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Rejuveinix (RJX) as a drug candidate for patients with systemic inflammatory response syndrome (SIRS): Supportive care considerations for COVID-19, cancer, and sepsis

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Sepsis is the consequence of a systemic host inflammatory response to an infection with bacteria, fungi or viruses that is further associated with profound metabolic alterations (1-9). Severe sepsis is frequently associated with septic shock leading to acute respiratory distress syndrome (ARDS) and a potentially fatal multiple organ dysfunction syndrome (MODS) with acute renal failure, disseminated intravascular coagulopathy and several poor prognostic circulatory, cellular, and metabolic abnormalities (6). Immunocompromised patients such as patients with cancer, AIDS, organ transplant recipients, as well as patients receiving immune-suppressive therapies for an inflammatory disorder (e.g. inflammatory bowel disease, autoimmune diseases) or receiving chemotherapy for cancer are at an increased risk for developing fatal ARDS and MODS as a result of severe sepsis. The case mortality rate of severe sepsis with septic shock is >50% in some high-risk patient populations plus
especially those who are older with several comorbidities (6). A study of sepsis prevalence among 7 million inpatients from 409 hospitals in the US documented between 2009 and 2014 recognized a persistently high annual incidence of 6% during hospitalizations of adult patients (2). According to the Global Burden of Disease Study (3), almost 50 million incident cases of sepsis and 11 million sepsis-related deaths were recorded globally in 2017. The highest rates of sepsis and sepsis-related mortality were observed in sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia (3).

After infection with SARS-CoV-2, high risk patient populations, especially older patients with comorbidities including advanced stage cancer, can develop ARDS with a high fatality rate despite best available supportive care (10-13). In these patients, the increased production of proinflammatory cytokines causes a severe form of viral sepsis with ARDS and cytokine release syndrome (CRS), that can lead to hypoxic injury and dysfunction of multiple organs, ultimately causing an irreversible and fatal multi-organ failure.(1-3) Therefore, there is an urgent and unmet medical need for treatments that can effectively reduce the risk of ARDS or its mortality rate in high-risk patients with COVID-19 pneumonia.(13)

Rejuveinix (RJX) is being developed as an intravenous (IV) therapy for

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patients with sepsis, including COVID-19 patients with viral sepsis and ARDS. RJX is a formulation of known physiologically compatible active ingredients, including ascorbic acid, magnesium sulfate heptahydrate, cyanocobalamin, thiamine hydrochloride, riboflavin 5' phosphate, niacinamide, pyridoxine hydrochloride, calcium d-pantothenate, and sodium bicarbonate, combined in specific ratios (Table 1) and dissolved in an aqueous acidic solution (electrolyzed sodium chloride and water for injection) (14). RJX components are divided into a 2-vial system to enhance stability and shelf-life.

Table 1: Quantitative Composition of RJX

Component	% Content	Content mg/10 mL
API (designated by numbers) Contained in Vial A		
1) Ascorbic Acid USP	8.9933	899.33
2) Thiamine HCl USP	0.6333	63.33
3) Magnesium Sulfate Heptahydrate USP	8.080	808.00
4) Cyanocobalamin Crystalline USP	0.0193	1.93
5) Niacinamide USP	1.188	118.80
6) Pyridoxine HCl USP	1.188	118.80
7) Riboflavin 5'Phosphate USP	0.0253	2.53
8) Calcium D-Pantothenate USP	0.0293	2.93
RJX drug product is stored in a two-vial system. Vial B contains Sodium Bicarbonate. The diluent for Vial A and Vial B is comprised of Water For Injection USP and Sodium Chloride (<0.1% mg/10mL). Abbreviations: USP = United States Pharmacopeia, API = Active Pharmaceutical Ingredient		

The RJX manufacturing utilizes an electrochemical water activation process step to create the acid species hydrochloric acid (HCl) and hypochlorous acid (HOCl), as well as hydrogen peroxide (H_2O_2) as sterilizers prior to addition of vitamin, mineral, antioxidant, and buffer products. Sodium bicarbonate acts as a buffer stabilizer and the product pH ranges between 6.3 and 6.5 pH when diluted in saline. Oxidative species, including HOCl and H_2O_2, are immediately resolved by reducing components in RJX to non-oxidative forms upon mixing so that the solution presents with a negative oxidative reduction potential (ORP) as administered.

Several of the API components of RJX, especially niacinamide, ascorbic acid, thiamine, pyridoxine, and magnesium sulfate exhibited promising activity in clinical studies involving ARDS patients and/or non-clinical studies in animal models of ARDS (15-25). Additionally, the buffered acid and ionic components in RJX may contribute to intracellular ionic exchange in an effect that is referred to as "micro-environment modulation". The clinical tolerability of RJX was confirmed in a recently completed double-blind, placebo-controlled Phase 1 dose-escalation study in healthy volunteers (ClinicalTrials.gov Identifier: NCT03680105).

The clinical development plan for RJX includes a Phase I/II study to evaluate its tolerability and activity in COVID-19 patients with hypoxemic respiratory failure receiving either non-invasive positive pressure ventilation (NIPPV) or mechanical ventilation (MV). The combined datasets from non-clinical studies taken together with the data from recent clinical studies with the API components of RJX as well as the Phase I study of RJX in healthy volunteers have informed the development of the study design for the projected COVID-19 study. It is hoped that RJX will reduce lung inflammation in COVID-19 patients with hypoxemic respiratory failure receiving either non-invasive positive pressure ventilation (NIPPV) or mechanical ventilation (MV) thereby shortening the time to resolution of the hypoxemic respiratory failure and reducing the case mortality rate when used in combination with standard of care.

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