APEIRON's APN01 shows clinical benefits for severely ill COVID-19 patients in phase 2 trial

- Treatment was safe and well tolerated and no drug-related severe adverse events were observed
- Significant improvement in mechanical ventilator-free Days and reduction in viral RNA load observed
- Biomarker development supports APN01's mode of action against SARS-CoV-2
- Investigators and experts recommend further development of APN01 in COVID-19

Vienna, Austria, 12 March 2021: APEIRON Biologics AG, a privately held biotech company developing breakthrough therapies to treat cancer and respiratory conditions, announced today that APN01 (alunacedase alfa) treatment showed statistically significant improvements in specific areas for severely ill COVID-19 patients. APEIRON designed this study in March 2020 as one of the first trials to treat hospitalized patients with the then new SARS-CoV-2 virus. The trial was conducted in Austria, Germany, Denmark and Russia.

The multi-center, double-blind, randomized, placebo-controlled, interventional phase 2 trial assessed the safety, tolerability and efficacy of APN01 in 178 patients with severe COVID-19 compared to placebo (clinical trials.gov NCT04335136). Both groups, APN01 (n=88) and placebo (n=90), also additionally received standard of care (SOC). Patients received treatment for 7 days with follow-ups until day 28.

The primary endpoint of the trial was a composite endpoint of all-cause death or invasive mechanical ventilation up to 28 days or until hospital discharge. The data showed that fewer patients treated with APN01 (n=9) died or received invasive ventilation compared to placebo (n=12), although statistical significance was not achieved due to the low total number of events. Standard of care has improved dramatically since study initiation, resulting in fewer deaths and less use of nvasive mechanical ventilation than at the time of design of the study.

Secondary objectives included mechanical ventilator-free days, change in viral RNA load, improvements according to the WHO 11-Point score system and the evaluation of relevant biomarker changes following treatment with APN01. Treatment with APN01 was safe and well tolerated and no drug-related severe adverse events were observed during the study. The data demonstrated a statistically significant improvement in mechanical ventilator-free days in alive patients and reduction in viral load in the group treated with APN01 compared to placebo. APN01 also demonstrated a positive impact on key biomarkers of the renin angiotensin system (RAS), demonstrating in vivo efficacy of the drug.

"We are delighted to see that treatment with APN01 has demonstrated promising clinical benefits for patients with severe COVID-19," **said Peter Llewellyn-Davies, Chief Executive Officer of APEIRON Biologics AG.** "Our treatment has now been evaluated for the first time in patients with COVID-19, and I would like to thank the patients and physicians as

well as our clinical and academic partners and our in-house team for their tremendous support for this trial. We will now discuss the further development of APN01 with investigators, advisors and regulatory authorities in order to realize an important therapeutic option for this deadly disease."

Patients with severe COVID-19 often need interventions to assist their breathing efforts, including invasive mechanical ventilation. The phase 2 trial showed a statistically significant increase in mechanical ventilator-free days in alive patients for the APN01 group compared to the control. Reducing the time on mechanical ventilation lowers the risk of medical complications and comorbidities associated with this invasive measure, while also reducing the burden on the Intensive Care Unit and the overall healthcare system.

A reduction in viral RNA load over time was observed in the APN01 treatment group. Viral RNA levels over time compared to baseline showed a statistically significant improvement with APN01 treatment on day 3 and 5 compared to placebo.

Further supporting data evaluated APN01 treatment according to the WHO 11-Point score system, which sets outcome measures to assess a patient's clinical burden of COVID-19 infection. These data showed improvements in important clinical parameters. In the APN01 treatment group, a tendency to faster recovery compared to the control group was observed.

The RAS plays an important role in many processes, including inflammation control, organ protection, or vascular integrity. While Angiotensin II (Ang II) is a pro-inflammatory and vasoconstrictive factor in RAS, Ang 1-7 and Ang 1-5 exhibit anti-inflammatory and vasodilative effects. Throughout the trial, plasma levels of Ang II were significantly reduced under APN01 treatment compared to control. APN01 treatment was shown to significantly increase Ang 1-7 and Ang 1-5 levels while no increase in these anti-inflammatory factors was seen in the placebo group. Suppression of Ang II and increase of Ang 1-7 and Ang 1-5 in addition to the observed reduction in viral RNA load under APN01 treatment support the mode of action shown in previous clinical trials and published in peer-reviewed journals.

"This important study supports the findings from our early research and APN01 development program targeting other SARS viruses and related severe respiratory diseases. As shown in this trial, APN01, a recombinant form of human ACE2, could potentially block the "door" which the virus uses to enter the cell and in addition protect tissues through regulation of Ang II and the RAS," commented **Prof. Josef Penninger, MD, co-inventor of APN01, founder of APEIRON Biologics AG, and member of its supervisory board,** "We are encouraged to continue the development of this promising therapeutic candidate. Importantly, with the recent emergence of virus variants that can escape antibody drugs and even vaccines but cannot escape binding to its receptor and entry door ACE2, APN01 could become a critical drug in the global therapy repertoire against virus variants, even against variants that might emerge in the future."

Christoph Wenisch, MD, Head of Department Infectious Diseases Unit, Klinik Favoriten in Vienna, Austria, and investigator of the APN01 trial added: "As a clinician who has treated COVID-19 patients since the start of the pandemic, I continue to see a great need to develop effective therapies. The results from this trial show that APN01 may help patients suffering from COVID-19, particularly in reducing days on mechanical ventilation, while the treatment is well tolerated with a good safety profile. The data from the trial suggest further development of APN01 is warranted to confirm the positive efficacy trends we have seen in the treatment of COVID-19 patients."

Detailed analyses of the study results are ongoing and are planned to be submitted for publication in a peer-reviewed medical journal.

About APN01 (alunacedase alfa)
APN01 is a soluble recombinant human Angiotensin Converting Enzyme 2 (rhACE2) which mimics ACE2, a receptor identified as the critical cellular entry receptor for the SARS-CoV-2 virus and therefore plays a crucial role in combating COVID-19. The virus' spike uses the ACE2 protein on the cell membrane to enter the cells. APN01 as a soluble form of ACE2, potentially prevents binding of the virus spike protein to the cell surface receptor and thereby preventing infection of cells. In addition, as shown in several studies human ACE2 is a key enzyme regulator of the Renin-Angiotensin-System (RAS), a peptide system involved in blood pressure, lung disorders, diabetic kidney disease, inflammation, or cardiovascular diseases. Specifically, ACE2 dials down the RAS and thereby reduces blood pressure, diminishes inflammation and protects multiple organs such as the heart, kidney, liver, lung or vasculature from damage. Thus, in addition to blocking the access of SARS-CoV-2 to its cell membrane-bound entry gate, the enzyme function of APN01, engineered into the same drug, potentially leads to reduction of organ injuries in COVID-19.

APN01 was first discovered and developed in response to the first SARS outbreak by the founder of APEIRON Biologics, Prof. Josef Penninger MD in 2003.

Before clinical development in COVID-19 started in April 2020, APN01 successfully completed several clinical trials in severe respiratory diseases like acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and pulmonary arterial hypertension (PAH). Lung injuries caused by ARDS are one of the major symptoms of severe COVID-19.

In these previous clinical trials, safety and tolerability of APN01 were demonstrated. A peer reviewed publication *The Lancet Respiratory Medicine* described the first named patient use of APN01, reporting encouraging data for APN01 for the treatment of COVID-19. The specific targeting of SARS-CoV-2 by APN01 was recently confirmed by preclinical results in human organoids (engineered human organs) and Vero E6 cells published in the peer reviewed journal *CELL*.

About APEIRON Biologics AG
APEIRON Biologics is a privately held European biotech company based in Vienna, Austria, focused on the discovery and development of treatments for respiratory diseases and novel cancer immunotherapies.

APN01 (rhsACE2, alunacedase alfa), a soluble recombinant version of the SARS-CoV-2 cell entry receptor ACE2, has three distinct potential clinical benefits for COVID-19 and has completed a double blind, placebo-controlled Phase 2 trial in Europe and Russia.

APEIRON received EU marketing approval for APN311 (Dinutuximab beta, Qarziba®) in 2017 for the treatment of pediatric neuroblastoma patients and out-licensed global, exclusive rights for this product to EUSA Pharma Ltd.

APN401´s proprietary process brings in a paradigm change in cancer treatment to fight hematological and solid tumors. The clinical program is a first-in-class ambulatory autologous cellular therapy to strengthen immune reactivity via an intracellular master checkpoint inhibitor, Cbl-b.

APEIRON Biologics´ projects and technologies are based on a strong patent portfolio and partnerships with leading pharmaceutical companies and academic institutions.

Further information, visit www.apeiron-biologics.com and connect with us on Twitter and LinkedIn.

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