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Relief Therapeutics and NeuroRx Expand Clinical Trial Evaluating RLF-100 in Critically Ill COVID-19 Patients with Respiratory Failure to Houston Methodist Hospital

•Clinical trial to enroll 144 patients total with expansion to additional sites

•Clinical trial expanded to patients treated with both noninvasive and mechanical ventilation in Critical COVID-19.

•RLF-100 is a patented formulation of Aviptadil (synthetic human Vasoactive Intestinal Polypeptide VIP), which inhibits pro-inflammatory cytokines and protects alveolar type-2 cells in the lungs inhibiting pro-inflammatory cytokines. Type 2 cells are essential to oxygen exchange and are preferentially targeted by the SARS-CoV-2 virus

HOUSTON, June 11, 2020 (GLOBE NEWSWIRE) -- RELIEF THERAPEUTICS Holding AG (SIX:RLF) "Relief" and its U.S. partner, NeuroRx, Inc. today announced that Houston Methodist Hospital is participating in their Phase 2 clinical trial evaluating RLF-100 as a research intervention for critically ill patients with COVID-19 and respiratory failure. RLF-100 is a patented formulation of Aviptadil, (synthetic human vasoactive intestinal polypeptide or VIP), which targets alveolar type 2 cells in the lungs that are a major target of the SARS-CoV-2 virus. VIP is known from numerous animal models of lung injury and lung disease to inhibit inflammatory cytokines and to protect pulmonary epithelial cells that line the air sacs (alveolae) of the lungs.

The multicenter clinical trial will enroll patients with COVID-19 and respiratory failure in the hopes that RLF-100 can decrease mortality in this condition and help to improve the ability of the patient's lungs to transfer oxygen to the body. Based on recent FDA guidance, the trial has been expanded to include patients treated with high flow nasal oxygen and noninvasive forms of ventilation, instead of only enrolling patients on mechanical ventilators.

The Principal Investigator at Houston Methodist Hospital is J. George Youssef, M.D., assistant professor of Critical Care Medicine & Pulmonology. Dr. Youssef was a co-investigator in the earlier study evaluating RLF-100 as a treatment for Acute Respiratory Distress (ARDS), a primary cause of COVID-19 related deaths, under the late Professor Sami Said, who discovered VIP in 1970 and treated the first patients.

"We are encouraged by findings from the previous clinical trial of RLF-100 as a treatment for ARDS in patients with sepsis which showed seven out of eight patients on mechanical ventilation experienced substantial improvement and six ultimately left the hospital alive," Dr. Youssef said. "If the early ARDS results can be replicated in critically ill COVID-19 patients with respiratory failure, this approach could present a significant advancement in the treatment of these patients."

Jonathan Javitt, M.D., MPH, CEO of NeuroRx, added, "We at NeuroRx are enormously excited to have Dr. Youssef join our study, in light of his long involvement in the VIP story. While we can read about Dr. Said's breakthrough, Dr. Youssef witnessed it firsthand and participated in the early clinical care of patients. It's rare to have science come full circle in service of patients."

The trial is being led by NeuroRx, Inc., the US development partner of Relief Therapeutics, whose clinical operations are based in Radnor, PA. Patients are being treated under an FDA Investigational New Drug clearance, as part of the FDA's Corona Treatment Acceleration Program (CTAP). Details of the study are posted on clinicaltrials.gov NCT04311697.

About VIP in Lung Injury

Vasoactive Intestinal Polypeptide (VIP) was first discovered by the late Dr. Sami Said in 1970. Although first identified in the intestinal tract, VIP is now known to be produced throughout the body and to be primarily concentrated in the lungs. VIP has been shown in more than 100 peer-reviewed studies to have potent anti-inflammatory/anti-cytokine activity in animal models of respiratory distress, acute lung injury and inflammation. Most importantly, 70% of the VIP in the body is bound to a rare cell in the lung, the Alveolar Type II cell, that is critical to transmission of oxygen to the body. VIP has a 20-year history of safe use in humans in multiple human trials for sarcoidosis, pulmonary fibrosis, asthma/allergy and pulmonary hypertension.

COVID-19-related deaths are primarily caused by Respiratory Failure. Before an acute deterioration in lung function, there is evidence of early viral infection of the alveolar type 2 cells. These cells are known to have angiotensin converting enzyme 2 (ACE2) receptors at high levels, which serve as the route of entry for the SARS-CoV-2 into the cells. Coronaviruses are shown to replicate in alveolar type 2 cells, but not in the more numerous type 1 cells.1,2 Since type 2 alveolar cells have high concentrations of VIP receptors on their cell surfaces, the research hypothesis is VIP administration could specifically protect these cells from injury.

Injury to the type 2 alveolar cells is an increasingly plausible mechanism of COVID-19 disease progression.3 These specialized cells replenish the more common type 1 cells that line the lungs. More importantly, type 2 cells manufacture surfactant that coats the lung and are essential for oxygen exchange. Other than RLF-100, no currently proposed treatments for COVID-19 specifically target these vulnerable type 2 cells.

About RLF-100

RLF-100 (Aviptadil) is a patented formulation of Vasoactive Intestinal Polypeptide (VIP) that was developed based on Dr. Said's original work and was originally approved for human trials by the FDA in 2001 and the European Medicines Agency in 2005. VIP is known to be highly concentrated in the lungs and to inhibit a variety of inflammatory cytokines. Relief's predecessor company, Mondo Biotech, was awarded Orphan Drug Designation in 2001 by the U.S. FDA for Aviptadil in the treatment of Acute Respiratory Distress Syndrome and in 2005 for treatment of Pulmonary Arterial Hypertension. Mondo was awarded Orphan Drug Designation by the European Medicines Agency in 2006 for the treatment of acute lung injury and in 2007 for the treatment of sarcoidosis. Both the U.S. FDA and the EMEA have granted Investigational New Drug licenses for human trials of Aviptadil.

About RELIEF THERAPEUTICS Holding AG

The Relief group of companies focus primarily on clinical-stage projects based on molecules of natural origin (peptides and proteins) with a history of clinical testing and use in human patients or a strong scientific rationale. Currently, Relief is concentrating its efforts on developing new treatments for respiratory disease indications.

Relief Therapeutics holds orphan drug designations from the U.S. Food and Drug Administration and the European Union for the use of VIP to treat ARDS, pulmonary hypertension, and sarcoidosis. Relief Therapeutics also holds a U.S. patent4 for RLF-100 and proprietary manufacturing processes for its synthesis.

RELIEF THERAPEUTICS Holding AG is listed on the SIX Swiss Exchange under the symbol RLF.

About NeuroRx, Inc.

NeuroRx draws upon more than 100 years of collective drug development experience and is led by former senior executives of Johnson & Johnson, Eli Lilly, Pfizer, and AstraZeneca, PPD. In addition to its work on RLF-100, NeuroRx has been awarded Breakthrough Therapy Designation and a Special Protocol Agreement to develop NRX-101 for the treatment of suicidal bipolar depression and is currently in Phase 3 trials. Its Board of Directors and Advisors

includes Hon. Sherry Glied, former Assistant Secretary, U.S. Dept. of Health and Human Services; Mr. Chaim Hurvitz, former President of the Teva International Group, Lt. Gen. HR McMaster, the 23rd National Security Advisor, Wayne Pines, former Associate Commissioner of the U.S. Food and Drug Administration, Judge Abraham Sofaer, and Daniel Troy, former Chief Counsel, U.S. Food and Drug Administration.

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1 US 8,178,489 Formulation for Aviptadil

2 Jonathan C. J. Perspective: The Potential Role of Vasoactive Intestinal Peptide in treating COVID-19 Authorea, DOI: 10.22541/au.158940764.42332418

3 Mason R. J. (2020). Pathogenesis of COVID-19 from a cell biology perspective. *The European respiratory journal*, *55*(4), 2000607. https://doi.org/10.1183/13993003.00607-2020

4 US 8,178,489 Formulation for Aviptadil

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