EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

SOLNATIDE FOR THE TREATMENT OF COVID-19

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Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**14/08/2020**	First version
V 1.1	**September 2020**	Literature searches, Literature screening, Data extraction
V 1.2	**09/09/2020**	Data extraction and analysis complete
V 1.3	**10/09/2020**	Check of data extraction and analysis
V 2.0	**15/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
	• No major changes (only the collaborators and secondary outcomes of ongoing studies in clinical trials registers were deleted; these data can be found in the Version 1.0, August 2020)

Disclaimer

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/services/covid-19/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Solnatide, a synthetic peptide of less than 20 amino acids; reported to activate epithelial sodium channels (ENaC), promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects

model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

Population	See project Scope
Intervention	Solnatide, a synthetic peptide of less than 20 amino acids; reported to activate epithelial sodium channels (ENaC), promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

The therapeutic molecule solnatide (INN) has been designed by APEPTICO (a privately-held biotechnology company from Vienna/Austria) for the therapeutic treatment of patients with Acute Respiratory Distress Syndrome (ARDS) and various forms of life-threatening Pulmonary Oedema (PPO). Solnatide is a synthetic peptide of less than 20 amino acids; it has been reported to activate epithelial sodium channels (ENaC), promoting lung alveolar fluid clearance through a novel mechanism of ENaC activation. This peptide directly binds to intracellular carboxy-terminal of the α-subunit of ENaC, which

increases the likelihood of the channel being open and thus enhances Na+ absorption [4, 5]. In 2013, APEPTICO successfully completed a phase I clinical study in healthy subjects, proving the safety of solnatide (AP301), as well as two phase II clinical studies (a randomized, double-blinded placebo-controlled trial using inhaled solnatide in mechanically-ventilated ARDS patients with lung oedema, NCT01627613, EudraCT 2012-001863-64 [5]; a randomized, placebo-controlled pilot study in patients suffering from primary graft dysfunction (PGD) following lung transplantation, EudraCT 2013-000716-21, [6]. Krenn et al. 2017 published results from a randomized, double-blind, placebo-controlled trial for proof of concept, which included 40 adult mechanically ventilated patients with ARDS. Patients were treated with inhaled AP301 (n = 20) or placebo (0.9% NaCl; n = 20) twice daily for 7 days. There was no difference in the PaO2/FiO2 ratio, ventilation pressures, Murray lung injury score, or 28-day mortality between the treatment groups. An exploratory subgroup analysis according to severity of illness showed reductions in EVLWI ($p = 0.04$) and ventilation pressures ($p < 0.05$) over 7 days in patients with initial sequential organ failure assessment (SOFA) scores ≥11 inhaling AP301 versus placebo, but not in patients with SOFA scores ≤10 [5]. Aigner et al. 2017 conducted and published a proof-of-concept randomized, placebo-controlled, single-center pilot-study; 20 patients with Primary graft dysfunction (PGD) after lung transplantation (LTx) were randomized 1:1 to AP301 (Group 1) or placebo (Group 2). As authors concluded, the study demonstrated relevant clinical effects of inhaled AP301 on patients with PGD after primary LTx. The improved gas exchange led to a significantly shorter duration of mechanical ventilation and a trend towards a shorter ICU stay [6]. Currently, solnatide is investigated in a phase IIB randomised, placebo-controlled, double-blind trial (EudraCT 2017-003855-47) for the treatment of pulmonary permeability oedema in patients with ARDS. The phase IIB clinical trial has been approved by the German and the Austrian Competent Authorities, as well by Ethic Committees of leading Medical University Hospitals in Germany as well Austria. Main objective of the trial is to assess the local and systemic safety of 7 days orally inhaled sequential multiple ascending doses of solnatide in 80 patients with pulmonary permeability oedema and moderate-to-severe ARDS [7].

3.2 Regulatory Status

Solnatide is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. In April 2020, solnatide has been approved for Compassionate Use by the Austrian Federal Office for Safety in Health Care (BASG) for the treatment of patients infected by the novel coronavirus SARS-CoV-2 and subsequently developing severe pulmonary dysfunction (severe COVID-19), as well as by the Italian Medicines Agency and the Ethics Committee of the National Institute for Infectious Diseases (Lazzaro Spallanzani-Rome), within the compassionate use program of drugs undergoing clinical trials for the treatment of COVID-19 patients suffering from pulmonary oedema and acute respiratory distress syndrome [7].

3.3 Level of Evidence

APEPTICO Forschung und Entwicklung GmbH has signed, together with the “solnatide consortium”, the Grant Agreement ID: 101003595 with the European Commission to accelerate the process of making the proprietary investigational medicinal product (IMP) solnatide available for medical treatment of patients severely affected by the novel coronavirus 2019 (SARS-CoV-2) disease, COVID-19. The Grant Agreement was made available via the Horizon2020 programme “Advancing knowledge for the clinical and public health response to the 2019-nCoV epidemic” (https://ec.europa.eu/commission/presscorner/detail/en/ip_20_386). The project started on 1 April 2020 and will end on 31 December 2021 [7].

One ongoing randomised, double-blind, placebo controlled, parallel assignment trial with aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema of 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS is registered in EUdraCT register (EudraCT number 2020-001244-26), https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001244-26/AT. Details can be found in Table 4-1.

As of September 09, 2020, no completed, withdrawn, suspended or terminated studies related to solnatide in COVID-19 patients were found in ClinicalTrials.gov and EUdraCT registers. No publications related to RCTs or prospective observational studies of solnatide in COVID-19 patients were found either.

4 SUMMARY

Currently, no publications related to RCTs of solnatide in COVID-19 patients were found. The same is true for prospective observational studies in COVID-19 patients.

At the moment, effectiveness and safety of solnatide in COVID-19 patients could not be assessed. Results from one ongoing randomised, double-blind, placebo controlled, parallel assignment trial with the aim to assess efficacy and safety of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema in 40 SARS-Cov-2 positive patients with moderate-to-severe ARDS are expected.

Table 4-1 Ongoing trials of single agent solnatide

Active substance	**Solnatide**
Sponsor	Department of Clinical Pharmacology, Medical University of Vienna, Vienna Austria
Trial Identifier	EUdraCT 2020-001244-26
Phase & Intention	Phase II, efficacy of 7 days orally inhaled 100 mg solnatide to treat pulmonary permeability oedema in SARS-Cov-2 positive patients with moderate-to-severe ARDS
Study design	Randomised, double-blind, placebo controlled, parallel assignment
Status of trial	Ongoing
Duration/End of Study	Start date: 11/04/2020
Study details	
Number of Patients	40
Disease severity	SARS-Cov-2 positive adult patients with moderate-to-severe ARDS
Setting	Intensive Care Unit (ICU) and under mechanical ventilation
Location/Centres	Austria
Intervention drug name and dosage	Solnatide 100 mg, inhalation use
Comparator (drug name and dosage)	Placebo, inhalation use
Duration of observation/ Follow-up	Baseline to day 7, respectively to day 14 or day 28
Primary Outcomes	Primary: Days free of mechanical ventilation (ventilator free days, VFD) within 28 days; Drug-related adverse events (through day 14); All adverse events through day 28; All-cause deaths through day 28; Vital signs daily through day 14 (heart rate, systolic and diastolic blood pressure, and body temperature); ECG parameters including heart rate PQ, QRS, QT and QTc intervals through day 7; Clinical laboratory assessments (haematology, clinical chemistry, blood gases and urine analysis) daily through day 14; 24-hour fluid balance through day 7; Hemodynamic parameters: mean arterial pressure, pulmonary blood volume (PBV), cardiac index and cardiac output assessed at screening and daily until end of treatment; Need for vasoactive drugs assessed at screening and daily until end of treatment
Results/Publication	Not applicable (ongoing study)

5 REFERENCES

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