the 14-day BT period (see Standard-of-care treatment and IMP-related exclusion criteria).

For centers in Bulgaria: Patients must be hospitalized during the entire treatment period i.e., from Day 0 to Day 14.

For centers in countries other than Bulgaria: In case of hospital discharge before Day 14, the following assessments should be done between hospital discharge and until Day 14 (patients should return for clinic visits at Day 6, if discharged before Day 6, and Day 14):

- On the day of hospital discharge:
  - All trial-related assessments and procedures are completed as per Table 1 and finalized (evening assessments should be done, even when the patient is discharged during the day)
  - The date and time of hospital discharge need to be documented
- Day 6 and Day 14:
  - The full lab assessments to be performed on Days 6 or 14, respectively (as indicated in Table 1)
  - Physical examination and ECG
  - Documentation of concomitant medications/procedures, AEs, temperature, vital signs, respiratory rate, type of oxygen supplementation, survival status, hospitalization status, assessment of WHO ordinal scale[1] (only once daily assessment required)
  - Return of IMP by patients and drug accountability (Day 14 only)

If the patent is discharged from the hospital before Day 14, the patient will receive the IMP and will take the remaining doses of IMP at home.

Day 28 Visit (EoS)

The patient should return for the final trial visit on Day 28 (EoS). If IMP is prematurely discontinued for any reason, the EoS visit should always be conducted on Day 28 and no earlier EoS should be performed. If patients withdraw from IMP prematurely, they should be encouraged to allow the EoS visit as part of the follow-up. If the patient dies during the trial, the investigator should indicate that this visit was not performed. However, even if no EoS visit was performed, information about patient status should be reported on the EoS page in the case report form. If the patient refuses any EoS visit or the patient is lost to follow-up, it is permissive in this trial that the investigator contacts the patient, the family of the patient or the referring physician by phone or email to obtain status of life information, or is able to search in registers or publicly available information for such status of life information.

Safety follow up

Following the Day 28/EoS examination, the investigator will contact the patient regularly (at least once) by phone or email to obtain health data until Day 60. The patient should be asked to return for an on-site visit if the investigator deems this necessary for follow-up.

Treatments

Test product

IMU-838 (vidofludimus calcium), a small molecule inhibitor of dihydroorotate dehydrogenase

Formulation: Tablets with 22.5 mg IMU-838

Administration: Tablets will be taken BID with a glass of water (if possible); one tablet each in the morning (15 to 50 min before a meal if applicable), and in the evening (2 hours after any meal if applicable).

The 1st IMP dose on Day 0 should always be the "evening dose of Day 0". To administer the 1st IMP dose as close as possible to time of randomization, the initial IMP dose ("evening dose of Day 0", Note: for this initial dose 2 tablets are to be given at once) can be administered between 12:00 noon on Day 0 to 02:00 a.m. on Day 1. The 2nd IMP dose is then given in the morning of Day 1, and dosing continues twice daily until the evening dose of Day 13 (last IMP dose). Except for the initial IMP dose (2 tablets), all other IMP doses will consist of 1 tablet. The timing of morning and evening doses (except for initial evening dose on Day 0) should be at the same time of the day, if possible.

If the patient is intubated for ventilation, IMP is to be given via a gastric tube. The tablet has no coating and a homogeneous content and can be crushed into smaller pieces (if necessary) for dosing via gastric tube.

Reference product

Matching placebo, twice-daily administration as described for the test product, identical number of tablets as given for IMU-838

Standard-of-care treatment

Any treatments, medications and procedures that investigators would customarily use to treat COVID-19 in their clinical practice should be used as SoC treatment. The investigator's choice of SoC can include supportive pharmaceutical treatments (including medications that are approved in other indications but that the investigator customarily uses in COVID-19 patients), medications with any approved antiviral indication, intravenous fluids, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, RRT, and ECMO. Investigational treatments not yet approved for commercial use in the respective country (for example obtained through an early access program) or parallel participation in different interventional trials are prohibited in this trial.

In addition, Arbidol and Colchicine are prohibited for centers in all countries. Chloroquine and Hydroxychloroquine are also prohibited for all centers in all countries unless already taken for indicated use before entering the trial.

Routine use of steroids is not recommended and should be reserved for patients with severe disease or with special circumstances. Concomitant use of steroids (e.g., required for existing pre-existing conditions) do not need to be discontinued when entering this trial, however, discontinuation should be considered.

Number of patients (total and for each treatment) planned

Part 1: MA1 approximately 200 patients; an additional 30 patients are expected (total of approximately 230 patients) until completion of Part 1

Part 2: determined based on the MA1, if applicable

Inclusion criteria

1. Male or female patients at least 18 years old (may only be extended to include children 12 years or older after MA1 following approval of a protocol amendment)
2. Admitted to the hospital or other medical in-patient treatment facility for treatment of COVID-19

   The hospitalization needs to be for medical reasons (treatment of COVID-19 disease) and cannot be for social reasons or due to housing insecurity.

   For US sites only: If the investigator would commonly hospitalize the patient but for healthcare resource reasons decides to treat the patient in a specially designed out-patient setting, then such patients are also allowed to enter the trial (please note that in this case the patient would be counted as clinical status category 3). The investigator then must assure

that the patient has at least a twice daily assessment by qualified trial personnel and all laboratory assessments can be adequately performed as per protocol. The Sponsor reserves the right to discontinue this option via administrative letter if such assurances cannot be met by any site.

3. SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction test in a nasopharyngeal, oropharyngeal or respiratory sample at ≤4 days before randomization
4. Moderate COVID-19 disease defined as fulfilling clinical status category 3 or 4 on the WHO 9-point ordinal scale[1]:
   - Category 3: Hospitalized (see note above for US only), virus-positive, no oxygen therapy with the following condition:
     - The hospitalization needs to be for medical reasons (treatment of COVID-19 disease) and cannot be for social reasons or due to housing insecurity
   - Category 4: Hospitalized, virus-positive, oxygen by mask or nasal prongs (excluding high-flow oxygen therapy) with the following conditions:
     - Peripheral capillary oxyhemoglobin saturation (SpO_2) >92% at maximum of 6 liters oxygen flow per minute
     - Stable respiratory rate ≤30 breaths/min at maximum of 6 liters oxygen flow per minute
5. Presence of at least 1 symptom characteristic for COVID-19 disease i.e., fever, cough or respiratory distress
6. Willingness and ability to comply with the protocol
7. Written informed consent given prior to any trial-related procedure
8. For women of childbearing potential: Application of a highly effective method of birth control (failure rate less than 1% per year when used consistently and correctly) together with a barrier method between trial consent and 30 days after the last intake of the IMP.

   Highly effective forms of birth control are those with a failure rate less than 1% per year and include:
   - oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation
   - oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation
   - intrauterine device or intrauterine hormone-releasing system
   - bilateral tubal occlusion

- vasectomized 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)
- 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 no acceptable methods of contraception)

Barrier methods of contraception include:

- Condom
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository

9. Male patients must agree not to father a child or to donate sperm starting at Screening, throughout the clinical trial and for 30 days after the last intake of the IMP. Male patients must also
   - abstain from sexual intercourse with a female partner (acceptable only if it is the patient's usual form of birth control/lifestyle choice), or
   - use adequate barrier contraception during treatment with the IMP and until at least 30 days after the last intake of the IMP, and
   - if they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 8
   - if they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP

Exclusion criteria

Underlying disease-related exclusion criteria

1. Involvement in the trial is not in the patient's best interest according to the investigator's decision, including the presence of any condition that would, in the assessment of the investigator, not allow the protocol to be followed safely

   Note: The investigator should particularly consider exclusion of patients at increased risk for serious or fatal AEs in case of worsening of the pulmonary perfusion. This includes, but is not limited to, pre-existing pulmonary hypertension, severe chronic respiratory disease, severely increased risk for thromboembolic complications and moderate to severe left ventricular ejection fraction (LVEF) dysfunction. In addition, other known risk factors of highest risk of mortality in COVID-19 patients should be considered.

2. Presence of respiratory failure, shock, and/or combined failure of other organs that requires ICU monitoring in the near foreseeable future
3. Critical patients whose expected survival time <48-72 hours

4. Presence of the following laboratory values at screening:
    - White blood cell count (WBC) <1.0 x 10^9/L
    - Platelet count <100,000/mm³ (<100 x 10^9/L)
    - Total bilirubin>2 x upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) or gamma glutamyl transferase (GGT) >5 x ULN
5. Participation in any other interventional clinical trial
6. Hospitalization primarily for reasons other than COVID-19 (including primarily for concomitant conditions during ongoing SARS-CoV-2 infection)
7. Anticipated transport to a different hospital or institution, in particular when such transport is anticipated for pending ECMO or RRT treatment
8. Clinical suspicion of a bacterial superinfection at Screening

IMP-related exclusion criteria

9. Patients who cannot take drugs orally
10. Allergic or hypersensitive to the IMP or any of the ingredients
11. Use of the following concomitant medications is prohibited from Screening to end of treatment with IMP in this trial (up to Day 14) if not indicated otherwise in this protocol:
    - Concurrent use of any mycophenolate mofetil or of methotrexate exceeding 17.5 mg weekly
    - Any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic™) as well as uricosuric drugs such as probenecid
    - Current treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafenib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
    - Any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs
    - Use of rosuvastatin at daily doses higher than 10 mg
    - Arbidol and Colchicine
    - Any use of other DHODH inhibitors, including teriflunomide (Aubagio™) or leflunomide (Arava™)
    - Chloroquine and Hydroxychloroquine during the entire trial, unless taken for indicated use before entering the trial
12. Patients with clinically relevant conditions leading to hyperuricemia
13. Use of any investigational product within 8 weeks or 5x the respective half-life before the date of informed consent, whichever is longer, and throughout the duration of the trial

General exclusion criteria

14. Patients who have a "do not intubate" or "do not resuscitate" order (unless the patient waives in writing this order and will allow intubation for the duration of the trial period)
15. Patients with pre-existing end-stage liver disease (Child Pugh B and C score)
16. Patients with known Gilbert syndrome (unless their indirect [unconjugated] bilirubin level is confirmed to be <1.2 x ULN, i.e. <1.1 mg/dL)
17. Patients with known acute or clinically relevant chronic renal failure, patients currently on dialysis, as well as patients with an estimated glomerular filtration rate value <30 mL/min/1.73 m² body surface area according to the Chronic Kidney Disease Epidemiology Collaboration equation for adults (or the Schwartz bedside equation for children and adolescents, if applicable)
18. 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.
19. Legal incapacity, limited legal capacity, or any other condition that makes the patient unable to provide consent for the trial
20. Pregnant or breastfeeding
21. An employee of an investigator or Sponsor or an immediate relative of an investigator or Sponsor
22. Patients institutionalized due to judicial order

Statistical methods

Part 1

All endpoints will be analyzed descriptively. In addition, exploratory confidence intervals will be calculated for the primary and key secondary endpoints (and for other endpoints as appropriate) using an alpha of 0.1 (2-sided). No formal statistical tests will be conducted. The primary analysis will be based on the full analysis set (all randomized patients who received at least one dose of IMP as randomized). Secondary/sensitivity analyses may be performed using the per-protocol analysis set and the set of only surviving patients until EoS and will be further specified in the statistical analysis plan.

For the primary endpoint and the key-secondary endpoints based on patient proportions odds ratios with 2-sided 90% confidence intervals will be calculated adjusted for the stratification factors age and antiviral therapy. For duration of ICU a 2-sided 90% confidence interval for the median of differences between treatment groups (location shift) will be calculated.

Patients who are lost to follow-up or discontinue the trial on or before Day 13 (last treatment day) due to any reason other than death and patients who discontinue with a last observed WHO clinical status no lower than that at Screening are considered treatment failures for the respective endpoints. For duration of ICU respective imputation methods will be implemented.

The "need for INV" (considered positive for the primary endpoint) will include patients:

1. placed on any INV method during the trial,
2. who had an active "do not intubate" or "do not resuscitate" order established during the trial conduct or refused intubation for any reason but were assessed by the investigator to have a medical need for INV,
3. who had a medical need for INV as assessed by the investigator but for reasons of medical resource exhaustion or due to triage decisions by the hospital had not received INV, or
4. who died mainly due to respiratory failure but had a need for INV as assessed by the investigator or before such needed INV could have been started.

Part 2

The primary endpoint (as selected during MA1) and the key secondary endpoints that include proportion of patients (e.g. patients without respiratory failure, 28-day all-cause mortality) will be evaluated for superiority of IMU-838 vs placebo with an exact Cochran-Mantel-Haenszel test, adjusted for the stratification factors age and antiviral therapy. In addition, logistic regression analyses will be conducted including the covariates age, antiviral therapy, sex, and country.

The distribution of any key secondary endpoints containing duration measurements (e.g. duration of ICU treatment) will be analyzed with the van Elteren test (stratified by age and antiviral therapy). In addition, time-to-event analyses using Kaplan Meier methodology and a stratified log rank test (stratification factors age and antiviral therapy) will also be performed.

The primary and key secondary endpoints for Part 2 will be tested confirmatory, using a global alpha of 0.025 (1-sided). Results of other endpoints will be considered exploratory, even when statistical tests are performed.

Confirmatory hypothesis testing of key secondary endpoints will be done only after the test of the primary efficacy endpoint was significant. Testing will be done strictly hierarchically in the given order to ensure the family wise error rate. Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

Further details will be given after MA1 assessment, if activity has been confirmed.

Sample size calculation

Part 1

As no formal hypothesis testing will be conducted in Part 1, no formal sample size calculation is deemed necessary. In previous protocol versions, a pooling of p-values of Part 1 and Part 2 was planned and a sample size of N = 200 enrolled patients (100 per group) was calculated. It is assumed that with the previously planned sample size a robust estimation of all efficacy and safety parameters can be conducted. Thus, no adaptations in sample size for Part 1 are necessary.

Previously, the following assumptions were made:

3-stage group sequential test design with O'Brien and Fleming shaped boundaries

Information rate for Part 1 analysis: 0.2

O'Brien and Fleming alpha level for end of Phase 2 analysis: <0.0001

Primary endpoint: Proportion of patients without any need for INV

Randomization ratio:	1:1 (45 mg/day IMU-838:placebo)
Power:	80%
Global significance level:	0.05, 1-sided
Proportions of patients with need for INV	
for 45 mg/day IMU-838:	32%
for placebo:	40%
Number of patients (Part 1):	188

Considering a 6% drop-out rate, a total of 200 patients (100 per group) were to be enrolled.

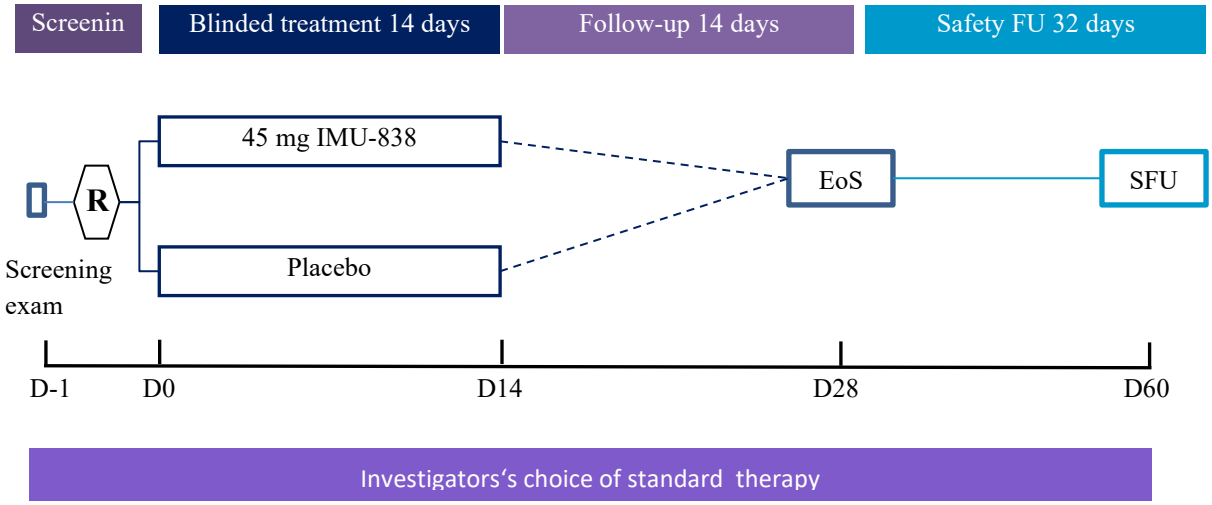
Part 2

If the trial is expanded to Part 2, the sample size of Part 2 will be determined based on the results of MA1.

The Part 2 (Phase 3, Expansion Phase) trial will be designed to keep a global 1-sided alpha level of 0.025 (one-sided). A 2-stage group sequential test adaptive design with O'Brien and Fleming shaped boundaries will be used. Stage 1 will be IA2 applying an overall information rate of 50% and using an alpha of 0.0026. The use of group sequential boundaries within the context of an adaptive design is enabled using the inverse normal method, combining the p-values of both stages with weights based on the sample sizes. Statistical analysis methods that control for the Type I error will be used.

Schedule of assessments and flow chart

Figure 1: Trial flow chart



BID = twice daily, D = day, EoS = end-of-study, EoT = end-of-treatment, exam = examination, SFU = safety follow-up.

Table 1: Schedule of assessments

Assessments	**Screening**	**Blinded treatment[l]**					**EoT**	**EoS**	**USV**
	D-2 to D0[g]	D0[g]		D1 - D5	D6	D7 - D13	D14	D28	***SFU***[p]
		Pre	Post					±1 d	
Informed consent	•								
Demographics, incl. high risk factors[f]	•								
In-/exclusion criteria	•								
Local screening labs performed or taken from existing labs[k]	•								
Confirmation of positive SARS-CoV-2 status	•[m]								
Randomization		•							
Medical history	•								
Concomitant medications/procedures	•		•	• (daily)	•	• (daily)	•	•	•
Physical examination	•				•		•	•	
Continuous monitoring with documentation of									
Status hospitalization/ status ICU[c]		Twice daily					•	•	•
Survival status		Twice daily					•	•[n]	
O_2 supplementation (incl. type of ventil.)		Twice daily					•	•	•[p]
Temperature		Twice daily					•		•[p]
Vital signs[r]		Twice daily					•		•[p]
Respiratory rate		Twice daily					•		•[p]
SpO_2		Twice daily					•		•[p]
Score assessment (9-point WHO scale)[b]	•	Once daily (evening)					•	•	•[p]
Vasopressor dose		Once daily (evening)					•	•	
Radiol. confirmation in clinical practice of interst. lung disease[i]		Once daily (evening)					•		
Document confirmation of any new infections[j]		Once daily (evening)					•		
Use of RRT		Once daily (evening)					•	•	• [p]
Use of ECMO		Once daily (evening)					•	•	• [p]

Table 1: Schedule of assessments *(continued)*

Assessments	Screening	Blinded treatment[l]					EoT	EoS	USV
	D-2 to D0[g]	D0[g]		D1- D5	D6	D7 - D13	D14	D28	***SFU***[p]
		Pre	Post					±1 d	
Lab assessments									
Blood biochemistry		•			•		•	•	•[p]
Hematology		•			•		•	•	•[p]
Coagulation[a]		•			•		•	•	
Urinalysis		•			•		•	•	•[p]
Disease markers[a]		•		• (daily)	•	• (daily)	•	•	
Biomarkers[a]		•			•		•	•	
IMU-838 trough levels[a]		•		• (daily)	•		•[o]	•	
SARS-CoV-2 viral load and SARS-CoV-2 status (qualitative)[e]		•		• (Days 2 & 4 only)	•	• (Days 8, 10 & 12 only)	•	•	•[p]
Serology: SARS-CoV-2 antibodies[h]		•			•		•	•	•[p]
Immune cell subtyping *(US only)*[q]		•			•		•	•	
Lab Kits used									
Kit A		•			•		•	•	•[p]
Kit B				• (daily)		• (daily)			
Kit C		•			•		•	•	
Kit PK		•		• (daily)	•		•[o]	•	
Kit D		•		• (daily)	•	• (daily)	•	•	•[p]
Kit E		•			•		•	•	•[p]
Immune cell subtyping (US only)[q]		•			•		•	•	
Safety									
AE assessment	•	▬						•	•
ECG		•	•	• (only Day 3)	•		•	•	
IMP									
IMP administration			▬						
Number of tablets		-	2	1 tablet each morning + evening					
Accountability							•		
SoC treatment	▬								

[a] Needs to be frozen at at least -20° C (-4° F) and sent to the central safety laboratory within 6 weeks.
[b] Clinical status on a 9-category ordinal scale (as proposed by the WHO master protocol)
[c] Including documentation of ICU admission and discharge times.
[d] Existing local lab values obtained within 48 hours of randomization as well as locally obtained screening lab values can be used for assessment of eligibility.

[e] At each time point only 1 nasopharyngeal swab and 1 sputum sample each will be taken. The viral load test will also be used as qualitative test (i.e. may be evaluated as absence or presence of virus in the quantitative SARS-CoV-2 assessments). Samples need to be frozen at at least -20° C (-4° F) and sent to the central virology laboratory within 7 days on dry ice.

[f] Includes: Age≥65; cardiovascular disease (including hypertension), pre-existing pulmonary disease, diabetes, current treatment for malignancy or within the previous 3 years, immunosuppression (due to ongoing use of immunosuppressive drugs or existing disease leading to impaired immune status), body mass index.

[g] Screening, randomization and first IMP administration can be performed the same day (Day 0). If screening is performed on Day 0, treatment will start with the evening dose.

[h] Plasma sample for serology SARS-CoV-2 (IgG and IgA detection) should be frozen at at least -20° C (-4° F) and sent to the central safety laboratory within 6 weeks.

[i] Confirmation of radiographic evidence of pulmonary infiltrates by chest X-ray or CT (only if done within the scope of routine clinical practice).

[j] Confirmation of presence of any new viral or non-viral infection (this is not a protocol-required procedure, only documentation when done within the scope of routine clinical practice). Site of infection and source of culture will be recorded.

[k] As performed during routine clinical practice in the center. Must include white blood cell count, platelet count, total bilirubin, alanine aminotransferase or gamma glutamyl transferase, serum creatinine, for women of childbearing potential: blood pregnancy test, and if the patient has known Gilbert syndrome: indirect [unconjugated] bilirubin.

[l] For assessments, if patients will be discharged from the hospital before Day 14, see *Blinded Treatment period (Day 0 to Day 13) and Day 14 (end-of-treatment)*. *For centers in Bulgaria only: Patients must be hospitalized during the entire treatment period.*

[m] Within 4 days of randomization.

[n] If no EoS visit was performed, information about patient status should be reported on the EoS page in the case report form. If the patient is lost to follow-up, the investigator must contact the patient, the patient's family or the referring physician by phone or email to obtain survival status, or it must be possible to search in registers or publicly available information for these survival data.

[o] Blood sampling must be performed in the morning around the time the morning dose was usually taken by the respective patient.

[p] Safety follow up assessments must be performed regularly (at least once) by phone or email between Day 28/EoS and Day 60 and documented as an unscheduled visit in the eCRF. The patients should be asked to return for an on-site visit if the investigator deems this necessary for follow-up. The assessments not to be done if the visit is performed as a telephone or email contact in the scope of the safety follow up are marked as •[p]

[q] *Optional for centers in the USA only: 2 blood samples will be collected to evaluate immune cell subtypes and immune reactions for future research studies. This will be shipped directly to a US research site and not to the central laboratory. Shipment needs to be done at ambient temperature and immediately the same day after sampling.*

[r] Height and weight only to be measured at D0, pre-dose.

AE = adverse event, CT = computed tomography, cont. = continued, D = day, ECG = electrocardiogram, ECMO = extracorporeal membrane oxygenation, EoS = end-of-study, EoT = end-of-treatment, ICU = intensive care unit, Ig = immunoglobulin, IMP = investigational medicinal product, incl. = including, interst. = interstitial, pre(post) = pre(post) IMP, RRT = renal-replacement therapy, Radiol. = radiological, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SFU = safety follow up, SoC = standard of care, SpO_2 = peripheral capillary oxyhemoglobin saturation, ventil. = ventilation, USV = unscheduled visit, WHO = World Health Organization.

2 Addresses and responsibilities

Sponsor's signatory	Dr Andreas Muehler Chief Medical Officer, Immunic AG Lochhamer Schlag 21 82166 Graefelfing, Germany Office: +49 89 2500 794 64 Mobile: +49 176 7873 8359 Fax: +49 89 2500 794 66 Email: andreas.muehler@imux.com
Coordinating investigator	Prof. Neera Ahuja Stanford University School of Medicine 500 Pasteur Drive Stanford, CA 94305 United States of America Phone: +1 650 497-7304 Fax: +1 650 723-8596 Email: nkahuja@stanford.edu
Drug safety officer and pharmacovigilance services	Dr med. Dipl. Inf. Susanne Kienzle-Horn SCRATCH Pharmacovigilance GmbH & Co. KG Schlossstrasse 25 35510 Butzbach, Germany Phone: +49 6033 74535 50 Fax: +49 6033 74535 59 Email: safety-immunic@scratch-pv.com
Central safety laboratory (including serologic markers and biomarkers)	LKF - Laboratorium für Klinische Forschung GmbH Lise-Meitner-Strasse 25-29 24223 Schwentinental, Germany Phone: +49 4307 8276 0 Fax: +49 4307 8276 79 Email: project@lkf-kiel.de

Central virology laboratory	Europe: Covance Central Laboratory Services Sàrl Rue Moise-Marchines 7 1217 Geneva Switzerland Phone: +41 58 8227000 Fax: +41 58 8226999 USA: Covance Central Laboratory Services LP 8211 SciCor Drive Indianapolis, Indiana 46214, USA Phone: +1 317 273 5307 Web site to order new lab kits: www.covance.com\kitordering

A complete list of trial personnel will be available in the trial master file.

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4 Abbreviations and definition of terms

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
BT	Blinded treatment
CA	Competent authority
cTn	Troponin
CFR	Code of Federal regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRP	C-reactive protein
CYP	Cytochrome P450
DHODH	Dihydroorotate dehydrogenase
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ED_{50}	Effective dose
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EoS	End-of-study
EoT	End-of-treatment
EU	European Union
FA1 (2)	Final analysis Part 1 (Part 2)
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
hCMV	Human cytomegalovirus
HCV	Hepatitis C virus
HIPPA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus(-antigen/antibody)
IA2	Interim analysis of Part 2
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee (IDMC)

IEC	Independent ethics committee
IFNγ	Interferon gamma
IgA(G)	Immunogobulin A(G)
IL	Interleukin
IMP	Investigational medicinal product
INV	Invasive ventilation
IRB	Institutional review board
IWRS	Interactive web-based response system
LDH	Lactate dehydrogenase
MA1	Main analysis of Part 1
NCI-CTCAE	Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OR	Odds ratio
PCT	Prolactin
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol set
RA	Rheumatoid arthritis
RBC	Red blood cells
RNA	Ribonucleic acid
RRT	Renal replacement therapy
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoC	Standard of care
SpO_2	Oxyhemoglobin saturation
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNFα	Tumor necrosis factor alpha
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	Upper limit of normal
URAT1	Urate anion transporter 1
USA	United States of America
WHO	World Health Organization

Drugs

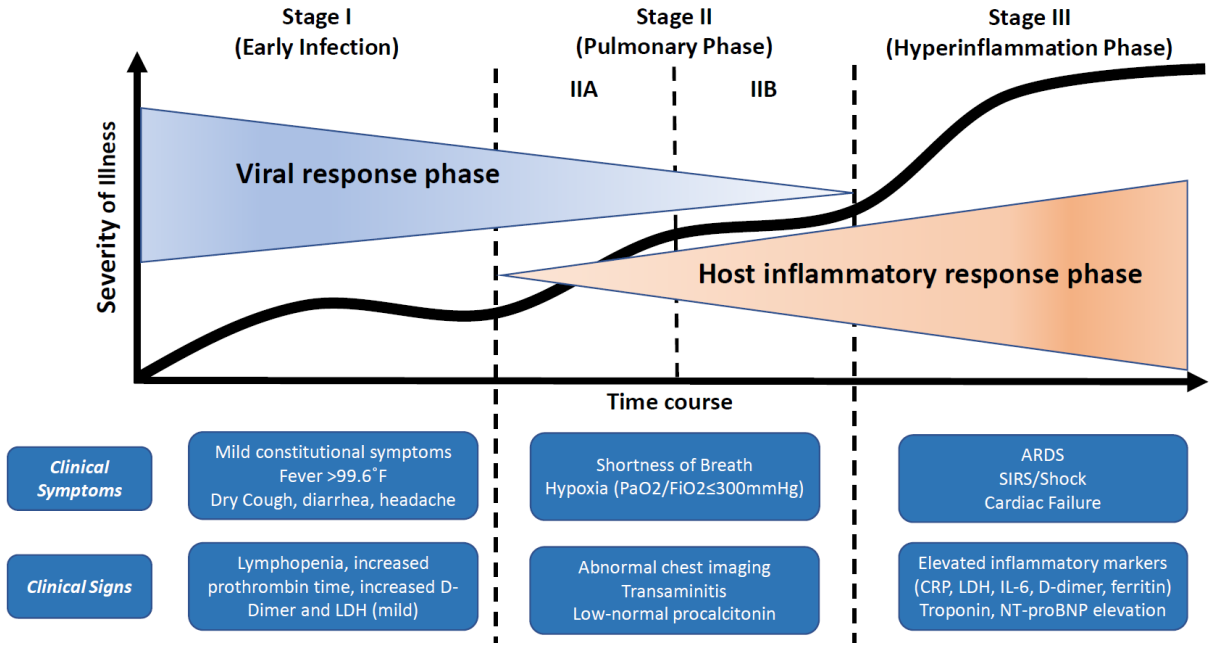
4SC-101	Tablet or capsule formulation containing vidofludimus free acid
IMU-838	Tablet formulation containing vidofludimus calcium

5 Introduction

5.1 Background COVID-19

The World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (causing coronavirus disease 2019, COVID-19) a pandemic on March 11, 2020. [3] Main clinical symptoms include fever, cough, myalgia or fatigue, expectoration, and dyspnea. [4] While most patients do not experience severe symptoms, one meta-analysis found that approximately 18% of cases were severe. [5] Fatality rates are estimated to be approximately 4-7% at this time. [4,5]

Figure 2: Classification of COVID-19: disease states and potential therapeutic targets



Taken from [6].

Two distinct but overlapping pathological pathways appear to be involved in the course of the disease. The first is triggered by the virus itself and the second comprises the host response.

A 3-stage classification of the disease was proposed by Siddigi and Mehra. [6] The initial stage occurs at the time of inoculation and early establishment of the disease. For most people, this involves an incubation period associated with mild and often non-specific symptoms such as malaise, fever and a dry cough. Treatment at this stage is primarily targeted towards symptomatic relief. Should a viable antiviral therapy be proven beneficial, targeting selected patients during this stage may reduce duration of symptoms, minimize contagiousness and prevent progression of severity.

In the second stage of established pulmonary disease, viral multiplication and localized inflammation in the lung is the norm. During this stage, patients develop an interstitial lung disease (viral pneumonia), with cough, fever and possibly hypoxia. Treatment would primarily consist of supportive measures and available antiviral therapies. If hypoxia ensues (Stage IIb), it is likely that patients will progress to requiring mechanical ventilation and, in that situation, the use of anti-inflammatory therapy may be useful.

A minority of COVID-19 patients will undergo transition into the third and most severe stage of illness, which manifests as an extra-pulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation appear to be elevated, including cytokines and interleukin (IL). In this stage, shock, vasoplegia, respiratory failure and even cardiopulmonary collapse are discernable. Systemic organ involvement, even myocarditis, would manifest during this stage. Tailored therapy in Stage III hinges on the use of immunomodulatory agents to reduce systemic inflammation before it overwhelmingly results in multi-organ dysfunction.

5.2 IMU-838

5.2.1 Background

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 has developed a new pharmaceutical form containing the calcium salt of vidofludimus (INNM: vidofludimus calcium) in a new pharmaceutical formulation (tablets containing a specific polymorph).

Both formulations depend on the same active moiety, i.e., vidofludimus which is released from the tablets in the gut and enters the blood stream. Hence, the 2 formulations share the same mechanism of action, pharmacology, and toxicology. Vidofludimus calcium may exhibit, however, superior pharmaceutical properties compared with the former vidofludimus free acid film-coated tablet.

At this time and counting both formulations, more than 500 human subjects and patients have been exposed to the active moiety vidofludimus.

5.2.2 Mode of action

IMU-838 is a small molecule investigational drug (vidofludimus calcium) under Phase 2 development as an oral tablet formulation for the treatment of relapsing-remitting multiple sclerosis, inflammatory bowel disease and other chronic inflammatory and autoimmune diseases.

IMU-838 selectively inhibits the human enzyme dihydroorotate dehydrogenase (DHODH), a key enzyme of pyrimidine *de novo* biosynthesis. Highly metabolically activated cells, such as hyperactivated lymphocytes in chronic inflammatory diseases, malignant transformed cells in cancer as well as virus infected cells, are highly dependent on DHODH. [1] In these cells, the

extraordinary demand of nucleotides cannot be sufficiently supported by recycling of nucleotides and therefore, the de novo synthesis of pyrimidines needs to be activated.

Inhibition of de novo pyrimidine biosynthesis is a well-recognized antiviral mechanism. 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. Therefore, DHODH inhibition ameliorates and blocks the viruses' ability to "hijack" the human host cell mechanisms of ribonucleic acid (RNA) production as a means to virus replication. This is a host cell mechanism with the advantage that it has broad viral activity, is not influenced by resistances or mutations of the virus and can be combined with other antiviral drugs targeting the virus itself. This direct, broad-spectrum antiviral effect has been observed in various virus infected cells, such as influenza virus infections, cytomegalovirus infections and even hemorrhagic fever-causing viruses, such as Lassa virus. Treatment with IMU-838 may also avoid virus reactivation of further clinically relevant viruses.

In addition to its antiviral activity, IMU-838 exhibits strong anti-inflammatory activities by selectively targeting activated lymphocytes, which express DHODH at high levels to satisfy their need for de novo pyrimidine synthesis. Resting lymphocytes and bone marrow cells satisfy their pyrimidine requirements through a DHODH-independent salvage pathway. The metabolic stress secondary to DHODH inhibition leads to a reduction of pro-inflammatory cytokine release including IL-17 (IL-17A and IL-17F) and interferon gamma (IFNγ), and to an increased apoptosis in activated lymphocytes. [2] IMU-838-mediated DHODH inhibition does not induce unselective immunosuppression.

One key advantage of DHODH inhibition is that it primarily targets metabolically active cells, and therefore may not negatively impact "normal" cells in a substantial fashion. In addition, no increased rates of neutropenia or other major antiproliferative effects as compared to placebo have been observed.

IMU-838 is further characterized by a short blood half-life of 30-40 hours making it ideal for once-daily dosing and resulting in only little accumulation after daily dosing (steady state concentrations are reached within 4-8 days with an accumulation factor of 2). Importantly due to the short blood half-life, the wash-out period for IMU-838 is considerably shorter than for teriflunomide.

5.2.3 Non-clinical studies

Pharmacodynamics

Vidofludimus strongly inhibits activated lymphocytes and reduces the release of pro-inflammatory cytokines and other physiologic effects of activated lymphocytes in *in-vivo* studies.

Vidofludimus demonstrated broad-spectrum antiviral activity *in-vitro* at concentrations below therapeutic blood levels achieved in treated patients.

- In cell culture experiments vidofludimus inhibited the viral replication of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV).
- Reverse transcriptase activity and the appearance of the specific HIV antigen p24 was evaluated in human peripheral blood mononuclear cells (seronegative for HIV and hepatitis B virus) that were infected *in vitro* with HIV-191US005 and incubated with various vidofludimus concentrations. These experiments demonstrated a median effective dose (ED_{50}) of vidofludimus of approximately 2 µM.
- In a human hepatoma cell line (Huh7) harboring an HCV sub genomic replicon, vidofludimus reduced replicon levels with a median ED_{50} of 4.64 µM.
- Vidofludimus was active against viruses of the herpes family. In an infection model of human fibroblasts infected with human cytomegalovirus (hCMV), vidofludimus showed an activity of around 7.4 µM. This activity was within the same range of Ganciclovir which is used in clinical practice to treat hCMV.
- Vidofludimus demonstrated activity against mammalian Arena virus infections, the RNA virus causing human hemorrhagic fever diseases like Lassa fever, with an IC_{50} (concentration causing 50% inhibition) of 2.8 µM. In this case, DHODH inhibition mediated effects were independent of IFN signaling.

Based on *in-vitro* data, vidofludimus was primarily metabolized via cytochrome P450 (CYP)2C8 with smaller contributions by CYP2C9. Vidofludimus is primarily eliminated via feces (about 70%).

Vidofludimus mildly to moderately inhibits several transport systems, including the urate anion transporter 1 (URAT1), the breast cancer resistance protein, the organic anion transporters 1 and 3, the organic anion transporting polypeptides 1B1 and 1B3, and the bile salt export pump.

5.2.4 Clinical trials

So far, no clinical trials investigating the antiviral activity of vidofludimus have been performed. However, several studies were or are investigating vidofludimus in the treatment of autoimmune and chronic inflammatory diseases.

Two clinical trials investigated the beneficial effects of 4SC-101, the previous vidofludimus free acid formulation, in patients with rheumatoid arthritis (RA). 4SC-101 improved various clinical parameters versus placebo. A pronounced effect was observed for inflammatory parameters.

In a small Phase 2 trial in patients with corticosteroid-dependent inflammatory bowel disease (Crohn's disease and ulcerative colitis), 4SC-101 showed beneficial effects in the remission

maintenance therapy. Compared with historical placebo data, 4SC-101 treatment showed a significantly higher response rate (88.5% total response) as well as a corticosteroid sparing effect.

No 4SC-101-associated clinically significant adverse reactions were observed at doses of <70 mg once daily including the potential target organs liver and kidney as identified in non-clinical or early clinical trials. At higher 4SC-101 doses (>70 mg/day or single doses of 210 mg) potential drug-related increases of red blood cells (RBC) in urine and hematurias were observed (see also Section 8.3).

Two Phase 1 clinical trials were performed for calcium vidofludimus (IMU-838). In Trial P1-IMU-838-SAD, doses from 10 to 40 mg IMU-838 resulted in dose-linear blood pharmacokinetics (PK) under fasted conditions. For the 30 mg dose (the dose expected to be closest to an effective dose), the terminal plasma half-life was approximately 40 hours and the median concentration peaked at 5 hours. Comparing single dosing of 10 mg under fasted and fed conditions, no detrimental effect of food intake was found. Single oral doses of 10 to 40 mg IMU-838 were well tolerated. No adverse events (AEs) of e.g., hematuria or clinically significant RBC in urine high were observed in that clinical trial.

In Trial P1-IMU-838-MAD, repeated oral dosing of IMU-838 over 14 days in doses from 30 to 50 mg resulted in dose-proportional blood PK under fasted conditions. Geometric mean half-life at steady state ranged from 28.6 to 30.4 hours. Overall, median peak concentration following multiple oral doses of IMU-838 occurred between 2 to 3 hours after the first and after repeated dosing. Steady-state levels were reached within about 4 days for 25 mg IMU-838, within 6-8 days for 30 mg, within about 6 days for 40 mg, and within about 8 days for 50 mg IMU-838. Repeated once-daily oral doses of 30 to 50 mg IMU-838 over 14 consecutive days were well tolerated. Mild or moderate treatment-emergent adverse events (TEAEs) were reported by 31 subjects (59.6%); overall 53 TEAEs, reported by 29 subjects (55.8%) were considered drug-related. The number of subjects with drug-related TEAEs or the number of drug-related TEAEs did not increase with increasing dose.

Most individual laboratory values were within the normal ranges. There were no clinically relevant differences between pre- and post-dose assessments and between the treatment groups for any parameter.

Currently ongoing studies with IMU-838 include 2 double-blind, randomized, placebo-controlled Phase 2 trials in patients with ulcerative colitis (CALDOSE-1) and relapsing-remitting multiple sclerosis (EMPHASIS). The primary objective of the ulcerative colitis trial is to determine the optimal dose of IMU-838 to induce symptomatic remission and endoscopic response in patients with moderate-to-severe disease. The primary objective of the multiple sclerosis trial is to evaluate the efficacy of IMU-838 based on magnetic resonance imaging assessments in the treatment of relapsing-remitting multiple sclerosis. Results of an interim analysis of the ulcerative colitis trial,

analyzed by an unblinded independent Data Review Committee showed that none of the doses used (10 mg, 30 mg, or 45 mg) was likely ineffective or intolerable. In addition, there is an ongoing open-label investigator-sponsored trial using IMU-838 in patients with progressive sclerosing cholangitis conducted in the USA under an Investigator IND.

5.2.5 Safety of IMU-838

At this time and counting both formulations, more than 500 human subjects and patients have been exposed to the active moiety of IMU-838, i.e., vidofludimus. Of these, 299 were dosed with 4SC-101 and approximately 360 with IMU-838 (some of the studies are still blinded and total exposure to IMU-838 can therefore only be estimated).

The safety analysis of all exposed subjects provided the following findings:

- No deaths
- No serious adverse event (SAE) during Phase 1 with IMU-838
- The most frequent AEs for IMU-838 during Phase 1 were:
    - Headache
    - Flatulence
    - Common cold
    - Positive urine dipstick for hemoglobin

IMU-838 is a selective DHODH inhibitor and did not inhibit any kinase (of a panel of over 100 tested protein kinases) at blood concentrations that are found at therapeutic dose levels. However, IMU-838 inhibits organic anion transporters such as URAT1, which potentially could affect renal uric acid elimination.

In conclusion, IMU-838 is expected to have a favorable safety profile, as in more than 400 patients (with RA, multiple sclerosis, or inflammatory bowel disease) or volunteers no increased events of diarrhea, nausea, alopecia or headache as well as no increases in abnormal liver function tests were observed.

5.3 Rationale for the trial

Acute viral infections, such as influenza virus, Ebola virus, and SARS-CoV-2 are an increasing and probably lasting health risk. [7] Broad-spectrum antivirals are clinically needed for the effective control of emerging and re-emerging viral infectious diseases. [9] However, besides intensive efforts to find therapeutic antiviral agents to manage such emergencies, reports on specific and effective drugs or vaccines with low toxicity are rare. [8] Thus, currently, there are no effective treatments against the new coronavirus SARS-CoV-2.

Literature data

Strong activity of DHODH inhibitors against SARS-CoV-2 *in vitro* were recently reported by Xiong et al. [9] However, established DHODH inhibitors show either an unfavorable PK profile (leflunomide/teriflunomide) or intolerable toxicity (leflunomide/Brequinar) and thus are not suitable as acute antiviral treatments. New DHODH inhibitors seem promising, although for most no animal or human safety data are available.

Xiong et al. [9] also demonstrated that a combination of DHODH inhibitors with antiviral drugs may improve therapeutic effects. Direct-acting antivirals, which target the viral replication cycle, are primarily effective in the early phase of infection while DHODH inhibitors which target a host cell factor, may also be effective in middle-to-late phases of infection or in patients with advanced respiratory disease.

DHODH inhibition selectively targets activated inflammatory and virus infected cells because normally growing cells are not substantially affected (see Section 5.2.2). For normally dividing cells, DHODH inhibition does not produce general immunosuppression. It was shown for teriflunomide that patients can be even vaccinated under therapy. [10, 11] DHODH inhibition by IMU-838 did not suppress bone marrow cells or inhibit fast-growing cells. In preclinical and clinical studies, IMU-838 did not show any off-target effects, such as neutropenia, diarrhea or alopecia, at rates that were above placebo.

A strong antiviral effect of DHODH inhibitors was described for several RNA and deoxyribonucleic acid viruses including Ebola [12,13], HIV [14], HCV [14], hCMV [15,16] and Influenza [14] viruses. While DHODH inhibitors are effective up to 12-16 hours after infection in *in-vitro* assays, other antiviral drugs can inhibit viral infection only up to 4 hours. [14,17]. DHODH inhibitors show a direct and an indirect antiviral effect both of which are linked to blocking pyrimidine de novo synthesis. In the direct pathway, the reduction of pyrimidine neosynthesis interferes with the viral transcription and replication. [14] However, the main antiviral effect might rather be an indirect effect via the induction or amplification of interferon-stimulated genes due to the reduced pyrimidine synthesis. [18] A large fraction of these genes plays a role in the host innate immune defense to viruses. While these genes are normally induced by interferons, the upregulation of these genes by DHODH inhibitors is independent of interferons. [12,18-20]

Antiviral activity of IMU-838 against SARS-CoV-2

Antiviral activity against SARS-CoV-2 of IMU-838 was investigated *in-vitro* in Vero 76 cells in a cytopathic effect assay. The virus was prepared in test media (Minimum Essential Media with 2% fetal bovine serum and gentamicin) to achieve the lowest possible multiplicity of infection that would yield >80% cytopathic effect within 5 days. Plates were infected prior to preparation and addition of compounds. IMU-838 was dissolved in dimethylsulfoxide to achieve a 100 mM stock and was serially diluted two-fold in media and added to the 80-100% confluent cell layer in triplicates, reaching a final concentration in the well starting from 100 µM down to 0.78 µM.

Controls in infected cells were M128533 (a protease inhibitor) as positive control and no treatment as negative control. The positive control performed as expected.

IMU-838 exhibited antiviral activity with an EC_{50} (concentration that prevents 50% of virus induced cell death in virus infected cells) of 5.7 µM. For reference, the average trough levels of IMU-838 at steady state conditions is expected to be approximately 17 µM using the dosing regimen of 45 mg IMU-838 proposed for this trial.

Conclusion

Based on these data and the pharmacodynamics of vidofludimus, IMU-838 may represent a novel and efficacious oral treatment option for COVID-19 combining a broad antiviral activity with a selective anti-inflammatory effect. It is also important that IMU-838 is not known to cause any neutropenia for a patient population where decrease of neutrophils and lymphocytes is a critical feature of the disease.

6 Investigators, trial administrative structure, and committees

The clinical trial is funded by Immunic AG and it is planned to include about 10 to 45 centers in the European Union, Bosnia and Herzegovina, Moldova, North Macedonia, Russia, Ukraine, and USA (and as back up countries: Croatia and Serbia). Prof. Neera Ahuja, Stanford University, School of Medicine will be the coordinating investigator.

The Sponsor will reserve the right to define maximum number of patients per site and country to ensure a balance per site and country regarding enrolled patients. For Part 1, the number of patients per center is limited to 100 patients, and the number of patients per country is limited to 160 patients. These limits may be re-evaluated if the trial is expanded into Part 2.

The Sponsor, Immunic AG, will be responsible for the overall supervision and administration of the trial. Data management, statistical analysis and medical writing services will be done by FGK Clinical Research GmbH, München, Germany (a contract research organization [CRO]). Further vendors include:

- LKF - Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany: central clinical safety laboratory
- SCRATCH Pharmacovigilance GmbH & Co. KG, Butzbach, Germany: pharmacovigilance services.
- Covance Central Laboratory Services, Geneva, Switzerland and Indiana, USA: central virology laboratory

Outside vendors will also be used for global and local project management, monitoring services, pharmacokinetics and IMP labeling, packaging, and distribution.

An **Independent Data Monitoring Committee (IDMC)** will be established to safeguard the interests of trial participants and to provide recommendations on trial conduct and sample size (for more details refer to Section 18). The IDMC will also fulfill the designated functions of a Data Safety Monitoring Board.

Addresses and telephone numbers of main responsible parties involved in the conduct of the trial are provided in Section 2.

7 Trial objectives and endpoints

Objective	Endpoint
Primary	
• To evaluate the efficacy of IMU-838 plus investigator's choice of standard of care therapy (SoC) vs placebo plus SoC in the treatment of coronavirus disease 2019 (COVID-19) based on the need for invasive ventilation (INV) up to 28 days	• Proportion of patients without any need* for INV until end-of-study (EoS)
Key secondary	
• To evaluate the efficacy of IMU-838 (+SoC) vs placebo (+SoC) in the treatment of COVID-19 based on surviving patients without respiratory failure, the duration of hospitalization in intensive care unit (ICU) and all-cause mortality up to 28 days	• Proportion of patients surviving without respiratory failure (defined as any need of ICU, INV, high-flow oxygen or extracorporeal membrane oxygenation [ECMO*] until EoS) • Duration of ICU treatment until EoS • 28-day all-cause mortality

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary	
Efficacy	

• To evaluate the efficacy of IMU-838 (+SoC) vs placebo (+SoC) in the treatment of COVID-19 based on a variety of further variables and time points (e.g., clinical status, renal impairment, oxygenation, hospitalization, concomitant vasoactive treatments, clinical recovery)	• Time to clinical improvement, defined as the time from first dose of investigational medicinal product (IMP) to an improvement of at least 2 points on the WHO 9-category ordinal scale [21], or live discharge from hospital without oxygen supplementation, whichever comes first
	• Duration of hospitalization (*for US sites only*: or treatment in special outpatient setting in lieu of hospitalization due to resource restraints)
	• Proportion of patients
	  • free of renal-replacement therapy (RRT)* until EoS
	  • free of ECMO* until EoS
	  • free of INV until Days 6 and 14*
	  • free of RRT until Days 6 and 14*
	  • free of ECMO until Days 6 and 14*
	  • with improvement of at least 2 points (from randomization) on the 9-category WHO ordinal scale [21] on Days 6, 14, and 28

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary *(continued)*	

Efficacy *(continued)*	• Proportion of patients
	  • with auxiliary oxygen therapy* (including all types of oxygen therapy) until Days 6, 14, and 28
	  • with clinical recovery defined as
	  • Axillary temperature ≤36.6 °C, or oral temperature ≤37.2 °C, or rectal or tympanic temperature ≤37.8 °C; and
	  • Respiratory frequency ≤24 times/min without oxygen inhalation; and
	  • Oxygen saturation ≥98% without oxygen inhalation
	  • With clinical improvement, defined as an improvement of at least 2 points on the WHO 9 category ordinal scale [21], or live discharge from hospital without oxygen supplementation, whichever comes first
	• Change in daily clinical patient status on the WHO 9-category ordinal scale [21]
	• Duration of INV
	• Duration of ECMO
	• Duration of RRT
	• Duration of auxiliary oxygen therapy (including all types of oxygen therapy)
	• Duration of hospitalization for survivors
	• Rate of ICU* admission until Days 6, 14, and 28
	• Hospital-free days

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary *(continued)*	
Efficacy *(continued)*	• Time from IMP treatment initiation to death • Time to first prescription of INV • Time to first prescription of RRT • Time to first prescription of ECMO • Time to first prescription of INV, RRT, and ECMO • Time to ICU admission • Cumulative dose of vasoactive therapies and days (daily until Day 14) with vasoactive therapies (until Day 14) • Time to clinical recovery
Pharmacokinetics	
To evaluate trough plasma levels of IMU-838	• Morning trough plasma levels of IMU-838 on Days 0, 1 through 6, 14, and 28 • Correlation of trough levels (quartiles) to selected clinical outcomes
Safety	
To evaluate safety and tolerability of IMU-838	• AEs and SAEs • Vital signs • Clinical laboratory parameters (blood chemistry, hematology, and urinalysis) • Electrocardiogram (ECG) parameters • Temperature

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary *(continued)*	
Disease markers	
To explore blood levels of disease markers	• D-dimer • Lactate dehydrogenase (LDH) • C-reactive protein (CRP) • Troponin I (cTn) • Procalcitonin (PCT) • Correlation of disease markers to selected clinical outcomes The analysis for all endpoints includes absolute values and absolute change from Baseline over time; for LDH log transformed values will be used.
Virologic markers, biomarkers, and serologic markers	***Virologic markers***

To explore viral titers, measures of viral virulence and inflammatory markers	• Severe Acute Respiratory Syndrome Coronavirus Virus (SARS-CoV-2) mean viral load - log10 copies in spontaneous sputum and nasopharyngeal swab samples
	  • Decrease of SARS-CoV-2 viral load
	  • Time course of SARS-CoV-2 viral load
	• Qualitative virologic clearance in spontaneous sputum and nasopharyngeal swab samples (= 2 consecutive negative SARS-CoV-2 reverse transcriptase polymerase chain reaction [RT-PC] tests at least 24 hours apart)
	• Rate of conversion to a negative SARS-CoV-2 (qualitative) test on Days 6, 14 and 28
	• Time to conversion to a negative SARS-CoV-2 (qualitative) test

Trial objectives and endpoints *(continued)*

Objective	Endpoint
Secondary ***(continued)***	

Virologic markers, biomarkers, and serologic markers (continued)	***Biomarkers***
	• Interleukin (IL)-17, IL-1ß, IL-6, interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα)
	Serologic markers
	• IgA and IgG antibodies against SARS-CoV-2
	  • Time to appearance of IgA and/or IgG antibodies
	  • Proportion of patients with IgA and/or IgG antibodies on Days 6, 14, and 28
	
	The analysis for all endpoints includes absolute values, relative and absolute change from Baseline over time, if applicable.

* Patients who are assessed by the investigator to have a medical need of the respective treatment (i.e., INV, ECMO, RRT, ICU, hospitalization) but do not receive these treatments for other reasons will be counted for this endpoint.

8 Trial design and design rationale

8.1 Overall trial design

The trial consists of 2 independent parts: a Phase 2 proof-of-activity phase (Part 1) with the option to continue enrollment (without interruption) to a confirmatory Phase 3 part (Expansion Phase, Part 2). Part 2 will only be started after results from main analysis of Part 1 (MA1) has been analyzed and results indicate activity of IMU-838 in COVID-19.

Both parts follow a multicenter, double-blind, placebo-controlled, randomized, parallel-group design to evaluate the safety and efficacy of IMU-838 as addition to investigator's choice of SoC treatment in patients with COVID-19. Eligible patients will be centrally randomized 1:1 to twice-daily (BID) oral 22.5 mg IMU-838 (45 mg/day + SoC) or placebo (+ SoC). Randomization will be stratified by age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals).

Part 1 and Part 2 will be analyzed independently from each other.

The unblinded main analysis of Part 1 (MA1) will be performed after approximately 200 patients have completed Day 28/EoS, either as scheduled or prematurely, while enrollment continues. Based on the MA1 results the trial may be expanded into Part 2, if activity of IMU-838 is observed, or stopped, if no activity of IMU-838 or safety issues are observed. A further 30 patients are expected to be enrolled and treated in a double-blind manner until the results of the MA1 are available (when no activity of IMU-838 was found) or until the enrollment in Part 2 has commenced (if MA1 indicated proof-of-activity). A final analysis of Part 1 (FA1) will be performed after completion of Part 1, using all enrolled patients, i.e. about 230 patients.

In addition, an early safety analysis will be performed and evaluated by an Independent Data Monitoring Committee (IDMC) after 30 patients in Part 1 have completed Day 28 to assess unblinded safety data.

For US centers only: Enrollment into the trial will be paused after these 30 patients have reached Day 28 until the IDMC has evaluated safety stopping criteria. If the trial safety stopping criteria are not fulfilled, the enrollment in the trial will be resumed and the IDMC will continue with a full review of the available safety data.

Further safety analyses can be initiated at any time by the IDMC or Sponsor when new safety signals are identified within this or other trials of IMU-838.

Apart from assessing the IMU-838 activity, the MA1 will also be used to establish the sample size, endpoint selection as well as possible other trial adjustments (e.g. changes for study conduct due safety or changes in the study population) for Part 2. The IDMC will also review MA1 results and act as a consultative capacity to assist the Sponsor in sample size calculations, endpoint selection and other adjustments for Part 2. The final design of Part 2 will be submitted as protocol amendment to regulatory authorities, and enrollment in Part 2 will only start after approval of the amended Part 2 protocol.

Part 2 of the trial, if performed, will use an adaptive sequential design with the IDMC reviewing unblinded data in an interim analysis during Part 2 (IA2) and providing the Sponsor with recommendations regarding modifications of sample size and trial conduct. The IA2 will be performed after approximately 50% of patients of the Part 2 sample size have been enrolled to adjust sample size and other trial features if needed. The final analysis of Part 2 (FA2) will be done after all patients have completed Part 2.

Screening

Patients can be screened for a maximum of 2 days (from Day -2 to Day 0) and eligible patients will be randomized on Day 0 and treated with IMP + SoC for 14 days. It is encouraged to screen potential participants immediately at the day of hospitalization (including informed consent, assessment of inclusion/exclusion criteria, screening laboratory tests all done locally, assessment of clinical and blood gas criteria) and randomize patients on the same day (Day 0). To assess

eligibility criteria, existing local laboratory values obtained within 48 hours of randomization can also be used, except for testing of positive status of SARS-CoV-2 infection where a 4-day window is allowed.

IMP administration should start as quickly as possible after randomization and first IMP dose intended to be given in the evening of the screening day (Day 0).

Blinded Treatment period (Day 0 to Day 13) and Day 14 (end-of-treatment)

The first dose of IMP (2 tablets) should always be given on Day 0 (allowed range for first dose: 12:00 noon on Day 0 to 02:00 a.m.). All further IMP doses are 1 tablet each in the morning and evening. For details of IMP administration see Section 11.1.5. Information about the status and patient care are continuously obtained and documented once or twice daily (see Table 3). Further examinations and tests, laboratory parameters, biomarkers, disease markers, and virologic parameters are to be assessed as outlined in Table 3.

After the last IMP dose in the evening of Day 13, the end-of-treatment assessments will be done on Day 14 (see Table 3). Blood sampling for IMU-838 trough values must be performed in the morning around the time the morning dose was usually taken by the respective patient. Patients may then continue to receive SoC without any further restrictions on concomitant medications as during the 14-day BT period (see Section 11.2.1 and IMP-related exclusion criteria).

The assessments to be performed in case of hospital discharge before Day 14 are described in Section 12.3. *For centers in Bulgaria only: Patients must be hospitalized during the entire treatment period i.e., from Day 0 to Day 14.*

Day 28 Visit (EoS)

The patient should return for the final trial visit on Day 28 (EoS). If IMP is prematurely discontinued for any reason, the EoS visit should always be conducted on Day 28 and no earlier EoS should be performed. If patients withdraw from IMP prematurely, they should be encouraged to allow the EoS visit as part of the follow-up. If the patient dies during the trial, the investigator should indicate that this visit was not performed. However, even if no EoS visit was performed, information about patient status should be reported on the EoS page in the case report form. If the patient refuses any EoS visit or the patient is lost to follow-up, it is permissive in this trial that the investigator contacts the patient, the family of the patient or the referring physician by phone or email to obtain status of life information, or is able to search in registers or publicly available information for such status of life information.

Safety follow up

Following the Day 28/EoS examination, the investigator will contact the patient regularly (at least once) by phone or email to obtain health data until Day 60. This should be documented as unscheduled visit in the eCRF. The patient should be asked to return for an on-site visit if the investigator deems this necessary for follow-up.

8.2 Trial design rationale

This is a placebo-controlled, double-blind, randomized trial, which is scientifically the strongest design. To mitigate any ethical concerns that may arise with the use of placebo, IMU-838 is evaluated as add-on therapy to SoC treatment as recommended by the WHO. [21]

A treatment duration of 14 days was chosen for this trial as similar drug treatments for COVID-19 had shown treatment effects within this treatment duration. [22]

In addition, large studies from the Wuhan region of China had shown that the disease will lead to recovery or to death within an average of 22 days [23], thus an overall trial duration of 4 weeks seems appropriate.

The distribution of male and female patients will be according to the natural distribution within the trial population, expecting more male than female patients. No corrective measures will be taken. However, as COVID-19 appears to affect women and men differently, the endpoints will be analyzed for sex-specific differences. This will be done without formal statistical testing.

The primary endpoint is the proportion of patients without any need for INV until EoS. The most prominent feature of severe COVID-19 disease is the development of an interstitial lung disease that leads to hypoxia and respiratory failure which is a major contributor to mortality in this disease. Severely ill patients require invasive ventilation to have a chance for survival and INV causes a critical strain on healthcare resources. For these reasons, the avoidance of invasive ventilation should be the primary goal of drug therapy in hospitalized COVID-19 patients.

The clinical status will be assessed based on the WHO proposed disease severity scale. [21]

To achieve balance across the key baseline factors participant inclusion will be stratified by age and use of antiviral therapy.

An IDMC is established to allow an independent assessment of safety and efficacy data to assure that trial participants are not exposed to unnecessary or unreasonable risks because of their trial participation, and to ensure scientific integrity of the trial.

8.3 Risk-benefit assessment

Risks

Based on pre-clinical and clinical studies with the precursor drug 4SC-101, the single and multiple dose Phase 1 studies with IMU-838, and ongoing clinical trials with IMU-838 no serious adverse reactions are expected with IMU-838 at doses of <70 mg once daily.

In clinical studies with 4SC-101, including 486 subjects of whom 299 received 4SC-101, no drug-associated clinically relevant adverse reactions were observed at doses of <70 mg once daily. This included the potential target organs liver and kidney identified in animals or during early clinical

trials. In a large placebo-controlled, randomized clinical trial of 4SC-101 in patients with RA, the AE profile of 35 mg/day 4SC-101 was similar to the AE profile of placebo. [24] No increased rate of infections and infestations were seen in the treatment arm as compared to placebo in the same trial. Additionally, no signal for hepatotoxicity was observed.

At high 4SC-101 doses (≥70 mg/day or single doses of ≥210 mg) potential drug-related decreases in blood uric acid and increases in urine RBC were observed, in very rare cases presenting as symptomatic hematuria during the first days of treatment. Laboratory findings were consistent with post-renal events and *de novo* precipitates in the urinary tract. However, no cases of symptomatic hematuria were seen at daily doses of 35 mg 4SC-101, the highest therapeutic dose used in previous clinical trials.

The underlying mechanism leading to increased RBC in urine appears to be an increased uric acid elimination during the initial days after drug administration. By inhibition of the urate transport system URAT1, IMU-838 may decrease the tubular re-uptake of uric acid in kidneys, leading to an increase in the urinary excretion of uric acid. Increased urine uric acid may in turn result in microcrystallization of uric acid in acidic urine and may lead to the occurrence of RBC in urine. Although this may not regularly lead to clinically relevant AEs or laboratory abnormalities at therapeutic doses, it may be important for patients with risk factors (including increased serum uric acid or higher propensity for urinary concrements) or in patients with a history of gout.

Thus, for patients with a history of nephrolithiasis, any underlying condition with a strong association of nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia, or history or clinical diagnosis of gout the protocol recommends a supplementation of either 2 x 750 mg oral bicarbonate (daily) or 2 tablets of Neoralit SR three times daily during meals or half an hour after meals for these patients (Section 15.1.7).

During clinical trials using the previous formulation 4SC-101, a single SAE of hepatitis was reported in a patient with Gilbert syndrome receiving 35 mg 4SC-101. Gilbert syndrome is a genetic disease characterized by a 70–80% reduction in the glucoronidation activity of uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1). IMU-838 is a moderate inhibitor of UGT1A1 which may have contributed to this AE. Patients with an elevation of total bilirubin above 2 x upper limit of normal (ULN) will therefore be excluded from this clinical trial.

A thorough analysis of the clinical data did not confirm a potential adverse effect of vidofludimus on liver function tests in patients other than those with Gilbert syndrome. However, patients with elevated alanine aminotransferase (ALT) and/or gamma glutamyl transferase (GGT) (>5 x ULN) will be excluded from trial participation and liver enzymes and bilirubin will be regularly assessed throughout the trial.

For more information please refer to the investigator's brochure.

Benefits

IMU-838 has currently not been clinically tested for its antiviral activity. However, beneficial effects are expected, based on pre-clinical findings demonstrating a broad-spectrum antiviral activity of IMU-838 *in-vitro* at concentrations that are below the therapeutic blood levels observed in treated patients. The antiviral activity of DHODH inhibition is further substantiated by numerous studies reported in the literature (see Section 5.3).

IMU-838 as a DHODH inhibitor exhibits many advantages compared to other antiviral treatment options: It targets host cells which provides broad-spectrum antiviral activity, blocks viral replication and overcomes potential viral mutagenesis. It may as well act directly on the virus replication in the infected cells. Targeting virulence factors, such as cytokines, would specifically lead to a benefit for more severe cases. DHODH inhibition is also selective towards activated and infected cells and therefore does not cause broad and difficult-to-manage side effects seen with antimetabolites.

Risk management

Risk minimization procedures are implemented for this trial to minimize and assess potential risks to participating patients. These include, but are not limited to:

- specific inclusion and exclusion criteria which ensure that patients who present with characteristics that may increase the risk for an adverse outcome are excluded
- close monitoring of patients with Gilbert syndrome
- a recommendation that patients with an increased risk for hematuria are supplemented with oral bicarbonate or oral Neoralit SR (see Section 15.1.7)
- regular monitoring of liver enzymes

In addition, the functions of a Data Safety Monitoring Board to periodically review and evaluate accumulated trial data for participant safety, trial conduct and progress, and, when appropriate, make recommendations to the Sponsor concerning the continuation, modification, or termination of the trial will be fulfilled by the IDMC.

Risk-benefit assessment

Considering the safety data available and the exposure of the active moiety in more than 500 human subjects and patients, the implemented risk minimization measures, the positive data in *in-vitro* assays, the promising data on antiviral effects of DHODH inhibitors in the literature, the expected benefits in the target population, and the urgent medical need for further treatment in SARS-CoV-2 induced infections, the benefit-risk evaluation is considered favorable.

9 Patient selection

9.1 Sample size

Part 1: MA1 approximately 200 patients; an additional 30 patients are expected (total 230 patients) until completion of Part 1

Part 2: determined based on the MA1, if applicable

For sample size calculation see Section 16.1.

9.2 Inclusion criteria

1. Male or female patients at least 18 years old (may only be extended to include children 12 years or older after MA1 following approval of a protocol amendment)
2. Admitted to the hospital or other medical in-patient treatment facility for treatment of COVID-19

   The hospitalization needs to be for medical reasons (treatment of COVID-19 disease) and cannot be for social reasons or due to housing insecurity.

   For US sites only: If the investigator would commonly hospitalize the patient but for healthcare resource reasons decides to treat the patient in a specially designed out-patient setting, then such patients are also allowed to enter the trial (please note that in this case the patient would be counted as clinical status category 3). The investigator then must assure that the patient has at least a twice daily assessment by qualified trial personnel and all laboratory assessments can be adequately performed as per protocol. The Sponsor reserves the right to discontinue this option via administrative letter if such assurances cannot be met by any site.
3. SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) test in a nasopharyngeal, oropharyngeal or respiratory sample at ≤4 days before randomization
4. Moderate COVID-19 disease defined as fulfilling clinical status category 3 or 4 on the WHO 9-point ordinal scale [21]:
   - Category 3: Hospitalized (see note above for US only), virus-positive, no oxygen therapy with the following condition:
     - The hospitalization needs to be for medical reasons (treatment of COVID-19 disease) and cannot be for social reasons or due to housing insecurity
   - Category 4: Hospitalized, virus-positive, oxygen by mask or nasal prongs (excluding high-flow oxygen therapy) with the following conditions:

- Peripheral capillary oxyhemoglobin saturation (SpO_2) >92% at maximum of 6 liters oxygen flow per minute
- Stable respiratory rate ≤30 breaths/min at maximum of 6 liters oxygen flow per minute

5. Presence of at least 1 symptom characteristic for COVID-19 disease i.e., fever, cough or respiratory distress
6. Willingness and ability to comply with the protocol
7. Written informed consent given prior to any trial-related procedure
8. For women of childbearing potential: Application of a highly effective method of birth control (failure rate less than 1% per year when used consistently and correctly) together with a barrier method between trial consent and 30 days after the last intake of the IMP.

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

   - oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation
   - oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation
   - intrauterine device or intrauterine hormone-releasing system
   - bilateral tubal occlusion
   - vasectomized 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)
   - 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 no acceptable methods of contraception)

   Barrier methods of contraception include:

   - Condom
   - Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository

9. Male patients must agree not to father a child or to donate sperm starting at Screening, throughout the clinical trial and for 30 days after the last intake of the IMP. Male patients must also
   - abstain from sexual intercourse with a female partner (acceptable only if it is the patient's usual form of birth control/lifestyle choice), or

- use adequate barrier contraception during treatment with the IMP and until at least 30 days after the last intake of the IMP, and
- if they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method as outlined in inclusion criterion 8
- if they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP

9.3 Exclusion criteria

A patient will not be eligible for inclusion if any of the following criteria applies:

Underlying disease-related exclusion criteria

1. Involvement in the trial is not in the patient's best interest according to the investigator's decision, including the presence of any condition that would, in the assessment of the investigator, not allow the protocol to be followed safely

   Note: The investigator should particularly consider exclusion of patients at increased risk for serious or fatal AEs in case of worsening of the pulmonary perfusion. This includes, but is not limited to, pre-existing pulmonary hypertension, severe chronic respiratory disease, severely increased risk for thromboembolic complications and moderate to severe left ventricular ejection fraction (LVEF) dysfunction. In addition, other known risk factors of highest risk of mortality in COVID-19 patients should be considered.

2. Presence of respiratory failure, shock, and/or combined failure of other organs that requires ICU monitoring in the near foreseeable future
3. Critical patients whose expected survival time <48-72 hours
4. Presence of the following laboratory values at screening:
   - White blood cell count (WBC) <1.0 x 10^9/L
   - Platelet count <100,000/mm³ (<100 x 10^9/L)
   - Total bilirubin>2 x ULN
   - Alanine aminotransferase (ALT) or gamma glutamyl transferase (GGT) >5 x ULN
5. Participation in any other interventional clinical trial
6. Hospitalization primarily for reasons other than COVID-19 (including primarily for concomitant conditions during ongoing SARS-CoV-2 infection)
7. Anticipated transport to a different hospital or institution, in particular when such transport is anticipated for pending ECMO or RRT treatment
8. Clinical suspicion of a bacterial superinfection at Screening

IMP-related exclusion criteria

9. Patients who cannot take drugs orally

10. Allergic or hypersensitive to the IMP or any of the ingredients
11. Use of the following concomitant medications is prohibited from Screening to end of treatment with IMP in this trial (up to Day 14) if not indicated otherwise in this protocol:
    - Concurrent use of any mycophenolate mofetil or of methotrexate exceeding 17.5 mg weekly
    - Any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic™) as well as uricosuric drugs such as probenecid
    - Current treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafenib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
    - Any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs
    - Use of rosuvastatin at daily doses higher than 10 mg
    - Arbidol and Colchicine
    - Any use of other DHODH inhibitors, including teriflunomide (Aubagio™) or leflunomide (Arava™)
    - Chloroquine and Hydroxychloroquine during the entire trial unless taken for indicated use before entering the trial
12. Patients with clinically relevant conditions leading to hyperuricemia
13. Use of any investigational product within 8 weeks or 5x the respective half-life before the date of informed consent, whichever is longer, and throughout the duration of the trial

General exclusion criteria

14. Patients who have a "do not intubate" or "do not resuscitate" order (unless the patient waives in writing this order and will allow intubation for the duration of the trial period)
15. Patients with pre-existing end-stage liver disease (Child Pugh B and C score)
16. Patients with known Gilbert syndrome (unless their indirect [unconjugated] bilirubin level is confirmed to be <1.2 x ULN, i.e. <1.1 mg/dL)
17. Patients with known acute or clinically relevant chronic renal failure, patients currently on dialysis, as well as patients with an estimated glomerular filtration rate value <30 mL/min/1.73 m² body surface area according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults (or the Schwartz bedside equation for children and adolescents, if applicable)
18. 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.

19. Legal incapacity, limited legal capacity, or any other condition that makes the patient unable to provide consent for the trial
20. Pregnant or breastfeeding
21. An employee of an investigator or Sponsor or an immediate relative of an investigator or Sponsor
22. Patients institutionalized due to judicial order

10 Randomization, blinding and unblinding procedures

10.1 Blinding

Trial participants, the investigator and all other personnel directly involved in the conduct of the trial will be blinded to the individual treatment assignments.

For the MA1 the IDMC and Sponsor will be unblinded, the blind will, however, be kept for patients and investigators until FA1.

To maintain the blind, IMU-838 and placebo tablets will have identical appearance, shape and color, and will have identical labeling and packaging. To minimize the potential for bias, treatment randomization information will be kept confidential by the responsible personnel and will not be released to investigators, other trial center personnel, or the Sponsor's designee(s).

10.2 Emergency unblinding

The premature breaking of the blind will be restricted to emergency cases in which knowledge of the administered drug is necessary for treatment of clinically significant AEs. Whenever possible but not required in emergency situations, the investigator must contact the Sponsor or the medical monitor before breaking the blind and evaluate if the knowledge of the administered drug would have any impact on treatment decisions for the AE. If the blind is broken, the respective patient will be withdrawn from further treatment in this trial and a written explanation must be given by the investigator to the Sponsor immediately. Emergency unblinding, if necessary, will be conducted via the interactive web-based response system (IWRS) of the electronic case report from (eCRF).

10.3 Patient identification

A 7-digit patient identifier consisting of 2 digits each for country (YY), center (XX) and 3 digits for patient (ZZZ) i.e., YYXX-ZZZ will be assigned to each screened patient.

10.4 Randomization

Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list with a 1:1 allocation. Randomization will be done by an IWRS within the eCRF.

Patients will be assigned respective IMP kits. The investigators will be provided with technical options and password information to selectively break the code for an individual patient in case of emergency via the IWRS (back-up by phone maybe established).

11 Treatments

11.1 Investigational medicinal product

All IMPs supplied by the Sponsor will be manufactured, tested, and released according to current Good Manufacturing Practice guidelines and local requirements.

11.1.1 IMU-838

Name:	IMU-838
Manufacturer:	Immunic AG
Active ingredient:	Vidofludimus calcium (IM90838)
Inactive ingredients:	Microcrystalline cellulose EP, polyvidon K25, crospovidone EP type A, talc, and magnesium stearate
Formulation:	Tablets containing a specific polymorph of vidofludimus calcium
Matrix:	White uncoated tablets, biconvex shape, diameter of 8 mm
Dose strength:	22.5 mg
Total daily dose:	45 mg

11.1.2 Placebo

The placebo tablets will be identical to the IMU-838 tablets in terms of appearance, constitution of inactive ingredients, and packaging.

11.1.3 Packaging, labeling and dispensing

All IMP will be packed and labeled according to applicable regulatory requirements.

The labels will contain at least the following information: route of administration, trial code, randomization number, batch number, expiry date, and instructions for storage.

IMU-838 and placebo tablets will be packaged in 30 mL polyethylene bottles containing 32 tablets.

For patients discharged from the hospital before Day 14, the patient will be allowed to take the IMP home to complete blinded treatment *(not applicable for centers in Bulgaria as all patients must be hospitalized between Day 0 and Day 14)*.

11.1.4 Storage and stability

The investigator is responsible for the safe and proper handling and storage of the IMP at the investigational site. The IMP must be stored in a locked facility with access limited to the investigator and authorized personnel. The investigator must ensure that the IMP is administered only to patients enrolled in this trial.

In stability studies, IMP was stable at ambient (25°C/60% relative humidity) and at accelerated storage conditions (40°C/75% relative humidity) and does not require any special storage conditions. However, the tablets should be protected from direct sun light, moisture, freezing, and extended periods of excessive heat (defined as any temperature above 40°C [104 F]). It should also be advised to keep the bottle tightly closed to protect tablets from moisture.

11.1.5 Treatment dose, dose selection, and administration

Tablets will be taken BID with a glass of water (if possible); one tablet each in the morning (15 to 50 min before a meal if applicable), and in the evening (2 hours after any meal if applicable).

The 1st IMP dose on Day 0 should always be the "evening dose of Day 0". To administer the 1st IMP dose as close as possible to time of randomization, the initial IMP dose ("evening dose of Day 0", 2 tablets to be given at once) can be administered between 12:00 noon on Day 0 to 02:00 a.m. on Day 1. The 2nd IMP dose is then given in the morning of Day 1, and dosing continues twice daily until the evening dose of Day 13 (last IMP dose). Except for the initial IMP dose (2 tablets), all other IMP doses will consist of 1 tablet. The timing of morning and evening doses (except for initial evening dose on Day 0) should be at the same time of the day, if possible (see Table 2).

Table 2: Administration of tablets

	Day 0		Day 1		Days 2 to 12		Day 13	
Time	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets		2	1	1	1	1	1	1
Dose IMU-838		45 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg	22.5 mg
		#	*	*	*	*	*	*

Day 0: Loading dose of 45 mg IMU-838 once daily given in the evening of Day 0.
* Day 1- Day 13: dosing of 22.5 mg IMU-838 BID (twice daily).

If the patient is intubated for ventilation, IMP is to be given via a gastric tube. The tablet has no coating and a homogeneous content and can be crushed into smaller pieces (if necessary) for dosing via gastric tube.

If the patent is discharged from the hospital before Day 14, the patient will receive the IMP and will take the remaining doses of IMP at home *(not applicable for centers in Bulgaria as all patients must be hospitalized between Day 0 and Day 14)*.

The 45 mg dose used in this trial is on the higher end of doses used in completed and ongoing clinical trials. A daily dose of 50 mg IMU-838 was found to be safe in a 14-day Phase 1 clinical trial (Trial P1-IMU-838-MAD). The 45 mg dose is also used in the ongoing Phase 2 studies in multiple sclerosis (P2-IMU-838-MS) and ulcerative colitis (P2-IMU-838-UC). In an interim analysis of Trial P2-IMU-838-UC during which unblinded safety data were evaluated by an independent Data Review Committee, no safety signal was found, and the 45 mg dose was considered as not intolerable. Based on the overall safety data, 45 mg IMU-838 is considered a safe dose. To maintain IMU-838 drug levels as stable as possible, the dose of 45 mg IMU-838 is to be given as 22.5 mg dose BID in this trial.

For patients with a hyperacute disease like COVID-19, it is imperative that therapeutic drug levels are quickly reached. Because of the short half-life (approximately 30 hours) and short time to maximum blood levels (3-4 hours after oral dosing) of IMU-838, therapeutic levels are reached rather quickly. In addition, the first dose (loading dose in the evening of Day 0) will be given as 45 mg dose of IMU-838 (2 tablets of 22.5 mg IMU-838 taken at the same time). This will ensure that therapeutic drug levels are expeditiously reached in this hyperacute disease.

The PK profile of IMU-838 based on the described dosing (loading dose of 45 mg IMU-838 on Day 0, then 22.5 mg IMU-838 BID for the remaining treatment days) should therefore result in a profile with a quick onset of therapeutic effects and stable therapeutic drug level over the 14-day treatment period.

11.1.6 Drug accountability and patient compliance

The IMP must not be used outside the context of this trial protocol. For patients discharged from the hospital the investigator must ask the patient to return excess IMP and all packaging materials (including empty containers) at Day 14 (see Table 3) for drug accountability. Unused IMP cannot be used outside the context of this trial protocol. Dispensed and returned IMP cannot be re-used for any other patients.

The investigator or authorized staff must document the receipt, dispensing, and return of all IMP received during this trial. These records will include but are not limited to dates, quantities, batch numbers, patient identifiers, and unique interactive response technology codes, as applicable. The investigators must maintain records documenting that patients were provided with the IMP as outlined in the protocol. Furthermore, investigators will reconcile all IMP received from the Sponsor and administered to or returned from the patient. It is the responsibility of the investigator to reason any discrepancies in IMP accountability. Forms will be provided to ease accountability.

At the end of the clinical trial, or as directed, all remaining and unused IMP must be accurately counted (final drug accountability) and destroyed according to the Sponsor's instructions, i.e., to e.g., return all remaining and unused IMP to the Sponsor or Sponsor's designee.

11.2 Prior and concomitant medications

All medications administered within 2 days before the day of informed consent and until EoS must be documented in the corresponding section of the eCRF. Vasopressor dose will be documented separately.

All medications taken by the patients after giving informed consent and all treatments given in addition to the IMP during the trial are regarded as concomitant treatments and must be documented in the eCRF.

11.2.1 Standard of care treatment and concomitant treatments

Any treatments, medications and procedures that investigators would customarily use to treat COVID-19 in their clinical practice should be included in SoC treatment. The investigator's choice of SoC can include supportive pharmaceutical treatments (including medications that are approved in other indications but that the investigator customarily uses in COVID-19 patients), medications with any approved antiviral indication, intravenous fluids, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, RRT, and ECMO. Investigational treatments not yet approved for commercial use in the respective country (for example obtained through an early access program) or parallel participation in different interventional trials are prohibited in this trial.

In addition, Arbidol and Colchicine are prohibited for centers in all countries. Chloroquine and Hydroxychloroquine are also prohibited for all centers in all countries unless already taken for indicated use before entering the trial.

11.2.2 Prohibited and restricted medication

The use of the following medications and treatments will be prohibited from Screening to end-of-treatment with IMP in this trial (up to Day 14) if not indicated otherwise in this protocol:

- Concurrent use of any mycophenolate mofetil or of methotrexate exceeding 17.5 mg weekly
- Any medication known to significantly increase urinary elimination of uric acid, in particular lesinurad (Zurampic™) as well as uricosuric drugs such as probenecid
- Current treatments for any malignancy, in particular irinotecan, paclitaxel, tretinoin, bosutinib, sorafenib, enasidenib, erlotinib, regorafenib, pazopanib and nilotinib
- Any drug significantly restricting water diuresis, in particular vasopressin and vasopressin analogs
- Use of rosuvastatin at daily doses higher than 10 mg
- Arbidol and Colchicine
- Any use of other DHODH inhibitors, including teriflunomide (Aubagio™) or leflunomide (Arava™)
- Chloroquine and Hydroxychloroquine are not allowed during the entire trial, unless already taken for indicated use before entering the trial

Routine use of steroids is not recommended and should be reserved for patients with severe disease or with special circumstances. Concomitantly used steroids (e.g., required for pre-existing conditions) do not need to be discontinued when entering this trial, however, their use should be carefully considered.

After the 14-day treatment period with IMP any drugs to treat the disease, including any anti-viral therapy, can be used at the investigator's discretion.

The concomitant administration of drugs metabolized for more than 70% by CYP2C8 (although not prohibited) should be carefully considered since it cannot be excluded that IMU-838 potentially increases their blood levels. Major substrates of CYP2C8 include:

- amodiaquine (anti-malarial)
- dasabuvir (anti-viral),
- enzalutamide (anti-cancer)
- montelukast (anti-asthmatic), and
- pioglitazone and repaglinide (anti-diabetics)

The use of the potent CYP2C8 inhibitor rifampicin and strong and moderate CYP2C8 inducers gemfibrozil and trimethoprim as concomitant medication is not prohibited during this trial. However, alternatives to these drugs should be considered, and patients should be carefully monitored for any indication of toxicity. Given the known narrow therapeutic window of ibuprofen, the use of ibuprofen should be carefully considered or, if possible, therapeutic alternatives should be used.

12 Trial schedule

12.1 Schedule of assessment

An overview of the trial conduct is provided in Table 3.

Table 3: Schedule of assessments

Assessments	**Screening**	**Blinded treatment[l]**					**EoT**	**EoS**	**USV**
	D-2 to D0[g]	D0[g]		D1 - D5	D6	D7 - D13	D14	D28	***SFU[p]***
		Pre	Post					±1 d	
Informed consent	•								
Demographics, incl. high risk factors[f]	•								
In-/exclusion criteria	•								
Local screening labs performed or taken from existing labs[k]	•								
Confirmation of positive SARS-CoV-2 status	•[m]								
Randomization		•							
Medical history	•								
Concomitant medications/procedures	•		•	• (daily)	•	• (daily)	•	•	•
Physical examination	•				•		•	•	
Continuous monitoring with documentation of									
Status hospitalization/ status ICU[c]		Twice daily					•	•	•
Survival status		Twice daily					•	•[n]	
O_2 supplementation (incl. type of ventil.)		Twice daily					•	•	•[p]
Temperature		Twice daily					•		•[p]
Vital signs[r]		Twice daily					•		•[p]
Respiratory rate		Twice daily					•		•[p]
SpO_2		Twice daily					•		•[p]
Score assessment (9-point WHO scale)[b]	•	Once daily (evening)					•	•	•[p]
Vasopressor dose		Once daily (evening)					•	•	
Radiol. confirmation in clinical practice of interst. lung disease[i]		Once daily (evening)					•		
Document confirmation of any new infections[j]		Once daily (evening)					•		
Use of RRT		Once daily (evening)					•	•	• [p]
Use of ECMO		Once daily (evening)					•	•	• [p]

Table 3: Schedule of assessments *(continued)*

Assessments	**Screening**	**Blinded treatment[l]**					**EoT**	**EoS**	**USV**
	D-2 to D0[g]	D0[g]		D1- D5	D6	D7 - D13	D14	D28	***SFU***[p]
		Pre	Post					±1 d	
Lab assessments									
Blood biochemistry		•			•		•	•	•[p]
Hematology		•			•		•	•	•[p]
Coagulation[a]		•			•		•	•	
Urinalysis		•			•		•	•	•[p]
Disease markers[a]		•		• (daily)	•	• (daily)	•	•	
Biomarkers[a]		•			•		•	•	
IMU-838 trough levels[a]		•		• (daily)	•		•[o]	•	
SARS-CoV-2 viral load and SARS-CoV-2 status (qualitative)[e]		•		• (Days 2 & 4 only)	•	• (Days 8, 10 & 12 only)	•	•	•[p]
Serology: SARS-CoV-2 antibodies[h]		•			•		•	•	•[p]
Immune cell subtyping *(US only)*[q]		•			•		•	•	
Lab Kits used									
Kit A		•			•		•	•	•[p]
Kit B				• (daily)		• (daily)			
Kit C		•			•		•	•	
Kit PK		•		• (daily)	•		•[o]	•	
Kit D		•		• (daily)	•	• (daily)	•	•	•[p]
Kit E		•			•		•	•	•[p]
Immune cell subtyping (US only)[q]		•			•		•	•	
Safety									
AE assessment	•	▬						•	•
ECG		•	•	• (only Day 3)	•		•	•	
IMP									
IMP administration			▬						
Number of tablets		-	2	1 tablet each morning + evening					
Accountability							•		
SoC treatment	▬								

[a] Needs to be frozen at at least -20° C (-4° F) and sent to the central safety laboratory within 6 weeks.
[b] Clinical status on a 9-category ordinal scale (as proposed by the WHO master protocol)
[c] Including documentation of ICU admission and discharge times.

[d] Existing local lab values obtained within 48 hours of randomization as well as locally obtained screening lab values can be used for assessment of eligibility.

[e] At each time point only 1 nasopharyngeal swab and 1 sputum sample each will be taken. The viral load test will also be used as qualitative test (i.e. may be evaluated as absence or presence of virus in the quantitative SARS-CoV-2 assessments). Samples need to be frozen at at least -20° C (-4° F) and sent to the central virology laboratory within 7 days on dry ice.

[f] Includes: Age≥65; cardiovascular disease (including hypertension), pre-existing pulmonary disease, diabetes, current treatment for malignancy or within the previous 3 years, immunosuppression (due to ongoing use of immunosuppressive drugs or existing disease leading to impaired immune status), body mass index.

[g] Screening, randomization and first IMP administration can be performed the same day (Day 0). If screening is performed on Day 0, treatment will start with the evening dose.

[h] Plasma sample for serology SARS-CoV-2 (IgG and IgA detection) should be frozen at at least -20° C (-4° F) and sent to the central safety laboratory within 6 weeks.

[i] Confirmation of radiographic evidence of pulmonary infiltrates by chest X-ray or CT (only if done within the scope of routine clinical practice).

[j] Confirmation of presence of any new viral or non-viral infection (this is not a protocol-required procedure, only documentation when done within the scope of routine clinical practice). Site of infection and source of culture will be recorded.

[k] As performed during routine clinical practice in the center. Must include white blood cell count, platelet count, total bilirubin, alanine aminotransferase or gamma glutamyl transferase, serum creatinine, for women of childbearing potential: blood pregnancy test, and if the patient has known Gilbert syndrome: indirect [unconjugated] bilirubin.

[l] For assessments, if patients will be discharged from the hospital before Day 14, see *Blinded Treatment period (Day 0 to Day 13) and Day 14 (end-of-treatment). For centers in Bulgaria only: Patients must be hospitalized during the entire treatment period.*

[m] Within 4 days of randomization.

[n] If no EoS visit was performed, information about patient status should be reported on the EoS page in the case report form. If the patient is lost to follow-up, the investigator must contact the patient, the patient's family or the referring physician by phone or email to obtain survival status, or it must be possible to search in registers or publicly available information for these survival data.

[o] Blood sampling must be performed in the morning around the time the morning dose was usually taken by the respective patient.

[p] Safety follow up assessments must be performed regularly (at least once) by phone or email between Day 28/EoS and Day 60 and documented as an unscheduled visit in the eCRF. The patients should be asked to return for an on-site visit if the investigator deems this necessary for follow-up. The assessments not to be done if the visit is performed as a telephone or email contact in the scope of the safety follow up are marked as •[p]

[q] *Optional for centers in the USA only: 2 blood samples will be collected to evaluate immune cell subtypes and immune reactions for future research studies. This will be shipped directly to a US research site and not to the central laboratory. Shipment needs to be done at ambient temperature and immediately the same day after sampling.*

[r] Height and weight only to be measured at D0, pre-dose.

AE = adverse event, CT = computed tomography, cont. = continued, D = day, ECG = electrocardiogram, ECMO = extracorporeal membrane oxygenation, EoS = end-of-study, EoT = end-of-treatment, ICU = intensive care unit, Ig = immunoglobulin, IMP = investigational medicinal product, incl. = including, interst. = interstitial, pre(post) = pre(post) IMP, RRT = renal-replacement therapy, Radiol. = radiological, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SFU = safety follow up, SoC = standard of care, SpO_2 = peripheral capillary oxyhemoglobin saturation, ventil. = ventilation, USV = unscheduled visit, WHO = World Health Organization.

12.2 Screening (Day -2 to Day 0) and Day 0

Patients for whom written informed consent (for consent procedures see Section 19.3) was obtained will undergo the assessments shown in Table 3. Patients will be screened for eligibility based on the trial's inclusion and exclusion criteria. The infection with SARS-CoV-2 must have been confirmed by RT-PCR within 4 days of randomization. To assess eligibility existing local laboratory values obtained within 48 hours of randomization will be used.

Whenever possible, screening, randomization and 1st IMP administration should be performed on the same Day (Day 0). In this case the Day 0 assessments (see Table 3) will be performed, as soon

as the eligibility is confirmed. Treatment will then start with the evening dose. For dosing recommendations how to dose on initial days see Section 11.1.5.

12.3 Blinded treatment period (Day 0 to Day 13) and Day 14 (end-of-treatment)

Patients will undergo the assessments and procedures as detailed in Table 3. Blood samples to assess IMU-838 trough levels will be taken pre-dose on Day 0 before first IMP dose is given. If patients will be discharged from hospital during the BT, they will be asked to return for a visit at Day 6 and Day 14, whatever is applicable *(not applicable for centers in Bulgaria as all patients must be hospitalized between Day 0 and Day 14)*. Treatment will be stopped at Day 13 with the evening dose on that day as the last IMP administration. After the last IMP dose in the evening of Day 13, the end-of-treatment (EoT) assessments will be done on Day 14 (see Table 3). Blood sampling for IMU-838 trough values must be performed in the morning around the time the morning dose was usually taken by the respective patient.

For centers in Bulgaria: Patients must be hospitalized during the entire treatment period i.e., from Day 0 to Day 14.

For centers in countries other than Bulgaria: If applicable, the patient will be asked to return all remaining IMP and its packaging (including empty bottles) to the trial center at Day 14 for IMP accountability checks.

In case of hospital discharge before Day 14, the following assessments should be done between hospital discharge and until Day 14 (patients should return for clinic visits at Day 6, if discharged before Day 6, and Day 14):

- On the day of hospital discharge:
  - All trial-related assessments and procedures are completed as per Table 3 and finalized (evening assessments should be done, even when patient is discharged during the day)
  - The date and time of hospital discharge need to be documented
- Day 6 and Day 14:
  - The full lab assessments to be performed on Days 6 or 14, respectively (as indicated in Table 3)
  - Physical examination and ECG
  - Documentation of concomitant medications/procedures, AEs, temperature, vital signs, respiratory rate, type of oxygen supplementation, survival status, hospitalization status, assessment of WHO ordinal scale [21] (only once daily assessment required)
  - Return of IMP by patients and drug accountability (Day 14 only)

If the patent is discharged from the hospital before Day 14, the patient will receive the IMP and will take the remaining doses of IMP at home.

12.4 Unscheduled visit

Unscheduled visits may be performed at any time during the clinical trial and will generally include the assessments listed in Table 3. Depending on the reason for the unscheduled visit, further appropriate assessments maybe done according to the investigator's discretion. Results of the assessments and any change in concomitant medications will be recorded in the eCRF. After an unscheduled visit, the regular scheduled visits must continue according to Table 3.

12.5 End-of-study (EoS, Day 28) and premature termination

Patients will undergo the assessments and procedures shown in Table 3**.**

In case of premature discontinuation, assessments of the EoS visit should be performed at Day 28 for the respective patients, whenever possible. Patients who were discharged *(for centers in Bulgaria only: between Day 14 and 28)*, will be asked to return at Day 28 for EoS assessments. If the patient dies during the trial, the investigator should indicate that this visit was not performed, however should fill out all information about patient status to be performed at the EoS visit. If the patient refuses any EoS visit or is lost to follow-up, at least the survival status should be ascertained e.g., by calling the patient, his/her relatives, or referring physician, or by searching registers or publicly available information for survival status information.

In case of premature withdrawal from the trial or IMP, reasons, circumstances and findings will be fully described on the corresponding page in the eCRF respecting the patient's rights.

12.6 Safety follow-up

Following the D28/EoS examination, the investigator will contact the patient regularly (at least once) by phone or email to obtain health data until Day 60. This should be documented as an unscheduled visit in the eCRF. The patients should be asked to return for an on-site visit if the investigator deems this necessary for follow-up.

13 Efficacy and baseline assessments and procedures

13.1 Demographics and other baseline assessments

During screening, demographics (including sex, age, height, weight, race, and ethnicity), presence of high-risk factors, a complete medical history, confirmation of SARS-CoV-2 infection status, and previous and concomitant therapy will be collected.

High risk factors include: Age ≥65, cardiovascular disease (including hypertension), pre-existing pulmonary disease, diabetes, current treatment for malignancy or within the previous 3 years, immunosuppression (due to ongoing use of immunosuppressive drugs or existing disease leading

to impaired immune status), and body mass index (BMI). The BMI will be calculated from patient's height and weight.

13.2 Clinical disease severity assessment

The clinical disease severity will be assessed based on the WHO Ordinal Scale for Clinical Status [21, and Table 4]. The WHO scale is a 9-category ordinal scale and was developed to have a standardized measure of the COVID-19 disease severity. The scale comprises patient status (outpatient or hospitalized), virus status (infected yes or no), limitation of activities, oxygen support, and organ support. For the clinical assessment in this trial the WHO scale is slightly modified.

Table 4: Modified WHO Ordinal Scale for Clinical Status

Patient state	Descriptor	Score
Uninfected or no longer infectious	No clinical or virological evidence of infection	0
Mild Disease	Ambulatory, virus-positive, no limitation of activities	1
	Ambulatory, virus-positive, limitation of activities	2
Moderate Disease	Hospitalized, virus-positive, no oxygen therapy	3
	Hospitalized, virus-positive, oxygen by mask or nasal prongs	4
Severe Disease	Hospitalized, virus-positive, non-invasive ventilation or high-flow oxygen	5
	Hospitalized, virus-positive, intubation and mechanical ventilation	6
	Hospitalized, virus-positive, ventilation plus additional organ support (pressors, RRT, ECMO)	7
Dead	Death	8

ECMO = extracorporeal membrane oxygenation, RRT = renal replacement therapy.
Based on [21].

13.3 Clinical and patient status assessments

The following will be recorded regularly, once or twice daily, during the course of the trial (see Table 3):

- Hospitalization and ICU admissions
- Survival status
- Score assessment (WHO scale, see Section 13.2)
- Use of invasive and non-invasive ventilations, auxillary oxygen supplementation (including type of ventilation e.g., ECMO), and RRT
- Vital signs and temperature

- Respiratory rate and SpO_2 (see Section 13.4)
- Vasoactive therapy (type and dose)
- Confirmation of radiographic evidence of pulmonary infiltrates by chest X-ray or computer tomography (if done within the scope of routine clinical practice)
- Documentation of presence of any new viral or non-viral infection (e.g., if blood cultures and sputum gram stain and culture are done within the scope of routine clinical practice). Site of infection and source of culture will be documented.

13.4 Assessment of respiratory rate and oxygen saturation

To assess the respiration of the patient, peripheral capillary oxyhemoglobin saturation (SpO_2) will be repeatedly reported (Table 3). Respiration rate will be assessed according to hospital staff's current clinical practice.

14 Pharmacokinetics, disease markers, and biomarkers

All laboratory samples for IMU-838 plasma trough levels, disease markers and biomarkers must be handled and labeled according to the respective laboratory manual i.e., virologic samples according to the manual from the central virology laboratory, all other samples according to the central safety laboratory manual.

14.1 Plasma trough levels of IMU-838

IMU-838 plasma trough level concentrations will be determined by validated direct liquid chromatography tandem-mass spectrometry. This method determines the concentration of the active moiety vidofludimus contained in IMU-838. Details of the assay will be described in a separate bioanalytical report.

Plasma samples for IMU-838 trough levels will be assessed centrally at Nuvisan. Samples will be collected and subsequently stored at at least -20°C (-4°F) at the site, and shipped to the central laboratory as frozen samples, as appropriate. Investigators will be provided with detailed written instructions how to collect, handle, store, and ship the samples.

Blood samples to assess IMU-838 serum trough values will be collected in all patients as specified in the schedule of assessments in the morning before the first IMP dose (Table 3).

Patients are required to withhold intake of the IMP until after the blood sample collection. Plasma trough will be assessed using Lab Kit PK.

14.2 Disease markers

The following blood biomarkers will be evaluated:

- D-dimer
- LDH
- CRP
- cTn
- PCT

Disease markers are part of Lab Kit B, must be frozen at at least -20°C (-4°F) and sent within 6 weeks (for more details on lab kits see also Appendix 1).

14.3 Biomarkers

The following biomarkers will be evaluated (in blood samples if not indicated otherwise):

- Serial viral load assessed by RT-PCR in spontaneous sputum and nasopharyngeal swab (samples must be frozen at at least -20°C [-4°F] and sent within 7 days, Lab Kit D)*
- Qualitative virus assessment: SARS-CoV-2 status (qualitative) in sputum and nasopharyngeal swab as derived from the viral load assessment (i.e. may be evaluated as absence or presence of virus in the quantitative SARS-CoV-2 RT-PCR assessments)
- Biomarkers: IL-17, IL-1ß, IL-6, IFNγ, and TNFα (assessed with Lab Kit C, samples must be frozen at at least -20°C [-4°F] and sent within 6 weeks)
- Serology: IgA and IgG antibodies against SARS-CoV-2 (Lab Kit E, samples must be frozen at at least -20°C [-4°F] and sent within 6 weeks)

For more details on lab kits, storage and shipment conditions see Appendix 1.

For the sputum sample, no induced sputum should be attempted. If spontaneous sputum cannot be obtained, this should be noted and no sample needs to be sent.

* At each time point indicated in Table 3 only 1 nasopharyngeal swab and 1 sputum sample will be taken. The results of the viral load test will also be used for the qualitative assessment.

For centers in the USA: 2 additional blood samples as indicated in Table 3 will be collected to evaluate immune cells and immune reactions for future research studies. Shipment needs to be done at ambient temperature and immediately the same day after sampling. Samples will be shipped directly to a US research site and not to the central laboratory. This blood collection is optional and only for patients agreeing to the extra biomarker assessment on the ICF.

15 Safety assessments

15.1 Adverse events documentation and reporting

15.1.1 Definitions

15.1.1.1 Adverse events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IMP, whether or not related to the IMP.

Overdosing, defined as intake of more than twice the intended dose, will not be considered an AE but must be documented as protocol deviation. However, symptoms associated with overdose are considered adverse drug reactions (ADR, for definition see below).

Untoward medical experiences occurring during pre-treatment periods do not meet the above-mentioned definition of AE. Nevertheless, they have to be documented in the same way as AEs, if they occur in the safety monitoring period, i.e., between signing the informed consent form and completion of the EoS visit. Should they already be present at Screening and don't worsen later on, they will only be documented as medical history.

A surgery or procedure scheduled to occur during the trial will not be considered an AE if the surgery or procedure will be performed for a pre-existing condition and the surgery or procedure was planned prior to trial entry. However, if the pre-existing condition deteriorates unexpectedly during the trial (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the surgery or procedure is being done will be considered an AE.

Diagnostic medical or non-surgical procedures will not be considered as AEs. Hospital admission for social, quarantine or convenience reasons will also not be recorded as AE.

AEs that occur between signing the informed consent form and the time when the patient first administers the IMP (Day 0) are defined as pre-treatment AEs.

Treatment-emergent adverse events are defined as any event not yet present prior to the first intake of IMP or any event already present that worsens in either intensity or frequency following exposure to the IMP.

A continuous event with changing intensities will be considered as one event of the most severe intensity documented. A continuous event with a changing seriousness will also be considered as one event, but the start and stop date of the time the event is serious must be separately documented. Clearly separated episodes of an event will be considered as separate events.

15.1.1.2 Adverse drug reactions and unexpected adverse drug reactions

All AEs judged by either the reporting investigator and/or the Sponsor as having a reasonable causal relationship to the IMP qualify as ADR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

An unexpected ADR is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational product or package insert or summary of product characteristics for an approved product). Reports that add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs, too. For example, an event more specific or more severe than described in the reference document would be considered 'unexpected'. Specific examples would be: acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis or hepatitis with a subsequent report of autoimmune hepatitis.

15.1.1.3 Serious adverse events

An **SAE** is any untoward medical occurrence that, at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital abnormality or birth defect

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe.

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These will usually also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. In addition, new malignancies that occur during the participation in the trial are defined as important medical events and must be reported as SAEs.

An SAE requires that the underlying event is considered an AE as defined in Section 15.1.1.1.

Hospitalizations due to a surgery or procedure during the trial will not be considered an SAE if the surgery or procedure will be performed for a pre-existing condition and the surgery or procedure was planned prior to trial entry. However, if the pre-existing condition deteriorates unexpectedly during the trial (e.g., surgery performed earlier than planned), then the deterioration of the condition leading to hospitalization will be considered an SAE. Hospital admission for social, quarantine, or convenience reasons will not be recorded as SAE. Hospitalization and death due to COVID-19 are anticipated clinical events of the underlying disease and cannot be used as reason for SAE classification without an underlying AE leading to hospitalization or death (see also Section 15.1.6).

15.1.1.4 Suspected unexpected serious adverse reaction

A **suspected unexpected serious adverse reaction (SUSAR)** is a serious adverse reaction (SAR) that is unexpected or for which the development is uncommonly (unexpected issue) observed during a clinical trial and for which there is at least a reasonable possibility of a causal relationship with the IMP.

15.1.2 Classification of adverse events

Classification of AEs will be performed by the investigator.

Causality

The causal relationship between the AE and the administration of the IMP or trial procedure will be assessed as follows:

- Related: Implies a reasonable possibility of a causal relationship between the event and the IMP or procedure. This means that there are facts (evidence) or arguments to suggest a causal relationship.
- Not related: Implies no reasonable possibility of a causal relationship between the event and the IMP or procedure. This means that there are neither facts (evidence) nor arguments to suggest a causal relationship.

Severity

The severity of AEs will be graded according to the National (US) Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. If not specifically defined in the NCI-CTCAE, the following grading applies:

Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*

Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

Outcome categories

Recovered:	The patient has fully recovered from the event or the condition has returned to the level observed at Baseline
Recovering:	The patient has recovered from the event, but the condition has not returned to the level observed at Baseline
Not recovered:	The event is ongoing at the time of reporting and the patient has still not recovered
Recovered with sequelae:	As a result of the AE, the patient suffered persistent and significant disability/incapacity (e.g., became blind, deaf or paralyzed)
Fatal:	The patient died due to the event. If the patient died due to other circumstances than the event, the outcome should be stated otherwise (e.g., not recovered or recovering)
Unknown:	If the outcome is not known or not reported

15.1.3 Documentation of adverse events

All AEs occurring between the time written informed consent was obtained and until the end of the safety follow-up period (safety observation period) must be recorded. Information on AEs will be derived by non-directive questioning of the patients in general terms at each visit if possible (e.g., "How do you feel?" or "How have you been since the last questioning?"), by patients' spontaneous reports, or by observation. Adverse events also may be detected when they are volunteered by the patient during or between assessments and/or visits or through physical examination, laboratory test, or other assessments.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

All AEs that occur during the safety observation period of the trial as described above will be recorded in the patient's AE section of the eCRF and will include the following information: a description of the AE, date of onset and resolution, severity, relationship to the IMP, relationship to trial procedure, action taken, and outcome. For SAEs, the SAE form must be completed (see Section 15.1.4).

15.1.4 Documentation and reporting of immediately reportable adverse events

Any SAE that occurs during this trial will be reported (via the "Serious Adverse Event Form") to the Sponsor immediately (i.e., within 24 hours). The information will include at least the following data:

- Name, address, and telephone number of the reporting investigator
- Investigational product(s)
- Trial code
- Patient identification number, sex, and date of birth
- Description of the AE, measures taken and outcome (at the time of reporting)
- Assessment of causality to the IMP by the investigator

Reports will be addressed to:

SCRATCH Pharmacovigilance GmbH & Co. KG	
Schlossstrasse 25, 35510 Butzbach, Germany	
E-mail:	safety-immunic@scratch-pv.com
Telephone:	+49 6033 74535 50
Fax:	+49 6033 74535 59

The sponsor ensures to keep detailed records of all AEs which are reported to him by the investigator or investigators. Reporting of SUSARs to the independent ethics committee (IEC) or institutional review board (IRB) and regulatory authorities will follow pertinent national legislation.

The Sponsor will inform as soon as possible and following pertinent national legislation the regulatory authorities and the IECs or IRBs about any event that necessitates reconsideration of the benefit-risk-ratio of the IMP. These events are in particular:

- single cases of expected SARs with an unexpected outcome,
- an increased incidence of expected SARs considered clinically significant,
- SUSARs occurring after a concerned person has completed the trial,

- events related to the conduct of the trial or the development of the tested IMP possibly affecting the safety of the concerned persons.

All additional measures deemed necessary through new findings and taken by the Sponsor or the investigator to protect the safety of the persons concerned and their triggering circumstances will be reported as soon as possible to the concerned regulatory authorities and the IECs or IRBs, if applicable.

Periodic safety reporting to regulatory authorities and the IECs will follow pertinent national legislation.

In the event of a fatality, the "Trial participant's insurer" will be informed by the Sponsor's designee within 24 hours of gaining knowledge of the event. In case of other SAEs, the "Trial participant's insurer" will be informed promptly.

15.1.5 Follow-up of adverse events

All SAEs judged to be related to the IMP must be followed by the investigator until the patient has recovered, recovered with sequelae, died, or until the investigator determines that the patient's condition is stable, whichever occurs first. All other AEs must be followed by the investigator until the conditions mentioned above are met or until the end of the safety follow-up period, whichever comes first, and until all AE-related queries for the patient have been resolved. The investigator will take all appropriate and necessary therapeutic measures required for resolution of the AE, if applicable. All efforts to collect follow-up information must be documented in the source data.

Follow-up information should be supplied on the respective forms of the eCRF.

During and following a patient's participation in this trial, the investigator must ensure that adequate medical care is provided to a patient for any AEs related to the trial, including clinically significant laboratory values.

15.1.6 Handling of anticipated clinical events of COVID-19

Typical COVID-19-related symptoms present at Baseline (examples such as fever, dyspnea, viral pneumonia, or hypoxia) and continuing during the trial without clinically unusual worsening* are considered anticipated clinical events of the underlying condition and will not be collected as AEs. In addition, disease characteristics and severity will be regularly captured within the scope of the clinical status assessment. Death, hospitalization, and use of ventilation, ECMO, or dialysis due to COVID-19 or its complications (which all are recorded as clinical endpoints for this trial) are not considered AEs (see Section 15.1.2) and should not be considered medically significant events by itself for the assessment of SAEs.

Any clinically unusual worsening* of COVID-19-related disease symptoms present at trial inclusion and any clinically relevant changes in clinical laboratory parameters, vital signs or other findings during physical examination which are considered unusual for COVID-19 disease and where a relationship to drug treatment cannot be excluded should be recorded as AEs.

* "Unusual worsening" means that, in terms of type or severity of symptoms, time frame or symptom fluctuations, the course of the disease progression is different from that in most patients with the same general conditions (disease status, age, health status, concurrent diseases).

15.1.7 Further safety precautions

Patients known or suspected to have Gilbert syndrome should be carefully monitored, and any clinically relevant increase in bilirubin, in particular indirect bilirubin, in these patients should be carefully considered in terms of benefit-risk assessment.

A daily supplementation of either 2 x 750 mg oral bicarbonate or 2 tablets of Neoralit SR three times daily during meals or half an hour after meals is recommended for patients with

- Known history of nephrolithiasis
- Underlying condition with a strong association of nephrolithiasis, including hereditary hyperoxaluria or hereditary hyperuricemia
- History or clinical diagnosis of gout

15.1.8 Pregnancies

Should a pregnancy occur in a female patient, or in a female partner of a male patient, it must be reported to the Sponsor within 24 hours of the first awareness of the event and be recorded on the appropriate pregnancy form. The trial participation of patients who become pregnant during the trial after signing the informed consent will be discontinued immediately.

A pregnancy is not regarded an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive method. Whenever possible, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality, maternal and/or new-born complications) must be followed up and documented even if the patient was discontinued from the trial. All reports of congenital abnormalities or birth defects are SAEs. Spontaneous miscarriages will also be reported and handled as SAEs. Elective abortions without complications will not be handled as AEs.

Pregnancy follow-up will be recorded on the pregnancy form and will include an assessment of the possible relationship of the IMP to any pregnancy outcome.

15.2 Safety laboratory investigations

Clinical safety laboratory tests will be performed at the times indicated in the schedule of assessments (Table 3).

Given that this is an acute treatment situation, existing local or locally obtained laboratory values obtained within 48 hours of randomization can be used to assess patient eligibility. However, all laboratory samples required in this trial will be sent to the central laboratory. Results will be available to the investigator within 1-3 days. The investigator is free to use local laboratory values for urgent treatment decisions. Reference ranges must be supplied by the local laboratory and used to assess the laboratory data for clinical significance.

All laboratory samples sent to the central laboratory must be clearly and fully labeled according to the central laboratory manual. The laboratory reports received from the central laboratory via email or fax will be printed, reviewed, signed, and dated by the investigator, and filed at the center. The laboratory results will be additionally imported into the eCRF.

Abnormal results will be assessed by the investigator and classified as clinically significant (yes/no). Clinically significantly abnormal values must be reported as AE, if not already clinically significantly abnormal at Baseline (i.e., pre-dose on Day 0) or if there are known circumstances unrelated to a disease or the medication (such as patient activities or sample handling) that are a likely explanation for the abnormal value.

Persistent clinically significant abnormal values must be followed up using local laboratory values until the cause is determined or until they returned to normal or to the level observed at Baseline (for follow-up of clinically significant laboratory values reported as AEs, see Section 15.1.5).

15.2.1 Pregnancy tests

Female patients of childbearing potential, i.e., not postmenopausal (where postmenopausal state is defined as no menses for 12 months without an alternative medical cause) or not surgically sterile, must have a local negative pregnancy test before the first intake of the IMP. A blood pregnancy test is required at Screening. Any local urine pregnancy test must be followed up with a confirmatory local blood pregnancy test.

For follow-up procedures in case of pregnancy see Section 15.1.8.

15.2.2 Blood chemistry, hematology, and coagulation

Blood chemistry, hematology and coagulation assessments will be performed as scheduled in Table 3. For more details an assessments, storage and shipment conditions please refer to Appendix 1.

Abnormal results will be classified as clinically significant (yes/no). Clinically significantly abnormal values, which were not clinically significantly abnormal at Screening, must be reported as AE.

Blood samples will be collected, handled and stored according to the instructions provided by the central laboratory (or local laboratory if applicable). Coagulation samples will be collected and stored at at least -20°C at the site and shipped within 6 weeks to the central laboratory for analysis. Dry ice shipments may be delayed for up to 2 weeks if another patient is expected to finish the respective visit.

15.2.3 Urinalysis

Urine assessments will be performed as scheduled in Table 3. For more details an assessments, storage and shipment conditions please refer to Appendix 1.

Urinalysis will be done centrally (see Section 6). Abnormal results will be classified as clinically significant (yes/no). Clinically significantly abnormal values must be reported as AE, if not already clinically significantly abnormal at Screening.

The handling and collection of urine samples will be detailed in the Laboratory Manual.

15.2.4 Screening laboratory

For screening local laboratory test will be used, these should include:

- Positive SARS-CoV-2 test (done locally or obtained within 4 days before randomization by another laboratory)
- Negative blood pregnancy test
- Hematology and blood biochemistry: white blood cell count, platelet count, total bilirubin, ALT, and GGT

15.3 Vital signs, physical examination, and ECG

Vital signs, routine physical examinations, and ECG will be performed as scheduled in Table 3.

Vital signs

Vital signs will include height and weight (both only at Screening), body temperature (ºC), pulse rates, systolic and diastolic blood pressures. Height in centimeters and weight in kilograms will be recorded without shoes.

Blood pressure (systolic and diastolic), and pulse must be measured with the patient in a seated position (if possible), after at least 5 minutes at rest.

Body temperature can be measured axillary, oral, rectal or tympanic, but should always be measured by the same method for a patient.

Changes in vital signs judged by the investigator as clinically significant will be reported as an AE.

Physical examination

Physical examinations will cover the following body systems: general appearance, skin, neck (including thyroid), throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, neurological systems, and, if applicable, others.

Any new clinically significant finding compared to Screening must be documented as AE.

Any clinically significant finding at Screening Visit 1 must be documented in the medical history section of the eCRF.

12-lead electrocardiogram

The 12-lead ECG (I, II, III, aVR, aVL, aVF, V_1-V_6) will be recorded in supine position after at least 5 minutes at rest (if applicable) using the local standard ECG machine. The ECG will be analyzed qualitatively (normal or abnormal, if abnormal clinically significant [yes/no]). The heart rate, PQ-, QRS-, and QT-intervals, as well as the heart rate-corrected QT_c interval (according to Bazett's formula) will be determined. All procedures will be done according to local practice. Any findings from ECGs collected after the IMP administration will be captured as AEs if, in the opinion of the investigator, there was a clinically significant change from Screening.

16 Biostatistical methods

16.1 Sample size calculation

Part 1

As no formal hypothesis testing will be conducted in Part 1, no formal sample size calculation is deemed necessary. In previous protocol versions, a pooling of p-values of Part 1 and Part 2 was planned and a sample size of N = 200 enrolled patients (100 per group) was calculated. It is assumed that with the previously planned sample size a robust estimation of all efficacy and safety parameters can be conducted. Thus, no adaptations in sample size for Part 1 are necessary.

Previously, the following assumptions were made:

3-stage group sequential adaptive test design with O'Brien and Fleming shaped boundaries

Information rate for Part 1 analysis: 0.2

O'Brien and Fleming alpha level for end of Phase 2 analysis: <0.0001

Primary endpoint: Proportion of patients without any need for invasive ventilation

Randomization ratio:	1:1 (45 mg/day IMU-838:placebo)
Power:	80%
Global significance level:	0.05, 1-sided

Proportions of patients with need for INV
for 45 mg/day IMU-838: 32%
for placebo: 40%
Number of patients (Part 1): 188

Considering a 6% drop-out rate, a total of 200 patients (100 per group) were to be enrolled.

Part 2

If the trial is expanded to Part 2, the sample size of Part 2 will be determined based on the results of MA1.

The Part 2 (Phase 3, Expansion Phase) trial will be designed to keep a global 1-sided alpha level of 0.025 (one-sided). A 2-stage group sequential test adaptive design with O'Brien and Fleming shaped boundaries will be used. Stage 1 will be IA2 applying an overall information rate of 50% and using an alpha of 0.0026. The use of group sequential boundaries within the context of an adaptive design is enabled using the inverse normal method, combining the p-values of both stages with weights based on the sample sizes. Statistical analysis methods that control for the Type I error will be used.

16.2 Analysis sets and types of analyses

Safety analysis set

The safety analysis set (SAF) will consist of all randomized patients who received at least one dose of IMP, i.e., any dose of IMU-838 or placebo. If it is uncertain if the patient has received any IMP, the patient will be included in the SAF. The analyses based on the SAF will be conducted on an "as treated" basis, i.e., all patients will be analyzed by the treatment they received.

Full analysis set

The full analysis set (FAS) will consist of all randomized patients who received at least one dose of IMP, i.e., any dose of IMU-838 or placebo. The analyses based on the FAS will be conducted on an intention-to-treat procedure, i.e., all patients will be analyzed by the groups to which they were randomized to.

Per-protocol set

All patients of the FAS will also be included in a per-protocol (PP) set if they did not violate any major protocol criteria. Protocol deviations will be identified and classified for each patient during a blind data review.

Assignment of analysis sets to analyses and allocation of patients

All efficacy analyses will be based on the FAS. The primary and the key secondary efficacy endpoints only will be additionally analyzed for the PP set. The analysis of the primary and the key

secondary efficacy endpoints using the FAS will be considered the primary analysis. All other analyses will be exploratory. Safety analyses will be based on the SAF.

The allocation of patients to the analysis sets for the final analysis will be done during a blind data review meeting.

16.3 Statistical analyses

16.3.1 General approaches

For qualitative variables, the frequencies (absolute and relative) will be calculated. Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum. The treatment groups will be separately tabulated. A detailed description of the statistical analyses for all scheduled analyses (i.e., early safety analysis, MA1 and FA1, and interim and FA2) will be provided in a statistical analysis plan and will be finalized before the respective data (e.g. MA1/FA1, IA2, FA2) will be analyzed.

In Part 1, all endpoints will be analyzed descriptively. In addition, exploratory confidence intervals will be calculated for the primary and key secondary endpoints (and for other endpoints as appropriate) using an alpha of 0.1 (2-sided). No formal statistical tests will be conducted.

The Part 2 (Phase 3 Expansion Phase) trial will be designed to keep a global 1-sided alpha level of 0.025 (1-sided). A 2-stage group sequential test adaptive design with O'Brien and Fleming shaped boundaries will be used. Stage 1 will be the IA applying an overall information rate of 50% and using an alpha of 0.0026. The use of group sequential boundaries within the context of an adaptive design is enabled using the inverse normal method, combining the p-values of both stages with weights based on the sample sizes. Statistical analysis methods that control for the Type I error will be used.

In Part 2, the primary and key secondary endpoints will be tested confirmatory. Results of other endpoints will be considered exploratory, even when statistical tests are performed.

Confirmatory hypothesis testing of key secondary endpoints will be done only after the test of the primary efficacy endpoint was significant. Testing will be done strictly hierarchically in the given order to ensure the family wise error rate. Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

The FAS (all randomized patients who received at least one dose of IMP; as randomized) will be the primary analysis population. The PP analysis set and the set of only surviving patients until EoS will be applied as secondary/sensitivity analysis for the primary and key secondary endpoints, if applicable.

16.3.2 Primary and key secondary efficacy endpoint analyses

In the following the analyses for the primary and key-secondary endpoints are described for Part 1. Since Part 1 and Part 2 will be independent parts, these endpoints may be changed for Part 2 after the MA1 analysis. More details and/or changes for evaluation in Part 2 will be specified in a protocol amendment and respective SAP when MA1 results are available.

Primary endpoint

The primary endpoint of the trial i.e., the proportion of patients without any need for INV until EoS. The "need for INV" (considered positive for the primary endpoint) will include patients:

1. placed on any INV method during the trial
2. who had an active "do not intubate" or "do not resuscitate" order established during the trial conduct or refused intubation for any reason but were assessed by the investigator to have a medical need for INV
3. who had a medical need for INV as assessed by the investigator but for reasons of medical resource exhaustion or due to triage decisions by the hospital had not received INV, or
4. who died mainly due to respiratory failure but had a need for INV as assessed by the investigator or before such needed INV could have been started

Patients who are lost to follow-up or discontinue the trial on or before Day 13 (last treatment day) due to any reason other than death and discontinue with a last observed WHO clinical status no lower than that at Screening, and patients who die and do not fall under Number 4 of the above-mentioned criteria will be considered treatment failures for the primary endpoint. A sensitivity analysis will be performed for patients who discontinued before EoS, using the available information on INV.

Invasive ventilation involves any instrument penetrating via the mouth (e.g., endotracheal tube), nose, or the skin (e.g., tracheostomy tube through a stoma) to serve as an artificial airway, and the manual or mechanical ventilation of the patient through such artificial airway.

For clarification, bilevel positive airway pressure (trademarked as BiPAP™ or VPAP™ by different manufacturers) and continuous positive airway pressure are not considered INV as they do not involve intubation. However, for classification of patient clinical status these methods are considered non-invasive ventilation (WHO Status 5, Table 4).

In Part 1, the primary endpoint will be displayed with frequency tables per stratification factor age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals) and overall. In addition, an odds ratio (OR) with an exact 2-sided 90% confidence interval will be conducted. The OR will be calculated adjusted for the stratification factors age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals).

Key secondary endpoints

Proportion of patients surviving without respiratory failure

Respiratory failure will be defined as the need of ICU, INV, high-flow oxygen or ECMO. Patients who are lost to follow-up or discontinue the trial on or before Day 13 (last treatment day) due to any reason other than death, and patients who discontinue with a last observed WHO clinical status no lower than that at Screening are considered respiratory failures. A sensitivity analysis will be performed for patients who discontinued before EoS, using the available information. Statistical analysis will follow the analysis of the primary endpoint.

Duration of ICU treatment until Day 28

The duration of ICU treatment until Day 28 will be analyzed in decimal days.

For patients who were transferred to ICU, the duration of ICU treatment will be calculated as [Time of discharge from ICU (date:hh:mm) - time of admission to ICU (date:hh:mm) + 1] / 1440. For patients who were discharged from ICU but readmitted the time from first admission until last discharge will be used. The time from investigator's decision to admit a patient to ICU until a patient is admitted will not be considered.

If the investigator decides that there is the medical need to admit a patient to the ICU but the patient is not admitted due to patient refusal, unavailability of ICU or due to rationing or triage decisions, the start time of ICU hospitalization will use the investigator's decision. The end of ICU duration will be imputed as Day 28 or, if ICU hospitalization occurs at a later study period, until end of actual ICU hospitalization.

The following imputation of concurrent events in the preferred analysis of ICU duration, creating the most conservative assessment approach will be performed: a) for all death cases that have no recorded or known ICU hospitalization in this trial, start date will be imputed as date/time of death, end date will be imputed as Day 28 b) if ICU treatment is known and started before the date of death, start date will be the actual ICU submission, end date will be imputed as Day 28.

For patients who are lost to follow-up or discontinue the trial on or before Day 13 (last treatment day) due to any reason other than death and patients who discontinue with a last observed WHO clinical status no lower than that at Screening, the following approach will be performed: a) for cases that have no recorded or known ICU hospitalization in this trial, start date will be imputed as date/time of discontinuation, end date will be imputed as Day 28 b) if ICU treatment is known and started before the date of study discontinuation, start date will be imputed as actual ICU submission, end date will be imputed as Day 28.

As sensitivity analyses, ICU duration imputation on available data will be done as follows:

- for patients who died, the study period of 28 days will be recorded as ICU treatment duration,
- for patients who discontinued the study prematurely or for patients who died before EoS, the available information on ICU treatment duration until day of discontinuation will be used.

In Part 1, the ICU duration will be displayed with basic statistics per stratification factor age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals) and overall. In addition, an exact 2-sided 90% confidence interval for the median of differences between treatment groups (location shift) will be conducted adjusted for the stratification factors age and antiviral therapy.

28-day all-cause mortality

28-day all-cause mortality will be derived as percentage of patients who died due to any cause from time of 1st IMP administration until EoS. In Part 1, 28-day all-cause mortality will be displayed with frequency tables per stratification factor age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals) and overall. In addition, an OR with exact 2-sided 90% confidence interval will be conducted. The OR will be calculated adjusted for the stratification factors.

Patients who discontinued the trial before Day 28 due to any other reason than death will be considered as deaths, unless survival status can be obtained by the investigator through other means (see Section 12.4).

In a sensitivity analysis, patients who discontinued before EoS due to reasons other than death, will be considered as survived, unless the investigator has any information of patient death after discontinuation.

In Part 2, the primary endpoint (as selected during MA1) and the key secondary endpoints that include proportion of patients (e.g. patients without respiratory failure, 28-day all-cause mortality) will be evaluated for superiority of IMU-838 vs placebo with an exact Cochran-Mantel-Haenszel test, adjusted for the stratification factors age and antiviral therapy. In addition, logistic regression analyses will be conducted including the covariates age, antiviral therapy, sex, and country. The distribution of primary endpoint or any key secondary endpoint containing duration measurements (e.g. duration of ICU treatment) will be analyzed with the van Elteren test (stratified by age and antiviral therapy). In addition, time-to-event analyses using Kaplan Meier methodology and a stratified log rank test (stratification factors age and antiviral therapy) will also be performed. All tests will be performed 1-sided keeping a global alpha level of 0.025 (1-sided).

16.4 Part 1 to Part 2 transition procedures

16.4.1 General approach

The MA1 (unblinded) will be performed after approximately 200 patients have completed Day 28, either as scheduled or prematurely, while enrollment continues.

Based on the MA1 results the trial may be expanded into Part 2, if activity of IMU-838 is observed, or stopped, if no activity of IMU-838 is observed. A further 30 patients are expected to be enrolled

and treated in a double-blind manner until the results of the MA1 are available (when no activity of IMU-838 was found) or until the enrollment in Part 2 has commenced (if MA1 indicated proof-of-activity). Criteria to assess activity of IMU-838 that will guide the decisions to expand the trial are based on efficacy, virology and biomarker endpoints and are defined in Section 16.4.2 below. The IDMC will also review MA1 results and act as a consultative capacity to assist the Sponsor in decision making, sample size calculations, endpoint selection and other adjustments for Part 2.

A final analysis of Part 1 (FA1) will be performed after completion of Part 1, pooling all enrolled patients, i.e. about 230 patients for any outcome evaluated in the MA1.

The sample size of Part 2 will be estimated based on the MA1 results. Possible other adjustments (e.g., modifications to endpoints, concomitant medications and to SoC, inclusion of children, and other adjustments) will be considered and discussed between the Sponsor and the IDMC. Part 2 will use an adaptive sequential trial design. An unblinded IA will be performed by the IDMC after approximately 50% of patients have been enrolled (based on the Part 2 sample size) to re-assess sample size based on available safety and efficacy data. The Part 2 of the trial will be designed to keep a global 1-sided alpha level of 0.025. A 2-stage group sequential test adaptive design with O'Brien and Fleming shaped boundaries will be used. The IA during Part 2 is assumed a Stage 1 analysis applying an overall information rate of 50% and using an alpha of 0.0026.

The use of group sequential boundaries within the context of an adaptive design is enabled by using the inverse normal method, combining the p-values of both stages with weights based on the sample sizes.

16.4.2 "Activity" criteria and further issues to be considered

The activity of IMU-838 will be evaluated based on the following endpoints:

- Proportion of patients without any need for INV until EoS (primary endpoint)
- Proportion of patients surviving without respiratory failure (defined as any need of ICU, INV, high-flow oxygen or extracorporeal membrane oxygenation [ECMO] until EoS, key secondary)
- Duration of intensive care unit (ICU) treatment until EoS (key secondary)
- 28-day all-cause mortality (key secondary)
- Rate of ICU admission until Day 28
- Duration of INV
- Proportion of patients with improvement of at least 2 points (from randomization) on the 9-category WHO ordinal scale
- Time to first prescription of INV
- Duration of hospitalization

- Time to ICU admission
- Time from IMP treatment initiation to death
- Analysis of virologic data:
  - Time to conversion to a negative SARS-CoV-2 (qualitative) test
  - Decrease of SARS-CoV-1 viral load
  - Time course of SARS-CoV-1 viral load
- Analysis of biomarkers: relative change from Baseline in interleukin (IL)-17, IL 1ß, IL-6, interferon gamma, and tumor necrosis factor alpha

IMU 838 will be considered active when one of the following applies:

- A moderate, descriptive effect on the primary endpoint: observed treatment effect is close to or higher than the assumed 20% relative difference between IMU-838 and placebo (e.g., 40% for IMU-838 and 32% for placebo group)
- A mild, descriptive effect on the primary endpoint and a moderate effect in at least one of the key secondary endpoints, defined as follows:
  - Mild effect in primary endpoint: at least a 10% relative difference between IMU-838 and placebo in favor of IMU-838 (e.g. 40% for IMU-838 group and 36% for placebo), **AND**
  - Moderate effects in at least one of the key secondary endpoints, defined as.
    - a 10% relative difference in the proportion of surviving patients without respiratory failure in favor of IMU-838,
    - the duration of ICU treatment until EoS is at least about 1.5 days shorter with IMU-838 (median values) than placebo,
    - the proportion of patients who died is at least 8% (relative difference) lower with IMU-838 than placebo
- A mild, descriptive effect on the primary endpoint as well as a moderate effect in at least three secondary endpoints plus one virologic endpoint as listed above: observed treatment effect is at least a 5% relative difference between IMU-838 and placebo for the primary endpoint. In addition, moderate effects within the secondary endpoints are observed and in addition at least one of the virologic endpoints should show a recognizable beneficial effect of IMU 838

In all 3 scenarios, the assessed clinical endpoints, virologic data, and/or biomarker must show an overall general pattern that is consistent with IMU-838 having clinical activity in COVID-19 patients.

A robust trend of IMU-838 activity versus placebo must be observed. If none of the above criteria is met without any robust trend on efficacy endpoints of IMU-838 versus placebo, Part 2 will not be initiated, and enrollment of Part 1 will be stopped.

If clinical activity of IMU-838 is confirmed, the following will additionally be evaluated

- Re-evaluation of the primary and key secondary endpoints
- The sample size for Part 2 based on the MA1
  - Assumptions:
    - 2-stage group sequential test design with O'Brien and Fleming shaped boundaries
    - Information rate for IA2: 0.50
    - O'Brien and Fleming alpha level for IA2: 0.0026
    - Primary endpoint: Proportion of patients without any need for INV (if not changed after MA1)
    - Randomization ratio: 1:1 (45 mg/day IMU-838:placebo)
    - Power: 80%
    - Global significance level: 0.025, 1-sided
    - Proportions in primary endpoint as observed during MA1A drop-out rate as observed during MA1 will be considered
- Re-evaluation of inclusion and exclusion criteria
- Inclusion of children and adolescents 12 years or older
- Modifications on dose and/or treatment duration
- Modifications on allowed or prohibited concomitant medications and medications to be considered for standard of care
- Safety review
  - Any safety signal which require a change in trial conduct
  - Are additional safety analyses before the next IDMC meeting required?
- Are any other adjustments to the trial conduct (not previously covered) needed?
- Re-evaluation of the number of patients per country and center

If activity and safety of IMU-838 is confirmed, enrollment will be stopped, when Part 2 is initiated, and FA1 will be performed.

17 Patient stopping rules and other reasons for patient withdrawal from trial participation

17.1 Patient stopping rules

Any SAE of Grade 3 or 4, when in the investigator's opinion the benefits do not outweigh the risk for continuing in the trial.

17.2 Other reasons for patient withdrawal from trial participation

Participation in the trial is voluntary and patients may withdraw from the trial at any time and for any reason. However, all patients will be encouraged to complete the trial and have EoS assessment performed (Day 28) (also refer to Section 12).

Patients must be withdrawn from the trial for any of the following reasons:

- Patient withdraws consent due to
  - AE(s)
  - COVID-19 related clinical events
  - other reason (to be specified)
    for all patient withdrawals it should be recorded whether the patient agrees to all non-interventional follow-up procedures
- Investigator decision due to
  - AE(s), 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
  - reasons other than AE or non-compliance (to be specified)
- Lost to follow-up (including transfer of patient to a different medical institution inaccessible to the investigator)
- Death
  - Primarily related to COVID-19 and its complications
  - Not primarily related to COVID-19 and its complications
- Pregnancy
- Treatment with prohibited concomitant medication (see Section 11.2, Prohibited and restricted medication)
- Violation of inclusion or exclusion criteria noted only after randomization

- The trial is terminated by the Sponsor

The primary reason for discontinuation from the trial is to be recorded in the source documents and on the early termination page of the eCRF.

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 allow to continue non-interventional follow-up procedures.

Patients who prematurely discontinue the trial will be treated according to the investigator's discretion and standard treatment guidelines, irrespective of the reason for withdrawal, and will not be replaced.

Reasonable efforts will be made to contact any patient lost to follow up, to complete assessments (including an EoS assessment) and to retrieve any outstanding data and IMP and supplies.

If the IMP will be prematurely discontinued, the primary reason for discontinuation is to be recorded in the appropriate section of the eCRF. Patients who discontinue therapy with IMP will be encouraged to continue with trial-related assessments (including EoS visit) until their trial completion.

18 Independent Data Monitoring Committee

An IDMC will be established including at least 3 members: an independent clinical virologist (or clinical infectious disease expert), an independent statistician, and an independent pharmacovigilance expert. The independent virologist will serve as Chair. However, additional independent experts may be added, as needed.

The IDMC will have access to efficacy and safety data and information regarding the quality of the data as outlined in the IDMC Charter.

The IDMC will have at least 4 planned formal meetings

- Inaugural meeting (at the start of the trial to discuss function and roles)
- Meeting for the early safety analysis
- Meeting for MA1
- Meeting for IA2, if applicable

More details on their responsibilities are outlined in Section 8.1.

If at the IA2 the IMU-838 therapy arm proves to be statistically significantly more beneficial, the patient enrollment will be stopped.

The IDMC may hold ad hoc teleconference meetings to discuss safety or trial conduct information as needed, or when new safety signals are observed in this trial or in other trials of IMU-838.

Further details on responsibilities and the working procedures of the IDMC will be specified in an IDMC charter.

19 Ethical and legal requirements

19.1 Ethical conduct of the trial

The trial will be conducted in a manner consistent with all applicable regulatory authority and IRB/IEC regulations (e.g., International Council for Harmonisation [ICH] Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95], the Declaration of Helsinki [in its currently acknowledged version], for centers in the USA: IRBs [21 CFR 56], and Obligations of Clinical Investigators [21 Code of Federal regulations [CFR] 312]) as well as in keeping with applicable local law(s) and regulation(s). The investigator must also comply with all applicable privacy regulations (e.g., USA: Health Insurance Portability and Accountability Act of 1996 [HIPAA]; European Union: General Data Protection Regulation [25]).

Financial disclosure by the investigator(s) pursuant to 21 CFR Part 54 will be obtained.

19.2 Independent ethics committee or institutional review board

Before the initiation of the clinical trial, the final protocol, any amendments if applicable, the patient information sheet and consent form, as well as any additional documents which are required by national regulations and the IEC or IRB will be submitted to the competent IEC or IRB for review. A favorable opinion for the clinical trial must be obtained from the IEC or IRB before any patient is enrolled at a center.

If appropriate, any additional requirements imposed by the IEC or IRB will be followed. Amendments to the trial documents will be notified to, or approved by, the IEC or IRB before implementation, if applicable.

19.3 Patient information and consent procedure

Before any clinical trial-related activities are performed, the investigator (or authorized designee) must review the informed consent form and explain the trial to potential trial participants. The investigator must ensure that the patient is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial. Before consenting, the patient must be left with ample time to consider and ask questions. It must be emphasized that participation is voluntary and that the patient has the right to withdraw from the clinical trial at any time without prejudice. The patient and the investigator must then sign and date the consent form before the conduct of any trial procedures.

A copy of the patient information and informed consent form will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this clinical trial.

If amendments to the final trial protocol affect the patient's participation in the clinical trial (e.g., a change in any procedure), the patient information and informed consent form must be updated to incorporate this modification, and patients must agree to sign the amended form indicating that they re-consent to participate in the clinical trial.

For sites in the United States of America: The investigator will comply with all applicable state and federal requirements, including the requirement of the HIPAA Privacy Rule. The authorization to use and disclose protected health information for research is part of the informed consent form, and a signed copy of the informed consent form must be placed in the trial record. Patients from whom additional blood samples will be collected to immune cell subtyping for further research studies will have to provide their consent to that optional additional procedure in the ICF.

19.4 Insurance coverage

Insurance coverage for damages emerging from the clinical trial will be provided according to applicable legal requirements. During the informed consent procedure, the investigator must inform the patient accordingly. Insurance details will be provided to the patient within the patient information sheet.

19.5 Submission to authorities

Documents required for the trial application will be submitted to the responsible competent authority (CA). The trial will not start until this authority has authorized the trial. Amendments to the trial protocol or to any other documents that must be reviewed by the CA will also be submitted to the CA in accordance with the regulatory requirements. If applicable, approval of the amendment must be awaited before implementing any changes.

19.6 Patient confidentiality

The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical trial, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

Personal patient data will be kept confidential in compliance with the General Data Protection Regulation [25], the HIPAA Privacy Rule, and other applicable international and national requirements.

The investigator must ensure that the confidentiality and anonymity of trial participants will be maintained and that their identities are protected from unauthorized parties. In eCRFs,

compensation documentation, or any other documents submitted to the Sponsor or Sponsor's designee, patients must be identified only by their identification codes; it is not allowed to use their names, addresses, telephone numbers, or similar information. The investigator will keep the original of the Patient Identification Log (including complete name and date of birth of each patient) in his/her file. The investigator must maintain these documents in strict confidence.

To allow compliance with GCP, all patients will be asked for consent regarding the access to their personal clinical trial-related data for monitoring, audits, and inspections as well as regarding transmission and storage of their pseudonymous data; a respective statement will be part of the informed consent form. Professionals getting access to source data for monitoring, audits and inspections are bound to preserve strict confidentiality.

20 Criteria for premature termination of the trial and criteria for initializing and closing a trial center

20.1 Trial safety stopping criteria

The trial will be stopped during the early and potential additional safety analyses when the following stopping criteria are fulfilled:

- ≥10% of patients experience at least one SAE Grade 3, or
- ≥5% of patients experience at least one SAE Grade 4

As outlined in Section 15.1.1.3, any SAE requires an underlying event that is considered an AE. Please consider the definitions in Section 15.1.6 when potentially COVID-19 related clinical events are considered an AE.

20.2 Other criteria for halting or terminating the trial

The Sponsor reserves the right to halt or terminate the trial at any time. Reasons for termination include but are not limited to:

- Potential health risk for the patients
- High withdrawal rate
- New scientific knowledge becomes available that makes the objectives of the trial no longer feasible or valid
- Insufficient enrollment of patients
- The IDMC requests termination of the clinical trial based on review of all clinical and laboratory data
- The Sponsor, Regulatory Agency or an IEC or IRB requests the termination of the clinical trial

20.3 Criteria for closing a trial center

A trial center may be closed for the following reasons:

- The center is unable to recruit sufficient patients within the agreed time frame
- The center does not respond to trial management requests
- Multiple significant protocol deviations or substantial non-compliance
- The approval of the IEC or IRB in charge of the clinical trial is permanently revoked
- Additional local criteria might be established by written agreements between the Sponsor and the trial center

The Sponsor will notify the relevant CA, IEC(s), IRB(s) and investigator(s) in writing about the termination of individual centers or the entire trial.

The investigator may terminate his/her participation prematurely. If the investigator decides to terminate his/her participation before the trial is completed, he/she will notify the Sponsor in writing stating the reasons for the early termination. In terminating the trial, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

The investigator will notify the relevant CAs, IEC(s), or IRB(s) in writing, if required, submit a copy of that notification to the Sponsor and return all IMPs and all related trial material, as applicable, to the Sponsor. Concerned eCRFs will be archived at the site. Authorization to access and edit the eCRF will be removed from the investigator and all authorized delegates.

21 Trial protocol, documentation and archiving of data

21.1 Amendments to the protocol

Any change to the protocol concerning the purpose of the trial, the trial design, or the patient's eligibility can only be made in the form of a written amendment to the trial protocol. Such amendments must be discussed and signed by the Sponsor and the investigator before implementation.

Substantial amendments, i.e., amendments likely affecting to a significant degree

- the safety or physical or mental integrity of the patients of the trial
- the scientific value of the trial
- the conduct or management of the trial, or
- the quality or safety of any IMP used in the trial

will be submitted to the CA and IEC or IRB for approval and favorable opinion as required by applicable regulations. If such amendments affect the patient's participation in the clinical trial (e.g., a change in any procedure), the patient information and informed consent form must be updated to incorporate this modification, and patients enrolled at the time of implementation of the amendment must re-consent to their participation in the clinical trial.

Non-substantial changes, e.g., minor corrections of administrative nature and/or rephrasing, which do not meet the above criteria for being substantial, are considered editorial changes. The IEC or IRB and CA do not need to be notified of such minor corrections. Non-substantial amendments will be signed by the Sponsor only.

If new events occur related to the conduct of the trial or the development of the tested IMP that may affect the safety of the patients, the Sponsor and the investigator will take appropriate safety measures to protect the patients against any immediate hazard. The Sponsor will immediately inform the CA and IEC or IRB of the new events and the measures taken.

21.2 Protocol deviations

A protocol deviation is a failure to follow, intentionally or unintentionally, the requirements of the protocol. As required by national regulation or guidelines, reports of deviations will be provided to the IEC or IRB.

In emergency circumstances, deviations from the protocol may proceed without prior consultation with the Sponsor and favorable opinion of the IEC or IRB, if the rights, safety and well-being of the patients need to be protected. Such deviations will be documented and reported to the Sponsor and the IEC or IRB as soon as possible in accordance with national regulations.

All protocol deviations will be listed. If concerned patients are evaluable for data analysis will be discussed in a data review meeting prior to statistical analyses.

21.3 Data retention

The trial center and the Sponsor or Sponsor's designee(s) will maintain all trial records according to ICH GCP and applicable regulatory requirement(s). Records will be retained until at least 2 years after the last approval of a marketing application in an ICH region, until there are no pending or contemplated marketing applications in an ICH region, until at least 2 years have elapsed since the formal discontinuation of clinical development of the tested IMP, and at least 15 years after the end of the trial, whichever period is longer. The final report will be kept for another 5 years after the tested IMP was taken off the market according to legal stipulations. The documents will be archived for a longer period, if required by the applicable regulatory authorities or if agreed with the Sponsor. It is the responsibility of the Sponsor to inform the investigators when these documents need not to be retained any longer.

The medical files of trial patients must be retained in accordance with local legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

22 Data collection, monitoring and quality assurance

22.1 Data collection

All data will be collected on an eCRF separately for each patient. eCRFs will be provided as a regulatory compliant, electronically secure and protected web-based database, and will be handled in accordance with the instructions provided. An audit trail will record all entries and corresponding changes.

All entered data will go through programmed edit checks (see Section 22.5).

The trial sites will be provided with secure access to and training on the eCRF.

All data generated after the patient provided informed consent must be recorded in the eCRF. The investigator is responsible for ensuring accurate and proper completion of the eCRF.

Only investigators and authorized designees will enter and edit data via a secure network and a secure access system. Completed data for each visit will be approved by the investigator or authorized designee using an electronic signature to confirm the accuracy of the data. Any change or addition will be recorded by an electronic audit trail system.

The investigator or designee must carefully answer queries issued by data management.

22.2 Source data

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial (see ICH GCP E6 R2, 1.51). Source records should be stored for a time period as defined by local regulations.

The investigator must keep a patient file (medical file, original medical records) on paper or electronically for every patient included in the trial.

It must be possible to identify each patient by using this patient file. Dates and authors of all source data entry and changes must be clearly identifiable.

Documents and data to be considered source data will be identified and agreed with the investigator in advance of the first visit. The location of all source data will be documented and filed in the Investigator Site File (source data location form or equivalent).

Electronic patient files will be printed whenever the monitor performs source data verification, if applicable. Printouts must be signed and dated by the investigator and filled at the center as required for other source data documents.

22.3 Monitoring

Critical data will be identified to ensure patients' safety and the reliability of trial results. The extent and details of monitoring including source data verification will be specified in the monitoring plan. All critical data require source verification by the monitor.

The trial center must not enroll any patient before the initiation was performed and final eligibility of the center is confirmed by the monitor and Sponsor. Depending on the pandemic situation of the centers site qualification and site initiation visits might be performed in a remote setting. During the trial, regular monitoring visits will be performed according to ICH GCP, the Sponsor's designee's or local CRO's standard operating procedures, and local regulations. The frequency and kind of monitoring visits will depend amongst other factors on the trial site's recruitment rate and current pandemic situation in each country and trial center.

Risk-based monitoring including reduced source data verification, triggered monitoring, centralized monitoring, and targeted monitoring will be conducted [26-29]. The extent and details of this monitoring methods will be defined in the monitoring plan.

Due to the current COVID-19 pandemic situation, physical monitoring visits at the centers may not be feasible or restricted for some time, and either a combined remote and on-site monitoring or full remote monitoring visit will be conducted during these periods. The Sponsor authorizes the designated local CROs to include remote monitoring visits according to the applicable guidelines and regulations into the monitoring activities. In line with local laws and regulations remote source data verification might be part of the remote monitoring visits and if so, has to be agreed between the Sponsor designee, the investigator and additional investigational staff at each center. The relevant trial documents (e.g., monitoring plan) will be adjusted to reflect these activities that will be held during the period when standard monitoring visits are not possible.

Options for remote monitoring - in compliance with the local, country specific regulations, requirements and relevant guidelines - might be phone calls, audio/videoconferencing, and sharing of medical records (e.g., direct access to Electronic Health Records [30, 31] sharing redacted/blinded medical records in a secured way, etc.), depending on the center's capability to contribute.

The ICH-GCP requirements and applicable data protection and privacy regulations must be met in any case and for any selected monitoring approach. As part of the informed consent form, the patients need to agree to a remote monitoring of data.

The investigators must permit the monitor access to the patient's medical records and all other applicable source documents. Throughout the trial, all data captured in the eCRF will only be identified by patient number. The data will be pseudonymized correspondingly in all data analyses.

It is the investigators' obligation to assure documentation of all relevant data in the patient's file, such as medical history and concomitant diseases, date of trial enrolment, visit dates, results of examinations, administrations of IMP and any concomitant medication, and AEs.

22.4 Audits and inspections

During the trial, audits may be performed by independent auditors. Audits of clinical research activities will be performed in accordance with corresponding standard operating procedures to ensure compliance with the principles of GCP.

Regulatory authorities may wish to conduct an inspection. If an inspection is requested, the investigator must inform the Sponsor or Sponsor's designee immediately.

The investigator must allow auditors or inspectors access to source data and documents and will answer any questions.

Depending on the COVID-19 pandemic situation of the centers with regards to center accessibility, remote audits might be considered in line with local laws and regulations and without adding additional burden to center staff.

22.5 Data management procedures

All data management activities will be conducted by the Sponsor's designee following their standard operating procedures.

Details on data handling will be described in the data management plan. Data entered into the eCRF will be validated through online edit checks and offline checks run by the data manager or designee according to the data validation plan. For all identified discrepancies, the data manager will raise a query in the electronic data capture application. The appropriate investigational personnel will answer the queries in the eCRF, which will be audit trailed by the electronic data capture application.

The Sponsor's designee will handle the data cleaning process, query process, and coding.

For the MA1, FA1, and FA2, the respective database will be locked when it is considered complete and accurate and after all changes following the data review meeting (if applicable) are included (i.e., all data cleaning activities performed). All changes will be tracked (audit trail). Sponsor approval prior to database lock is mandatory.

22.6 Trial report and publications

The results of Part 1 (MA1 and FA1) and Part 2 (FA2) of the trial will be each summarized in a clinical trial report according to the ICH E3 Note for guidance on structure and content of clinical trial reports.

The main conclusions of the early safety analysis, MA1 and IA2 will be submitted to investigators as well as to regulatory authorities and IECs, as appropriate, within the timeframes defined per national regulation or by the IEC or IRB.

The preparation and submission of abstracts of manuscripts including the trial results must be in line with the process specified in the investigator's clinical trial agreement and shall be organized by the Coordinating Investigator. The publication or presentation of any trial results shall comply with all applicable privacy laws, for example, the USA's HIPAA and he European Union's General Data Protection Regulation [25].

23 Trial periods

Part 1:

Phase 2 (Proof-of-Activity Phase, Part 1):

Estimated start (first patient in):	May 2020 (actual 12-Jun-2020)
Estimated recruitment period:	4 months
Estimated end of trial (last patient out):	Nov 2020

Optional Phase 3 (Part 2):

To be defined after MA1, if applicable

The end of the trial is defined as last patient last visit in the entire trial.

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25 Approval and signatures

Protocol agreed to by Sponsor:

ANDREAS MUEHLER

Sponsor's signatory name (print)

Sponsor's signatory signature

04-SEP-2020

Date

Protocol agreed to by coordinating investigator:

Neera Ahuja, MD

Coordinating investigator name (print)

Neera Ahuja, MD

Coordinating investigator signature

9/8/2020

Date

Principal investigator agreement page for the protocol

I agree:

- To assume responsibility for the proper conduct of the clinical trial at this site, and to conduct the trial in compliance with national law, the valid version of the Declaration of Helsinki, the GCP-guidelines, the present trial protocol including its amendments, and with any other trial conduct procedures provided by the Sponsor or authorized representatives.
- Not to implement any deviations from or changes to the protocol (including protocol amendments) without agreement from the Sponsor and prior review and favorable opinion from the ethics committee and approval from the competent authority, if applicable, except where necessary to eliminate an immediate hazard to the patient(s), or for administrative aspects of the clinical trial (where permitted by all applicable regulatory requirements).
- That I am familiar with the appropriate use of the investigational medicinal product as described in this protocol and any other information provided by the Sponsor including, but not limited to, the current investigator's brochure or equivalent document provided by the Sponsor.
- To ensure that all persons assisting me with the clinical trial are adequately informed about the investigational medicinal product and of their trial-related duties and functions.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or the trial product, and more generally about his/her financial ties with the Sponsor. The Sponsor will use and disclose the information solely for the purpose of complying with regulatory requirements.

_____

Principal investigator name (print)

_____ _____

Principal investigator signature Date

26 Appendices

Appendix 1 Central Laboratory Kits

A-Table 1: Central Laboratory Kits

Lab Kit Designation (Laboratory)	Parameters	Storage/shipping conditions
Kit A (Central safety laboratory)	**Hematology** Full differential blood cell count erythrocytes, leucocytes, differential leucocyte count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets. **Biochemistry** *Liver function monitoring:* aspartate amino transferase, alanine amino transferase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, unconjugated (indirect) and conjugated (direct) bilirubin. *Renal function monitoring*: creatinine, uric acid, blood urea nitrogen (BUN). Estimated glomerular filtration rate (eGFR) will be calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for adults and according to the Schwartz bedside equation for children and adolescents.[a] *Other parameters:* Sodium (Na), potassium (K), magnesium, chloride (Cl), inorganic phosphate (P), calcium (Ca), creatine phosphokinase, amylase, lipase, total protein, albumin, glucose, hemoglobin A1c, triglycerides, cholesterol, ferritin **Urinalysis** pH, nitrites, hemoglobin, protein, albumin, glucose, ketones, creatinine. Microscopic examination of the urine sediment only for cases when positive hemoglobin test is detected	Ambient shipment on day of sampling
Kit B (Central safety laboratory)	D-dimer, lactate dehydrogenase (LDH) and C-reactive protein (CRP) Troponin I (cTN) Procalcitonin (PCT) NT-proB-type Natriuretic Peptide (BNP)	At least -20°C (-4°F) on site, dry ice shipment within 6 weeks
Kit C (Central safety laboratory)	Everything included in Kit B plus: Coagulation: Prothrombin time, partial thromboplastin time, and international normalized ratio (INR) Interleukin (IL)-17, IL-1ß, IL-6, interferon gamma (IFNγ), and tumor necrosis factor alpha (TNFα)	At least -20°C (-4°F) on site, dry ice shipment within 6 weeks
Kit PK (Central safety laboratory)	Trough level IMU-838	At least -20°C (-4°F) on site, dry ice shipment within 6 weeks

A-Table 1: Central Laboratory Kits (*continued*)

Lab Kit Designation	Parameters	Storage/shipping conditions
Kit D (Central virology laboratory)	SARS-CoV-2 status (qualitative)[b] and viral load by reverse transcriptase polymerase chain reaction (RT-PCR) in nasopharyngeal swab and spontaneous sputum	At least -20°C (-4°F) on site, dry ice shipment within 7 days
Kit E (Central safety laboratory)	IgA and IgG antibodies against SARS-CoV-2	At least -20°C (-4°F) on site, dry ice shipment within 6 weeks

[a] Fadrowski JJ, Neu AM, Schwartz GJ, Furth SL. Pediatric GFR estimating equations applied to adolescents in the general population. Clin J Am Soc Nephrol 2011;6(6):1427-35.
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[b] Qualitative assessment of SARS-CoV-2 status may be evaluated as absence or presence of virus in the quantitative SARS-CoV-2 RT-PCR assessments.

Appendix 2 Local laboratory tests required at Screening

The following local laboratory tests are required at Screening to check for eligibility

- White blood cell count
- Platelet count
- Total bilirubin
- Alanine aminotransferase (ALT) or gamma glutamyl transferase (GGT)
- Serum creatinine
- For women of childbearing potential: blood pregnancy test
- If the patient has known Gilbert syndrome: indirect [unconjugated] bilirubin
- SARS-CoV 2 qualitative test (within 4 days before randomization)

For exclusion criterion 17, the estimated glomerular filtration rate value (eGFR) must be calculated as follows:

- For adults according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

  $$GFR\ [mL/min/1.73\ m^2] = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

  where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

- For children and adolescents (12 to 17 years) according to the Schwartz bedside equation

  $$GFR\ [mL/min/1.73\ m^2] = 0.413 \times (height/Scr)$$

  where Scr is serum creatinine (mg/dL) and height expressed in centimeters.

Appendix 3 Modified WHO Ordinal Scale for Clinical Status

Patient state	Descriptor	Score
Uninfected or no longer infectious	No clinical or virological evidence of infection	0
Mild Disease	Ambulatory, virus-positive, no limitation of activities	1
	Ambulatory, virus-positive, limitation of activities	2
Moderate Disease	Hospitalized, virus-positive, no oxygen therapy	3
	Hospitalized, virus-positive, oxygen by mask or nasal prongs	4
Severe Disease	Hospitalized, virus-positive, non-invasive ventilation or high-flow oxygen	5
	Hospitalized, virus-positive, intubation and mechanical ventilation	6
	Hospitalized, virus-positive, ventilation plus additional organ support (pressors, RRT, ECMO)	7
Dead	Death	8

ECMO = extracorporeal membrane oxygenation, RRT = renal replacement therapy.
Based on [21].