LB1148 for the Treatment of Critically Ill Patients with COVID-19

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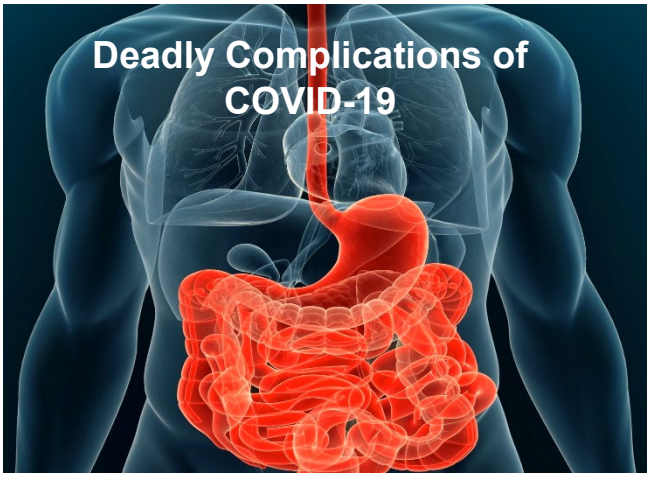

As the COVID-19 pandemic intensifies, Leading BioSciences is investigating our lead drug, LB1148, as a potential therapy for patients with coronavirus-associated acute respiratory distress syndrome (ARDS) and multiorgan dysfunction syndrome (MODS). LB1148 is under development to support organ health and reverse the potentially lethal complications of organ dysfunction associated with sepsis, shock, and the post-surgical setting. This novel therapeutic has (1) a good safety profile, (2) shown preliminary efficacy in phase 2 clinical studies for surgical indications, (3) open investigational new drug (IND) application with the United States (US) Food and Drug Administration (FDA) for the treatment of septic shock, vasodilatory shock or critical illness with risk of multiorgan dysfunction syndrome, and (4) a good manufacturing practice (GMP) clinical supply ready to be tested in patients. LB1148 is poised for rapid deployment in clinical studies in the fight against COVID-19 and associated organ dysfunction.

COVID-19 poses a serious global concern for patients and the healthcare system (Zhi 2020). Studies in the *New England Journal of Medicine* report 70% of critically ill COVID-19 patients had a shock/hypotension episode. A case fatality rate of 49% is reported for COVID-19 patients who develop respiratory failure, septic shock, or MODS. Treatment of shock-associated organ damage in patients with COVID-19 may improve mortality and morbidity. Most forms of shock, including septic shock, feature damage to the gastrointestinal (GI) mucosal barrier, leading to the escape of active digestive enzymes and subsequent organ/tissue damage. LB1148 is a novel oral liquid formulation of the well-characterized digestive enzyme inhibitor tranexamic acid. LB1148 has a good safety profile, has shown proof of concept efficacy in surgical clinical studies, and increased survival in multiple models of shock. With two distinct mechanisms of action (MOA), we believe LB1148 could preserve the GI mucosal barrier during respiratory dysfunction and halt the progression of the COVID-19 disease to ARDS/MODS and death.

LB1148 inhibits digestive enzyme activity and preserves gut integrity during intestinal stress (i.e. shock, cardiovascular events, infections, surgeries). Evidence suggests that digestive enzyme leakage from the GI tract causes the organ dysfunction, morbidity, and mortality associated with shock. When the GI barrier is disrupted, powerful digestive enzymes escape from the intestines, triggering a dangerous cascade of inflammation, cytokine storm, autodigestion of tissues, and organ failure, including ARDS.

A joint press-release from four US GI societies concluded coronavirus is found in the stool of COVID-19 patients. GI symptoms present in ~50% of infected patients. Many patients present first with diarrhea, nausea, vomiting, and/or abdominal discomfort before respiratory symptoms.

Further COVID-19 patients with digestive symptoms have a longer time from onset to admission and worse clinical outcomes compared to those without digestive symptoms (Pan 2020). Experience with another coronavirus with high case fatality rates, severe acute respiratory syndrome (SARS; SARS-CoV-1), shows that patients who developed GI symptoms required more ventilator support, required longer intensive care unit (ICU) stays, and had higher mortality risk (Leung 2003). We hypothesize that COVID-19 infection of the GI tract leads to intestinal barrier collapse and the widespread release of digestive enzymes to drive pulmonary dysfunction including MODS.

In preclinical studies, LB1148 prevented MODS and mortality in models of septic shock by maintaining mucosal barrier integrity, inhibiting pancreatic digestive enzymes, and preventing intestine leakage. LB1148 has demonstrated proof of principle improvements in GI function after cardiovascular surgery and GI surgery in clinical studies. LB1148 is now advancing to phase 3 studies for surgical indications. We initiated a clinical study of LB1148 to reduce MODS and death in septic shock. Although this study was terminated due to low enrollment, 1 of 5 subjects who received LB1148 had an extraordinary reversal of organ dysfunction and survival.

Additionally, LB1148 has an exciting, proposed MOA that would limit the viral load in patients with COVID-19 and the spread of infection. SARS-CoV-2 uses the ACE2 receptor which is highly expressed in the lung and GI tract to infect epithelial cells of these organs (Hamming 2004). Recent work has shown that protease inhibitors can block enzymatic activity required for COVID-19 infection through the ACE2 receptor (Hoffman 2020). By preventing viral entry, the lysine analog and potent trypsin inhibitor LB1148 may also reduce viral shedding and slow progression.

There are currently no therapeutics approved for the treatment of COVID-19. Deployment of existing development assets for immediate clinical testing is a promising opportunity to curb the death rate of the growing pandemic. Currently, Leading BioSciences has an active IND in the US for treating shock or any critical illnesses resulting in MODS and is in discussions with the FDA to test LB1148 in patients with COVID-19. We have adequate clinical supply to perform a trial in 250 patients and are poised for rapid deployment of LB1148 for compassionate use in patients suffering from COVID-19. For more information on LB1148 or about clinical trial participation, please contact:

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