Clinical trial results:
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

Summary

EudraCT number	2020-001264-28
Trial protocol	DE BG RO GR HU
Global end of trial date	23 February 2021

Results information

Result version number	v1 (current)
This version publication date	25 October 2022
First version publication date	25 October 2022
Summary attachment (see zip file)	Final Clinical Trial Report Synopsis (P2-IMU-838_CALVID_final_18AUG2021_Final Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	P2-IMU-838-COV

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04379271
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Immunic AG
Sponsor organisation address	Lochhamer Schlag 21, Gräfelfing, Germany, 82166
Public contact	Chief medical officer, Immunic AG, andreas.muehler@imux.com
Scientific contact	Chief medical officer, Immunic AG, andreas.muehler@imux.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2021
Global end of trial reached?	Yes
Global end of trial date	23 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The trial was conducted in a manner consistent with all applicable regulatory authority and institutional review board (IRB)/independent ethics committee 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 centres in the USA: IRBs [21 Code of Federal regulations [CFR] 56], and Obligations of Clinical Investigators [21 CFR 312]) as well as in keeping with applicable local law(s) and regulation(s).
Before any clinical trial-related activities were performed, the investigator (or authorized designee) had to review the informed consent form and explained the trial to the patient. The investigator ensured that the patient was fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial.
An Independent Data Monitoring Committee (IDMC) was established to safeguard the interests of the patients and to provide recommendations on trial conduct and sample size. The IDMC also fulfilled the designated functions of a Data Safety Monitoring Board.
Further risk minimisation procedures included:
• specific inclusion and exclusion criteria which ensured that patients who presented with characteristics that may have increased the risk for an adverse outcome were excluded
• close monitoring of patients with Gilbert syndrome
• a recommendation that patients with an increased risk for haematuria were supplemented with oral bicarbonate or oral Neoralit SR
• regular monitoring of liver enzymes.

Background therapy:

All patients received SoC treatment that included any treatments, medications, and procedures that investigators customarily used to treat COVID-19 in their clinical practice e.g., supportive pharmaceutical treatments, medications with any approved antiviral indication, intravenous fluids, supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal replacement therapy, and extracorporeal membrane oxygenation.

Evidence for comparator: -

Actual start date of recruitment	11 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Bulgaria: 71

Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Moldova, Republic of: 54
Country: Number of subjects enrolled	North Macedonia: 8
Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	223
EEA total number of subjects	120

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	168
From 65 to 84 years	54
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial started to enrol patients on 11-Jun-2020 and concluded recruitment on 11-Dec-2020. Overall, 27 sites were initiated of which 20 sites recruited patients.

Pre-assignment

Screening details:

A total of 234 patients were screened and 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).

Period 1

Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	IMU-838

Arm description:

Patients were randomized to receive oral 22.5 mg IMU-838 twice daily (45 mg/day) in addition to SoC.

Arm type	Experimental
Investigational medicinal product name	IMU-838
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets (22.5 mg IMU-838) were taken twice daily 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).

Arm title	Placebo

Arm description:

Patients were randomized to receive placebo twice daily in addition to SoC.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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

Number of subjects in period 1[1]	IMU-838	Placebo
Started	110	110
Completed	93	97
Not completed	17	13
Adverse event, serious fatal	2	2
Patient could not/refused to attend clinic visits	5	-
Consent withdrawn by subject	8	10
Adverse event, non-fatal	1	-
Poor general health condition	1	-
Violation of eligibility criteria	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Three patients were enrolled in the trial but not treated and are not included in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	IMU-838
Reporting group description:	
Patients were randomized to receive oral 22.5 mg IMU-838 twice daily (45 mg/day) in addition to SoC.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to receive placebo twice daily in addition to SoC.	

Reporting group values	IMU-838	Placebo	Total
Number of subjects	110	110	220
Age categorical Units: Subjects			
Adults (18-64 years)	83	83	166
From 65-84 years	27	26	53
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	54.5	53.7	
standard deviation	± 13.4	± 14.2	-
Gender categorical Units: Subjects			
Female	55	46	101
Male	55	64	119

End points

End points reporting groups	
Reporting group title	IMU-838
Reporting group description:	
Patients were randomized to receive oral 22.5 mg IMU-838 twice daily (45 mg/day) in addition to SoC.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to receive placebo twice daily in addition to SoC.	

Primary: Need for invasive ventilation (INV)	
End point title	Need for invasive ventilation (INV)
End point description:	
Number of patients without any need for INV until end-of-study (EoS).	
End point type	Primary
End point timeframe:	
Throughout the trial (Day 0 to Day 28)	

End point values	IMU-838	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: Pateints	98	101		

Statistical analyses

Statistical analysis title	Odds ratio
Statistical analysis description:	
An odds ratio (OR, IMU-838/placebo) with an exact 2-sided 90% confidence interval was calculated. The OR was calculated adjusted for the stratification factors age (< or ≥65 years) and antiviral therapy (no antivirals, hydroxychloroquine and chloroquine, all other antivirals).	

Comparison groups	IMU-838 v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.4426
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5997
upper limit	3.4959

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse event data were collected until Day 60 after randomization.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	IMU-838
Reporting group description:	
Patients were randomized to receive oral 22.5 mg IMU-838 twice daily (45 mg/day) in addition to SoC.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized to receive placebo twice daily in addition to SoC.	

Serious adverse events	IMU-838	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 110 (1.82%)	4 / 110 (3.64%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 110 (0.91%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 110 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	IMU-838	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 110 (73.64%)	67 / 110 (60.91%)	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Systematic			

subjects affected / exposed	5 / 110 (4.55%)	6 / 110 (5.45%)	
occurrences (all)	5	6	
Glycosylated haemoglobin increased			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 110 (9.09%)	6 / 110 (5.45%)	
occurrences (all)	10	6	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 110 (5.45%)	4 / 110 (3.64%)	
occurrences (all)	8	8	
Hypertensive crisis			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 110 (5.45%)	3 / 110 (2.73%)	
occurrences (all)	8	3	
Cardiac disorders			
Bradycardia			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 110 (3.64%)	6 / 110 (5.45%)	
occurrences (all)	6	9	
Sinus bradycardia			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 110 (5.45%)	5 / 110 (4.55%)	
occurrences (all)	6	5	
Tachycardia			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 110 (6.36%)	2 / 110 (1.82%)	
occurrences (all)	7	2	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 110 (7.27%)	5 / 110 (4.55%)	
occurrences (all)	9	6	
Blood and lymphatic system disorders			

Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 110 (3.64%)	6 / 110 (5.45%)	
occurrences (all)	4	6	
Thrombocytosis			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 110 (5.45%)	8 / 110 (7.27%)	
occurrences (all)	6	8	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 110 (0.91%)	6 / 110 (5.45%)	
occurrences (all)	1	7	
Hepatobiliary disorders			
Hepatocellular injury			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 110 (2.73%)	7 / 110 (6.36%)	
occurrences (all)	4	7	
Renal and urinary disorders			
Haematuria			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 110 (6.36%)	4 / 110 (3.64%)	
occurrences (all)	7	4	
Metabolism and nutrition disorders			
Hyperglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 110 (4.55%)	8 / 110 (7.27%)	
occurrences (all)	7	8	
Hypertriglyceridaemia			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 110 (20.91%)	13 / 110 (11.82%)	
occurrences (all)	24	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2020	Main changes included: • Included that chloroquine and hydroxychloroquine were prohibited for all centres in all countries unless already taken for indicated use before entering the trial (in Version 1.0 it was only prohibited for all centres in Germany and allowed with special recommendations in other countries) • Included that use of other dihydroorotate dehydrogenase inhibitors, including teriflunomide or leflunomide was prohibited • Secondary endpoints: "Clinical patient status on the 9-category WHO ordinal scale on Days 6, 14, and 28" changed to "Change in daily clinical patient status on the WHO 9-category ordinal scale" • 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 was 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 was to be used for adults. Respective references were added.
04 September 2020	• Specified that a safety follow-up was to be performed after D28/EOS examination until Day 60 • "Proportion of patients surviving without respiratory failure" added as key secondary endpoint and respective objective • Specified that Part 1 and Part 2 were to be handled as independent parts and respective changes in analysis, sample size and trial conduct implemented • Patients with clinically relevant conditions leading to hyperuricaemia excluded (Exclusion Criterion 12) • Patients with known Gilbert syndrome (unless their indirect [unconjugated] bilirubin level was confirmed to be <1.2 x upper limit of normal i.e. <1.1 mg/dL) excluded (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/1.73m² body surface area according to the CKD-EPI equation for adults (or the Schwartz bedside equation for children and adolescents, if applicable) excluded (Exclusion Criterion 17) • Patients with Child Pugh B liver impairment excluded • Schedule of assessment updated • Clarified that for the main analysis (MA1) the IDMC and Sponsor were unblinded, the blind, however, was to be kept for patients and investigators until final analysis (FA1). • Specified that also COVID-19 related symptoms with clinically unusual worsening during the trial weere to be reported as adverse events • Statistical analysis updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For sample size calculation the proportion of patients needing INV was assumed to be 32% (IMU-838) and 40% (placebo). The actual observed frequency was substantially lower (<1%), which prevented the primary endpoint from being evaluable.

Notes: