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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

"Rolling Collaborative Review" of Covid-19 treatments

APN01 FOR THE TREATMENT OF COVID-19

Project ID: RCR09

Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V1.0	**14/08/2020**	First version
V2.0	**15/09/2020**	Second version
V3.0	**15/10/2020**	Third version
V4.0	**15/12/2020**	Fourth version
V5.0	**15/02/2021**	Fifth version
V6.0	**17/05/2021**	Sixth version
V7.0	**15/07/2021**	Seventh verison

Major changes from previous version

Chapter, page no.	Major changes from version [4.1]

Methods,	• Methods have changed
	  ○ The search of observational studies has become optional.
	  ○ The search for RCTs is no longer performed by DEPLazio. The authoring team is responsible for all searches.
	• The PICO has been described in more detail, clarifying that, whenever feasible and sensible, we depict outcome by disease severity (mild to moderate COVID-19 versus severe to critical COVID19.

Disclaimer

The content of this "Rolling Collaborative Review" (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Rolling Collaborative Review team

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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

ACE2	Angiotensin-converting Enzyme 2
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
DOI	Declaration of interest
ECMO	Extracorporeal Membrane Oxygenation
EUnetHTA	European Network of Health Technology Assessment
FiO2	Fraction of Inspired Oxygen
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ITT	Intention-to-treat
MAH	Marketing Authorisation Holder
MD	Mean Difference
mmHg	Millimetres of Mercury
NA	Not applicable
NMA	Network Meta-analysis
PAH	Pulmonary Arterial Hypertension
PaO2	Arterial Partial Pressure of Oxygen
RCR	Rolling Collaborative Review
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
rhACE2	Recombinant Human Angiotensin-converting Enzyme 2
RR	Relative Risk
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SMD	Standardized Mean Difference
SoF	Summary of Findings
SOP	Standard Operating Procedure
SpO2	Saturation of Oxygen
WHO	World Health Organisation
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/covid-19-treatment/) 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	APN01: recombinant form of the human angiotensin-converting enzyme 2 (rhACE2)
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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: Efficacy: • Length of hospital stay, • Viral burden (2019-nCoVRT-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: randomised controlled trials and, optional, 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 two main mandatory sources and one optional source 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 provided until the 31st of May 2021 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.

From June 2021, the literature search is used from COVID-NMA initiative according living review protocol[1],[2],[3], or is conducted by authors of this RCR in the following databases:

The literature search is conducted in the following databases:

- PubMed
- 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-nCoVRT-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:

The search results are screened, full texts of studies are assessed and study characteristics and outcome data are extracted according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [4] or reused from one living SR/MA source [2]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for RCTs [5].

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 [7]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [8].

From June 2021, if new RCTs are published, certainty of evidence have been reused from already published living systematic reviews/meta-analysis (SRs/MA) source from the international COVID-NMA initiative.

- Sources: for SoF https://covid-nma.com/

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

From July 2021, only RCTs are used for assessment of safety.

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 of AEMPS/AETSA is searching and extracting the data for the eligible studies. At the drafting stage of each update, the authoring team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-1.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

APN01 is a recombinant form of the human angiotensin-converting enzyme 2 (rhACE2), and it may have the potential to prevent the entry of SARS-CoV-2 into in the host cell and reduce lung injury [9].

APN01 has a dual mode of action. APN01 imitates the human enzyme ACE2. The ACE2 receptor is expressed in human airway epithelia as well as lung parenchyma and it has been identified as the essential gateway used by SARS-CoV-19. The virus binds to soluble ACE2/APN01, instead of ACE2 on the cell surface and therefore, the virus may no longer infect the cells. By preventing ACE2-mediated SARS-CoV-2 interaction, APN01 could prevent the harmful inflammatory reactions in the lungs and protect against acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [9]. APN01 is administered intravenously as an infusion [10].

3.2 Regulatory Status

APN01 was developed by APEIRON biologics for the treatment of ALI, ARDS and PAH. After licensing from APEIRON in February 2010, GlaxoSmithKline (GSK) conducted several clinical trials from 2014 to 2017 to treat ALI/ARDS and PAH patients. In 2019, APEIRON obtained the APN01 licenses back from GSK for further clinical development [10].

APN01 is currently under investigation. No licenses have been granted for this product.

3.3 Level of Evidence

The safety of APN01 has been investigated in a total of 89 healthy volunteers and patients with pulmonary arterial hypertension (PAH) and ALI/ARDS in previously completed Phase I and Phase II clinical trials. The product candidate is currently in Phase II development by APEIRON Biologics for the treatment of PAH and ALI/ARDS [10].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

The identified RCT (EudraCT Number: 2020-001172-15) is completed and results have not been published for yet.

4.2 Safety evidence from observational studies

There are no published observational studies for APN01 on Covid-19 or ongoing studies for APN01 in combination with another agent.

4.3 Ongoing studies

The randomized, double-blind Phase II trial will compare APN01 to placebo in up to 200 patients at 10 sites in Austria, Denmark and Germany. The primary objective of the trial is to assess the clinical efficacy and safety of APN01 in severe COVID-19 patients using, among other criteria, the need for invasive mechanical ventilation. Secondary objectives include the evaluation of measurable biological biomarker changes following treatment with APN01.

4.4 Scientific conclusion about status of evidence generation

APN01 is a rhACE2 that is being studied as a treatment for patients with COVID-19 in a single RCT. The RCT is completed and no results have been published up to date.

Table 4-1 Ongoing trials of single agent APN01

Trial Identifier/registry ID(s)/contact	NCT04335136 APN01- 01-COVID19 EudraCT Number: 2020-001172-15 Sonja Höller, Dr. [sonja.hoeller@apeiron-biologics.com] Tph. 43 1 865 65 77 128
Study design, study phase	Phase 2. Randomised clinical trial,
Recruitment status	Completed
Number of Patients, Disease severity*	200 patients. Severity not specified but clinical condition is not deteriorating rapidly
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	Intravenous RhACE2APN01 twice daily
Comparator (standard care or generic drug name and dosage)	Placebo (physiological saline solution, twice daily)
Primary Outcome(s)	All Cause-death or invasive mechanical ventilation [Time Frame: 28 days] The primary endpoint is a composite endpoint of all cause-death or invasive mechanical ventilation up to 28 days or hospital discharge
Sponsor/ lead institution, country (also country of recruitment if different)	Apeiron Biologics. 22 study locations: Austria, Denmark, Germany, Russian Federation, United Kingdom https://clinicaltrials.gov/ct2/show/NCT04335136?term=apn01&draw=1&rank=1 [11]

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

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12. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines 2021 [Available from: https://www.covid19treatmentguidelines.nih.gov.

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

From June 2021, literature search strategy and results from COVID-NMA initiative were used, according living review protocol [1, 3]. Randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with COVID-19 were included. Early-phase clinical trials, single-arm trials, non-randomized studies or modelling studies of interventions for COVID-19 were excluded, as well as studies about prognosis, systematic reviews and meta-analyses and diagnostic test accuracy studies. Details can be found in COVID-NMA Protocol[2].

6.2 Search strategy to identify ongoing studies

AEMPS/AETSA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and APN01 are described in Appendix Table 6-1 Search strategy to identify ongoing studies1.

Table 6-1 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" [adapt if you used "Advanced search mode"] Terms used at Condition or disease: • covid-19 Terms used at "other terms": • APN01	01/07/2021	[12] [0] new
ISRCTN	https://www.isrctn.com/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and APN01	01/07/2021	[0] [0] new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 AND **APN01**	01/07/2021	[12] [0] new

***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".