PROTOCOL SYNOPSIS

CLINICAL TRIAL TITLE	Effect of dexamethasone in patients with ARDS and COVID-19 – prospective, multi-centre, open-label, parallel-group, randomized controlled trial
SHORT TITLE	REMED
EUDRACT NUMBER	2020-005887-70
SPONSOR	University Hospital Brno Jihlavská 20 625 00 Brno, Czech Republic
INDICATION	Acute respiratory distress syndrome (ARDS) associated with COVID- 19 pneumonia
INVESTIGATIONAL DRUG	Dexamethasone
PHARMACEUTICAL FORM AND ROUTE OF ADMINISTRATON	Solution for injection/infusion, intravenous administration (i.v.)
DOSE	Control group: administration of dexamethasone 6 mg i.v. on Day 1- 10 Intervention group: administration of dexamethasone 20 mg i.v. on Day 1-5 , followed by dexamethasone 10 mg on Day 6-10
OBJECTIVES	The primary objective of this study is to test the hypothesis that administration of dexamethasone 20 mg is superior over 6 mg in adult patients with moderate or severe ARDS due to confirmed COVID-19. Primary endpoint: Number of ventilator-free days (VFDs) at 28 days after randomization. The secondary objective is to investigate the efficacy and safety of dexamethasone 20 mg versus dexamethasone 6 mg. Secondary endpoints: a) Mortality from any cause at 60 days after randomization; b) Dynamics of inflammatory marker (CRP) change from Day 1 to Day 14;

	c) WHO Clinical Progression Scale at Day 14 (range 0–10; 0 = no illness, 1–9 = increasing level of care, and 10 = death; d) Adverse events related to corticosteroids (new infections, new thrombotic complications) until Day 28 or hospital discharge; e) Independence at 90 days after randomization assessed by Barthel Index The exploratory objective of this study is to assess long-term consequences on mortality and quality of life at 180 and 360 days.
PHASE	Phase II
INCLUSION CRITERIA	1. Adult (≥ 18 years of age) at time of enrolment; 2. Present COVID-19 (infection confirmed by RT-PCR or antigen testing); 3. Intubation/mechanical ventilation or ongoing high-flow nasal cannula (HFNC) oxygen therapy; 4. Moderate or severe ARDS according to Berlin criteria: • Moderate – PaO2/FiO2 100–200 mmHg; • Severe – PaO2/FiO2 < 100 mmHg; 5. Admission to ICU in the last 24 hours.
EXCLUSION CRITERIA	1. Known allergy/hypersensitivity to dexamethasone or excipients of the investigational medicinal product (e.g. parabens, benzyl alcohol); 2. Fulfilled criteria for ARDS for ≥ 14 days at enrolment; 3. Pregnancy or breastfeeding; 4. Unwillingness to comply with contraception measurements from the enrolment to at least 1 week after the last dose of dexamethasone (sexual abstinence is considered as the adequate contraception method); 5. End-of-life decision or patient is expected to die within next 24 hours; 6. Decision not to intubate or ceilings of treatment in place; 7. Immunosuppression and/or immunosuppressive drugs in medical history: a) Systemic immunosuppressive drugs or chemotherapy in the past 30 days; b) Systemic corticosteroids use before hospitalization; c) Corticosteroids administration (dexamethasone equal or less than 8 mg per day or other corticosteroids in equivalent dose) during the present hospital stay for COVID-19 for more than last 5 days before enrolment; d) Systemic corticosteroids during present hospital stay for other conditions than COVID-19 (e.g. septic shock); e) Dexamethasone more than 8 mg per day or other corticosteroids in equivalent dose during the present hospital stay for COVID-19 for more than one single dose; 8. Present haematological or generalized solid malignancy; 9. Any of contraindications of corticosteroids, e.g. • intractable hyperglycaemia;

	• active gastrointestinal bleeding; • adrenal gland disorders; • a presence of superinfection diagnosed with locally established clinical and laboratory criteria without adequate antimicrobial treatment; 10. Cardiac arrest before ICU admission; 11. Participation in another interventional trial in the last 30 days.
INFORMED CONSENT	Patient consent or the consent of an independent physician is required in case the patient is unable to give consent. An abbreviated version of the study information will be provided to patients with impaired perception. A patient who was unable to sign an initial consent will sign an informed consent to continue participation in the study after recovery. The person close confirms by the signature that he/she was informed about the inclusion of the patient in the study.
SAMPLE SIZE	300 participants, 150 subjects in each arm
DURATION OF CLINICAL TRIAL	360 days after the enrolment of the last subject
STATISTICAL ANALYSIS	Primary efficacy endpoint (number of VFDs at day 28) will be calculated for both treatment arms separately with corresponding 95% confidence intervals. Comparison between arms will be based on parametric or non-parametric test (following the type of data distribution) and will be adjusted for relevant baseline covariates (stratification parameters). Secondary and exploratory efficacy endpoints will be analysed following the type of data (Chi-square test or Fisher's exact test for binary data and ANOVA or a non-parametric alternative tests for continuous and ordinal data, if appropriate). The primary population for analysis of efficacy will be Intention-To-Treat population (ITT), and results will be confirmed on the Per-Protocol Population (PP). The safety will be analysed in all patients who received any dose of study treatment and provided at least one post-dose safety assessment. All adverse events will be coded and tabulated by system organ class and preferred term for individual events within each system organ class and will be presented in descending frequency. Adverse events will also be tabulated by severity and relationship to the study medication. Serious adverse events will be summarized separately.
FUNDING	REMED is an academic clinical trial funded by the CZECRIN research infrastructure and by University Hospital Brno.