



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: Patients | 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 | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 30 April 2020 | <p>Main changes included:</p> <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 $<1.2 \times$ 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 were 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: