EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

APN01 FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V0.1	**July 2020**	Literature searches, Literature screening, Data extraction
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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 Trancriptase 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, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the 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	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-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.pdf)

	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. **Table 1 - Summary of findings (SoF) 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 table1 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 (Higgins et al., 2019).

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 (DerSimonian 1986).Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used.

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

2. **Table 2 - 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	APN01: recombinant form of the human angiotensin-converting enzyme 2 (rhACE2)
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Observational studies (comparative or single-arm prospective studies and 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 3 - 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

APN01 is the recombinant form of the human angiotensin-converting enzyme 2 (rhACE2), and has the potential to block the infection of cells by the novel SARS-CoV-2 virus, and reduce lung injury.

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, which means that the virus can no longer infect the cells. At the same time, APN01 reduces the harmful inflammatory reactions in the lungs and protects against acute lung injury (ALI) /acute respiratory distress syndrome (ARDS). APN01 is administered intravenously as an infusion [3].

3.2 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 [3].

3.3 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 [3].

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

4 SUMMARY

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.

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

Table 4-1 Ongoing trials of APN01 as a single agent

Active substance	APN01	APN01
Sponsor/Collaborator	Apeiron Biologics	The First Affiliated Hospital of Guangzhou Medical University
Trial Identifier	NCT04335136 APN01- 01-COVID19 EudraCT Number: 2020-001172-15	NCT04287686 GIRH-APN01
Phase & Intention	Phase 2	Not applicable
Study design	Randomised clinical trial	Randomised clinical trial
Status of trial	Ongoing	Withdrawn
Duration/End of Study	Primary completion: September 2020. Study completion: November 2020	NA
Study details		
Number of Patients	200	0
Disease severity	Severe patients (patient whose clinical condition is deteriorating rapidly are excluded)	Respiratory variables (meets one of the following criteria):Respiratory rate: RR ≥25 breaths/min, Oxygen saturation ≤93% at rest on room air, PaO2/FiO2 ≤300 mmHg（1 mmHg=0.133 KPa), Pulmonary imaging showed that the lesions progressed more than 50% within 24-48 hours and the patients were managed as severe (exclusion of patient on invasive mechanical ventilation or ECMO)
Setting	Hospital	Hospital
Location/Centres	Austria, Denmark, Germany. Centres are available at: https://clinicaltrials.gov/ct2/show/NCT04335136?term=apn01&draw=2&rank=1 [1]	China, Guangdong
Intervention drug name and dosage	Intravenous RhACE2 APN01 twice daily	Recombinant human angiotensin-converting enzyme 2 (rhACE2) 0.4 mg/kg
Comparator (drug name and dosage)	Placebo intravenously twice daily	No intervention. Standard of care.
Duration of observation/ Follow-up	28 days	14 days
Endpoints **Primary Outcomes Secondary Outcomes**	Primary: composite endpoint of all Cause-death or invasive mechanical ventilation [Time Frame: 28 days] Secondary: LDH level (as a surrogate marker for organ damage (powered secondary endpoint) [Time Frame: Day 5], Mortality. [Time Frame: 28 days] ,Ventilator-free days up to 28 days or hospital discharge . [Time Frame: 28 days], Time to death. [Time Frame: 28 days].	Primary: Time course of body temperature (fever) [Time Frame: 14 days], Viral load over time [Time Frame: 14 days] Secondary: PaO2/FiO2 ratio over time [Time Frame: 14 days], Sequential organ failure assessment score(SOFA score) over time [Time Frame: 14 days], Pulmonary Severity Index (PSI) [Time Frame: 14 days], Image examination of chest over time [Time Frame: 14 days]. Other secondary outcomes are available at: https://clinicaltrials.gov/ct2/show/NCT04287686?term=APN01&draw=2&rank=3 [2]

Active substance	APN01	APN01
Results/Publication	No available	No available

5 REFERENCES

[1] ClinicalTrials.gov (NCT number): NCT04335136. [Internet]. [cited August 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT04335136?term=apn01&draw=2&rank=1

[2] ClinicalTrials.gov (NCT number): NCT04287686. [Internet]. [cited August 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT04287686?term=APN01&draw=2&rank=3.

[3] Phase 2 Clinical Trial of APN01 for Treatment of COVID-19 Initiated [Internet]. [cited August 2020]. Available from: https://www.technologynetworks.com/drug-discovery/news/phase-2-clinical-trial-of-apn01-for-treatment-of-covid-19-inititated-332897.