Final Clinical Trial Report

Synopsis

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)

P2-IMU-838-COV

Final Analysis (Part 1)

EudraCT No.: 2020-001264-28

ClinicalTrials.gov: NCT04379271

IND: 149,167

Investigational product:	IMU-838
Clinical development phase:	2
Indication:	COVID-19 disease
Sponsor:	Immunic AG Lochhamer Schlag 21 82166 Gräfelfing Germany
Coordinating investigator:	Dr. Neera Ahuja, Stanford University School of Medicine Stanford, CA, USA
Coordinating investigator (from 11 September 2020 onwards):	Prof. Dr. Maria Vehreschild, Goethe-University Frankfurt, Frankfurt am Main, Germany
Date of first patient enrolled:	11 June 2020
Date of last patient completed:	23 February 2021
Sponsor's signatory name:	Andreas Muehler, MD
Prepared by:	VCLS
Report version and date:	Final Version (18 August 2021)

This trial was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents.

1 Synopsis

Name of sponsor/company: Immunic AG
Name of product: IMU-838
Name of active ingredient: Vidofludimus calcium

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 (CALVID-1)

Trial registry: NCT04379271 (ClinicalTrials.gov), 2020-001264-28 (EudraCT)
Protocol number: P2-IMU-838-COV

Principal investigator(s) and trial center(s):
27 clinical sites in Bulgaria, Germany, Greece, Hungary, Moldova, North Macedonia, Romania, Ukraine and the United States

Coordinating investigator: Dr. Neera Ahuja,
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From 11 September 2020 onwards:
Prof. Dr. Maria Vehreschild,
Goethe-University Frankfurt,
Frankfurt am Main, Germany

Publication (reference): Not applicable

Studied period:
11 June 2020 (first patient in) to 23 February 2021 (last patient completed)

Reporting period:
Main trial period, Part 1: Screening to Day 28/End-of-study (EoS)

Clinical phase: 2

Objectives:
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

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

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)

Pharmacokinetics

- To evaluate trough plasma levels of IMU-838

Safety

- To evaluate safety and tolerability of IMU-838

Disease markers

- To explore blood levels of disease markers

Virologic markers, biomarkers, and serologic markers

- To explore viral titers, measures of viral virulence and inflammatory markers

Methodology:

The trial was to consist 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 was only to be started after results from main analysis of Part 1 (MA1) had been analyzed and indicated activity of IMU-838 in COVID-19.

Both parts were to follow a multi-center, 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 were centrally randomized 1:1 to twice-daily (BID) oral 22.5 mg IMU-838 (45 mg/day + SoC) or placebo (+ SoC). Randomization was stratified by age (< or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals).

An early safety analysis was performed and evaluated by an Independent Data Monitoring Committee (IDMC) after 30 patients in Part 1 had completed Day 28 to assess unblinded safety data. Enrollment in US centers was paused after these first 30 patients to allow evaluation of safety stopping criteria by the IDMC. The IDMC requested that an additional safety analysis be performed after complete safety data had been accrued from an additional 30 patients.

The unblinded MA1 was performed after approximately 200 patients had completed Day 28/ EoS, either as scheduled or prematurely, while enrollment continued. Following the MA1

analysis, it was decided not to progress into Part 2 of the trial. A further 30 patients were enrolled into Part 1 and treated in a double-blind manner until the results of the MA1 were available. A final analysis of Part 1 (FA1) was performed after completion of Part 1, using all enrolled patients, i.e. 234 patients and is described in the present clinical study report.

Screening

Patients were screened for a maximum of 2 days (from Day -2 to Day 0) and eligible patients were randomized on Day 0 and treated with investigational medicinal product (IMP) + SoC for 14 days. It was encouraged to screen potential trial patients 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 could also have been used, except for testing of positive status of Severe Acute Respiratory Syndrome Coronavirus Virus -2 (SARS-CoV-2) infection where a 4-day window was allowed.

IMP administration was to start as quickly as possible after randomization and first IMP dose was 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 have always been given on Day 0 (allowed range for first dose: 12:00 noon on Day 0 to 02:00 a.m.). All further IMP doses were 1 tablet each in the morning and evening. Information about the status and patient care were continuously obtained and documented once or twice daily. Further examinations and tests, laboratory parameters, biomarkers, disease markers, and virologic parameters were assessed.

The last IMP dose was administered in the evening of Day 13 and the end-of-treatment assessments were done on Day 14 (T-Table 1). Blood sampling for IMU-838 trough values were performed in the morning around the time the morning dose was usually taken by the respective patient. Only samples from patients who received IMU-838 were assessed. Patients then continued to receive SoC without any further restrictions on concomitant medications as during the 14-day blinded treatment period.

Assessments were to be performed in case of hospital discharge before Day 14. *For centers in Bulgaria only: Patients must have been hospitalized during the entire treatment period i.e., from Day 0 to Day 14.*

Day 28 Visit (EoS)

The patient was to return for the final trial visit on Day 28 (EoS). If IMP was prematurely discontinued for any reason, the EoS visit was to be conducted on Day 28 and no earlier EoS should have been performed. If patients withdrew from IMP prematurely, they were to be encouraged to allow the EoS visit as part of the follow-up. If the patient died during the trial, the investigator was to indicate that this visit was not performed. However, even if no EoS visit was performed, information about patient status was reported on the EoS page in the case report form. If the patient refused any EoS visit or the patient was lost to follow-up, it was 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 search in registers or publicly available information for such status of life information.

Safety follow up

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

Number of patients (total and for each treatment) planned and analyzed:

Planned: Approximately 200 patients were planned to be randomized 1:1 to treatment with 45 mg/day IMU-838, or placebo (100 patients each) in the treatment period.

Analyzed: 223 patients were randomized; 220 patients were treated and included in the full analysis and safety data set (110 patients each in the 45 mg IMU-838 group and the placebo group).

Diagnosis and main criteria for inclusion and exclusion:

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 World Health Organization (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 adverse events (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 extracorporeal membrane oxygenation (ECMO) or renal replacement therapy (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 dihydroorotate dehydrogenase (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

Test product, dose, mode of administration, batch no.:
IMU-838 (vidofludimus calcium), a small molecule inhibitor of DHODH

Formulation: Tablets with 22.5 mg IMU-838

Batch numbers: D022E, D025E, G028E, H018E.

Administration: The first dose of IMP (2 tablets) were given on Day 0 (allowed range for first dose: 12:00 noon on Day 0 to 02:00 a.m.). All further IMP doses were 1 tablet each in the morning and evening to Day 13.

Reference product, dose, mode of administration, batch no.:
Matching placebo, oral administration of 1 or 2 tablets, as described for the test product, batch numbers: D022E, D025E, G028E, H018E.

Duration of treatment: 14 days

Criteria for evaluation:
Primary

Efficacy

Proportion of patients without any need for INV until EoS

Key secondary

Efficacy

- Proportion of patients surviving without respiratory failure (defined as any need of ICU, INV, high-flow oxygen or ECMO* until EoS)
- Duration of ICU treatment until EoS
- 28-day all-cause mortality

Secondary

Efficacy

- Time to 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[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 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 [1] on Days 6, 14, and 28

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 [1], 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
- 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
- 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

* 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 were counted for this endpoint.

Pharmacokinetics

- 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

- AEs and serious adverse events (SAEs)

- Vital signs
- Clinical laboratory parameters (blood chemistry, hematology, and urinalysis)
- Electrocardiogram (ECG) parameters
- Temperature

Pharmacokinetics

- D-dimer
- Lactate dehydrogenase (LDH)
- C-reactive protein (CRP)
- Troponin I (cTn)
- ProB-type natriuretic peptide (BNP)
- Procalcitonin (PCT)
- Correlation of disease markers to selected clinical outcomes

Virologic markers

- 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

Biomarkers

- Interleukin (IL)-17, IL-1ß, IL-6, interferon gamma (IFNγ), tumor necrosis factor α (TNFα)

Serologic markers

- Immunglobulin (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

Statistical methods:

In Part 1, all endpoints were analyzed descriptively. In addition, exploratory confidence intervals were 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 were conducted.

The primary endpoint was 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 was conducted. The OR was calculated adjusted for the stratification factors age (<or ≥65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all

other antivirals). The OR corresponds to the odds for need of INV in IMU-838 group / odds for need of INV in placebo group. An OR < 1 indicates that the chance of receiving INV is higher for patients treated with placebo than for patients treated with IMU-838 after adjusting for age (< or ≥ 65 years) and antiviral therapy (no antivirals, Hydroxychloroquine and Chloroquine, all other antivirals).

For qualitative variables, the frequencies (absolute and relative) were calculated. Quantitative parameters were described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, and maximum. The treatment groups were separately tabulated.

Kaplan Meier estimates (including quartile and 90% quantile estimates) were performed for time to event analyses.

SUMMARY-CONCLUSIONS

Patient disposition

A total of 234 patients were screened and 223 patients were randomized. Of these, 111 were randomized to the IMU-838 group and 112 to the placebo group. All randomized patients were treated, except for 3 patients, 1 randomized to the IMU-838 group and 2 randomized to the placebo group. Of the 110 treated patients in the IMU-838 group, 93 (84.5%) completed the trial. In the placebo group, 97 (88.2%) of the 110 treated patients completed the trial.

Demographics and Baseline characteristics

Overall, slightly more men (54.1%) than women (45.9%) were included; there was a greater proportion of women in the patients randomized to the IMU-838 group (50.0%) than to the placebo group (41.8%). Except for 2 patients all screened patients were White. Most were not receiving antiviral therapy at randomization (overall 82.3%); patients under antiviral therapy were equally distributed between the treatment groups (13.6% in the IMU-838 group and 14.5% in the placebo group). Overall, 166 patients (75.5%) were below the age of 65 years. The mean age of the patients in the 45 mg IMU-838 group was 54.5 years (range 24 to 83 years) and was 53.7 years (range 20 - 85 years) in the placebo group.
A total of 61 (55.5%) of the patients in the IMU-838 group and 57 (51.8%) of the patients in the placebo group reported at least 1 high risk factor, with some risk factors tending to be more common in the IMU-838 group than the placebo group, potentially implying a more severe disease course in IMU-838 treated than placebo-treated patients. The most frequently reported risk factor in both treatment groups was cardiovascular disease; 51.8% of the patients in the IMU-838 and 42.7% of the patients in the placebo group reported cardiovascular disease, including hypertension, followed by an age ≥65 years (approximately 24% of the patients in each group).

Efficacy results

The primary efficacy endpoint was the proportion of patients without any need for INV through Day 28. In contrast to the relatively high rates of ventilation reported in the first COVID-19 wave in early 2020, the actual confirmed rate of INV for hospitalized patients with moderate COVID-19 was less than 1% (i.e., 1 patient in each treatment group). This

very low event rate, consistent with the findings of many recent third-party trials in COVID-19, prevented a valid and meaningful analysis of the primary endpoint.

Regarding the key secondary endpoints, the trial was designed to investigate the ability of IMU-838 to reduce the probability of major complications for COVID-19 patients, such as 28-day mortality, survival without respiratory failure, and the probability of use of ICU treatment. Similar to the low ventilation rates discussed above, the trial found a confirmed rate of less than 2% for 28-day mortality, balanced between the 2 arms, and less than 4.5% of patients were admitted to the ICU during the trial. Based on the very low complication rates in this trial and due to the known variability of the disease course, it is believed that the evaluation of these key secondary endpoints is neither valid nor meaningful. It should also be noted that all assessments which included an evaluation of health status using the WHO 9 ordinal scale (clinical improvement, change in clinical status) or hospitalization were confounded by the requirement that Bulgarian patients (who represented approximately 25% of the enrolled patients) remain hospitalized to Day 14.

The variability of the clinical course also resulted in the inability to provide evidence of a relationship between viral load decrease or seroconversion to clinical recovery or to clinical improvement in patients in this trial.

Despite the low mortality and INV rates observed in this trial, the clinical activity of IMU-838 was shown based on multiple secondary clinical endpoints. Compared to placebo, more patients in the 45 mg IMU-838 group had reached clinical recovery at Day 7 and Day 28. Kaplan-Meier analysis of the time to clinical improvement indicated that whereas the time to clinical improvement at the 50% quartile was similar between groups, clinical improvement at the 75% percentile was reached within a shorter timeframe in patients in the IMU-838 group compared to the placebo group (by approximately 1 day). The proportion of patients with clinical improvement at Day 28 was similar in the 2 treatment groups (91.7% in the IMU-838 group versus 88.2% in the placebo group). There were indications that the duration of hospitalization could be shortened with IMU-838 and the treatment appeared to provide more benefit when given to high risk patients or to the sub-group of elderly patients. Similar to other antiviral medications, starting treatment with IMU-838 early (within 9 days of symptoms) provided a shorter time to clinical improvement as compared to a delayed treatment start as shown by a post-hoc analysis.

Safety results

The incidence of treatment-emergent AEs (TEAEs) was higher in the IMU-838 group (73.6%) than the placebo group (61.8%) and the most frequently reported TEAEs were hypertriglyceridemia (20.9% of patients in the IMU-838 group and 11.8% of patients in the placebo group), increased glycosylated hemoglobin (9.1% and 5.5% of patients, respectively); headache, thrombocytosis and hyperglycemia appeared without relevant differences between treatment groups.

The incidence of TEAEs related to IMP/trial procedures was higher in the IMU-838 group (18.2%) than the placebo group (9.1%). However, common related TEAEs (hepatitis toxic, ALT increase, GGT increase, hematuria) were equally distributed amongst the 2 groups. Of note, headaches – although not frequent - were reported only in the IMU-838 group.

Most TEAEs were of mild or moderate severity; Grade 3 TEAEs were reported at a slightly lower frequency in the IMU-838 group than in the placebo group (6.4% and 9.1%, respectively), as were Grade 4 events (0% and 1.8%, respectively). Grade 5 events were reported at a frequency of 1.8% in both treatment groups.

The incidence of SAEs was also lower in the IMU-838 group; a total of 7 SAEs were reported (2 in the IMU-838 group and 5 in the placebo group), including 1 severe SAE (deep vein thrombosis), 2 life-threatening SAEs (COVID-19 pneumonia and respiratory distress) and 4 SAEs that led to the patient's death (hypoxia, cardio-respiratory arrest, bradycardia and acute respiratory failure). None of the SAEs was considered to be related to IMP/trial procedures; 5 SAEs (3 which led to death and 2 which did not) were considered as COVID-19 related TEAEs.

The incidence of TEAEs leading to discontinuation of IMP was similar between the 2 treatment groups; of the 8 events leading to discontinuation of IMP, 5 were reported as related to IMP (2 in the IMU-838 group and 3 in the placebo group).

Clinically significant increases in ALT, GGT, ferritin, triglycerides and glycated hemoglobin were reported in both treatment groups.

No trends in vital sign abnormalities were observed.

The incidence of TEAEs of increased severity related to COVID-19 was lower in the IMU-838 group (8 [7.3%] patients) than in the placebo group (13 [11.8%] patients).

Pharmacokinetic results

An increase in IMU-838-level was observed at Day 1, and trough levels increased through the treatment period to reach steady state at approximately Day 5-6, where the mean (standard deviation [SD]) and median levels of plasma IMU-838 were 4.3607 (2.4872) and 4.0400 at Day 6, respectively. At Day 14, mean and median trough values were 4.6514 µg/mL and 4.2200 µg/mL, respectively. IMU-838 levels had returned to Baseline values by Day 28. The number of days to clinical recovery tended to be fewer with higher IMU-838 trough levels. This effect was more pronounced at the 25% and 50% percentiles than at the 75% percentile of recovery. A higher trough level of IMU-838 was shown to reduce the days to clinical recovery by more than 50%.

Disease markers

Analysis of the plasma level of disease markers (D-dimer, LDH, CRP, cTn, BNP, and PCT) showed no sustained clinically relevant differences between treatment groups. No relationship between disease markers and time to clinical recovery or to clinical improvement could be evidenced.

Virologic markers, biomarkers, and serologic markers

The profiles of immune system biomarkers (IFN γ, IL 1β, 6, 17 and TNFα) were not markedly different in the 2 treatment groups.

Overall, > 80% of patients had developed IgA / IgG antibodies against SARS-CoV-2 by Day 6, and virtually all patients had detectable antibodies at Day 28. The rate and timing of

appearance of IgA and IgG antibodies was not markedly different between treatment groups, indicating that treatment with IMU-838 did not interfere with the development of anti-SARS-CoV-2 antibodies.

Concomitant infections were reported in 34.8% of the patients in the IMU-848 group and 46.2% of the patients followed for this parameter.

As expected, SARS-CoV-2 viral load decreased over time during the trial. At Day 28, 57.0% of the patients in the IMU-838 group and 61.2% of the patients in the placebo group were negative for SARS-CoV-2 in nasopharyngeal samples analyzed by the central laboratory. Kaplan-Meier estimations indicated that the virus negativity at the 50% quartile for viral negativity was reached after 14.0 days for the IMU-838 group and 13.8 days for the placebo group.

Conclusions:

Although a beneficial effect of IMU-838 on the disease course in patients with moderate COVID-19 could not be formally demonstrated in this trial due to low rates of complications and design issues resulting from the requirement for some patients to remain hospitalized for the duration of treatment, the good safety profile and the positive, concentration-dependent effect of IMU-838 observed on some clinical parameters such as clinical improvement and clinical recovery warrant the further assessment of IMU-838 in the clinical trial setting for COVID-19.

References

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