EXPANDED ACCESS PROTOCOL

Intermediate-size Patient Population

For patients with Critical COVID-19 with respiratory failure who do not quality for Protocol RLF-100-001

Protocol#: RLF-100-EA-1

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IND Number: Phase:	**IND 149152** Expanded Access Protocol
Version Date	V.1.0 July 15, 2020

1. SYNOPSIS

Name of Investigational	RLF-100
Name of Active Ingredient:	Aviptadil
Reference Product(s):	Vasoactive Intestinal Polypeptide (synthetic)
Title of Study:	RLF-100-EA-1: Expanded Access Protocol for Patients with Critical COVID-19 with Respiratory Failure Who do not Qualify for Protocol RLF-100-001
Phase of Development:	Phase 2b/3: Expanded Access
Study Site(s):	All active RLF-100-001 study sites
Total Participant Number:	Up to 100 patients
Study Duration:	28-day total follow-up
Background and Rationale:	RLF-100 is currently being studied in Protocol RLF100-001 in patients Critical COVID-19 with respiratory failure. This Expanded Access Protocol is intended to provide RLF-100 to investigators for use in critically ill patients who do not qualify for the ongoing study.
Objectives:	1. To provide RLF-100 to critically ill patients who do not quality for Study RLF-100-001. 2. To collect safety data 3. To collect effectiveness data
Efficacy Endpoints:	Primary Outcome Measures: 1. Percent of patients alive and free of respiratory failure at 144 hours from start of treatment 2. Percent of patients with radiographic improvement at 96 hours from start of treatment Secondary outcome measures 1. Days on ventilation or high flow post treatment 2. Days in ICU post treatment 3. Improvement on NIAID scale at 96 hours and 144 hours

Study Design:	This is an open label study of patients with Critical COVID-19 with respiratory failure who do not quality for Protocol RLF-100-001. Patients must be receiving Maximal Standard of Care (SOC) therapy that includes non-invasive high pressure or mechanical ventilation Patients will receive intravenous Aviptadil + Maximal SOC, in dosage escalating from 50 pmol/kg/hr to 150 pmol/kg/hr.
Inclusion Criteria:	1. Critical COVID-19 with respiratory failure by NIH/FDA definition requiring either mechanical ventilation, non-invasive ventilation, or high flow rate nasal cannula at minimum 20L flow and 50% FIO_2. 2. Physician commitment to maximal Standard of Care treatment – as deemed necessary (i.e. patients on a "no code" status are not eligible).
Inclusion Criteria for Expanded Access Protocol: Patients may be enrolled into the Expanded Access Protocol if any of the following condition are present	1. Pregnancy 2. Age <18 years 3. Mechanical ventilation for more than 7 days in primary cohort. Mechanical ventilation>21 days in the exploratory cohort 4. Mean Arterial Pressure < 65 mm Hg with use of pressor per ICU protocol 5. Irreversible condition (other than COVID-19) with projected fatal course 6. ECMO 7. Current or recent (within 30 d) enrollment in another investigational trial of anti-IL6 drug; 8. Active diagnosis of Acquired immune deficiency syndrome; 9. Transplant patients currently immunosuppressed; 10. Chemotherapy-induced neutropenia (granulocyte count <1000/mm3); 11. Cardiogenic shock; congestive heart failure – NYHA Class 3 or 4; 12. Recent myocardial infarction – within last 6 months and troponin > 0.5uria (urine output < 50 ml/d) or other signs of multi-organ failure; 13. Severe liver disease with portal hypertension; 14. Recent stroke or head trauma within last 12 months 15. Increased intracranial pressure, or other serious neurologic disorder; 16.
Exclusion Criteria	1) Eligible for enrollment in Protocol RLF-100-001 (NCT04311697) 2) Liquid Diarrhea more than 3x/day; defined as more than 3 non-bloody watery stools within a 24-hour period, requiring additional fluid and electrolyte supplementation
Safety Assessments:	Adverse Events Serious Adverse Events Vital Signs Complete Blood Count

	ECG
Dosage, Route of Administration, and Schedule:	Three escalating doses of RLF-100 (Aviptadil): 50,100, and 150 pmol/kg/hour administered over 12 hours via IV infusion on successive days. If side effects are detected during the infusion, dose reduced or halted.
Statistical Methods:	Descriptive statistics will be used to analyze the data.

2. PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, 45 CFR 46, to GCP, as described in ICH guideline E6 and to hospital Institutional Review Boards.

_____ _____

Clinical Site Investigator Signature Date

_____

Clinical Site Investigator Printed Name

_____ _____

Investigator-Sponsor Signature Date

_____

Investigator-Sponsor Printed Name

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4. LIST OF ABBREVIATIONS

AA	Amino Acid
ALI	Acute Lung Injury
ARDS	Associated Acute Respiratory Distress Syndrome\
COVID-19	Corona Virus Disease 2019
ECMO	Extracorporeal membrane Oxygenation
ED	Erectile Dysfunction
EMR	Electronic Medical Record
Fas	Cell Surface Death Receptor
HCl	Hydrogen Chloride
ICU	Intensive Care Unit
ITT	Intent-to-Treat
IL	Interleukin
IND	Investigational New Drug
IV	Intravenous
SOC	Maximal Intensive Care
MERS	Middle East Respiratory Syndrome
MMRM	Mixed model repeated measures
RDR	Respiratory Distress Ratio
SOC	Standard of Care
SAE	Serious Adverse Events
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS-Coronavirus 2
TNFα	Tumor Necrosis Factor Alpha
VIP	Vasoactive Intestinal Peptide

5. INTRODUCTION

5.1 Executive Summary

RLF-100 (aviptadil) is a synthetic form of Vasoactive Intestinal Polypeptide (VIP), a ubiquitous, naturally synthesized human peptide with extensively documented anti-inflammatory, anti-cytokine cascade properties. It has been granted FDA Fast Track Designation for treatment of Critical COVID-19 with Respiratory Failure. A phase 2/3 trial is underway that has passed its first evaluation at 30 patients for safety and futility. This expanded access protocol is designed to offer access to investigational use of RLF-100 to patients who do not qualify for inclusion in Protocol RLF-100-001 (NCT04311697) either on the basis of specific medical exclusions or because there is no accessible study site available to the prospective participant.

5.2 Definition of Critical COVID-19

In May 2020, FDA defined Critical COVID-19 to be used in clinical trials and disease staging as follows:

Critical COVID-19	• Positive testing by standard RT-PCR assay or an equivalent test
	• Evidence of critical illness, defined by at least one of the following:
	  ○ Respiratory Failure defined on resource utilization requiring at least one of the following:
	  ▪ Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
	  ○ Shock (defined by systolic blood pressure <90 mmHg, or diastolic blood pressure <60 mmHg or requiring vasopressors)
	  ○ Multi-organ dysfunction/failure

Acute Lung Injury in COVID-19 is characterized by progressive failure of corporeal oxygenation, attributed on large part by SARS-CoV-2 infection of Alveolar Type II cells (Mason 2020). Extensive nonclinical studies document that 70% of VIP in the body binds to receptors on the Alveolar Type II cell, where VIP is known to block cytokine production and upregulate production of surfactant.

Severity of COVID is associated with and graded by a progressively worsened state of oxygenation. This is seen in the PaO_2/FIO_2 ratio, which reflects the status of oxygenation for patients on high pressure oxygen and mechanical ventilation. In patients breathing room air, disease severity is assessed by SpO_2. Many patients with Critical COVID meet the clinical definitions of Acute Respiratory Distress Syndrome (ARDS). However, there is increasing recognition that respiratory distress in COVID-19 has different characteristics than ARDS in the setting of bacterial sepsis and other common presentations of ARDS.

The pathologic hallmark of COVID-19 lung injury is diffuse alveolar damage, vascular endothelium damage, and damage to the surfactant-producing type II cells which results in loss of the integrity of the alveolar-capillary barrier, transudation of protein-rich fluid across

the barrier, pulmonary edema, and hypoxemia from intrapulmonary shunting. Typically, patients who have progressed to Critical COVID-19 require care in an intensive care unit (ICU). The mortality rate is approximately 50%. Deaths usually result from multisystem organ failure rather than lung failure alone.

5.3 RLF-100 Experimental Therapy in COVID-19

Under this protocol, patients with Critical COVID-19 will be treated with RLF-100 (Aviptadil) with the aim to support pulmonary alveolar function, combat the cytokine-induced inflammation, improve blood oxygenation, and reduce mortality.

5.4 Clinical Rationale

Given by intravenous infusion in appropriate concentrations, RLF-100-001 has been shown in clinical trials to have a manageable safety profile with no observed SAEs to date that would rise to the level of a black box warning.

6. OBJECTIVES

6.1 Primary Objective

The primary objective of this study is to measure the effectiveness and safety of RLF-100 + maximal standard of care (SOC) in treating Critical COVID-19 with Respiratory Failure.

6.2 Secondary Objective

The key secondary objective is to test the hypothesis that RLF-100 improves blood oxygenation as measured by SaO_2.

7. STUDY DESIGN

7.1 Overview

This study, RLF100-EA-001, is an expanded access protocol for patients with Critical COVID-19 with respiratory failure who do not quality for Protocol RLF-100-001 (NCT04311697), as posted on www.clinicaltrials.gov. Patients who enroll in this study will be treated with RLF-100 + Maximal SOC. Aviptadil will be administered as a 12-hour IV infusion one thee consecutive days. Primary endpoints will be measured at five (5) days post infusion with 28 days of follow-up. Patients with Critical COVID-19 infection who are not eligible for enrollment in Protocol RLF-100-001 will be offered the opportunity to participate in this study.

Informed consent will be obtained from the patient or a responsible party. Once enrolled, patients will receive RLF-100 will be given RLF-100 by IV infusion, each dose given over 12-hour period at the same time on consecutive days, in escalating doses from 50pmol/kg/hr to 150 pmol/kg/hr of RLF-100. The primary outcome to be measured following RLF-100 infusion is recovery from respiratory failure by day 7. Numbers of participants surviving will be compared to historical controls and to the placebo arm of Protocol RLF-100-001. The

declared secondary outcome to be measured following RLF-100 infusion will be improvement in blood oxygen saturation (SaO_2) as measured by pulse oximetry.

7.2 Design

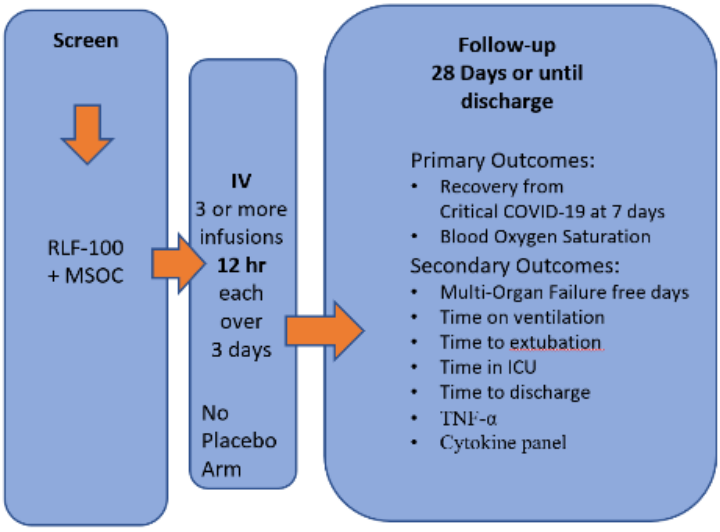
Open-label, expanded access protocol in patients with Critical COVID-19 and respiratory failure who do not meet the criteria for Protocol RLF-100-011 (NCT04311697) or cannot feasibly access an existing clinical trial site.

Following informed consent, patients will be administered escalating doses of RLF-100 from 50 pmol/kg/hour IV to 150 pmol/kg/hour as three (3) 12 hour infusions each at the same time of day on subsequent study days 1, 2, and 3.Vital signs and telemetry will be monitored throughout the infusion and for 48 hours after completion of all 3 infusions. Pulmonary, cardiovascular, hepatic, CNS, renal, and coagulation functions will be assessed daily for 5 days, chest x-rays and plasma levels of selected cytokines will be requested as a condition of voluntary participation in this protocol. The primary efficacy outcome is recovery from respiratory failure secondary to Critical COVID-19. Secondary outcomes will include oxygenation levels as other outcome measures.

7.3 Number of Participants

Initially, the study is limited to 100 participants. As additional safety data emerge and availability of investigational product increases, the number of participants is expected to increase.

7.4 Study Design



- Expanded access study of RLF-001 50 pmol – 150 pmol/kg/hr in 3 ascending doses, each administered over a 12 hr IV infusion on consecutive days
- Check vitals two (2) hours after each dose begins for Side effects (See Flow Chart, Figure 2)
- Endpoint outcomes and assessments for recovery, Blood 0_2, organ failure and TNF-α

* MSOC = Maximal Standard of Care

Figure 1 shows a graphical schema of the RLF100-001 protocol study design.

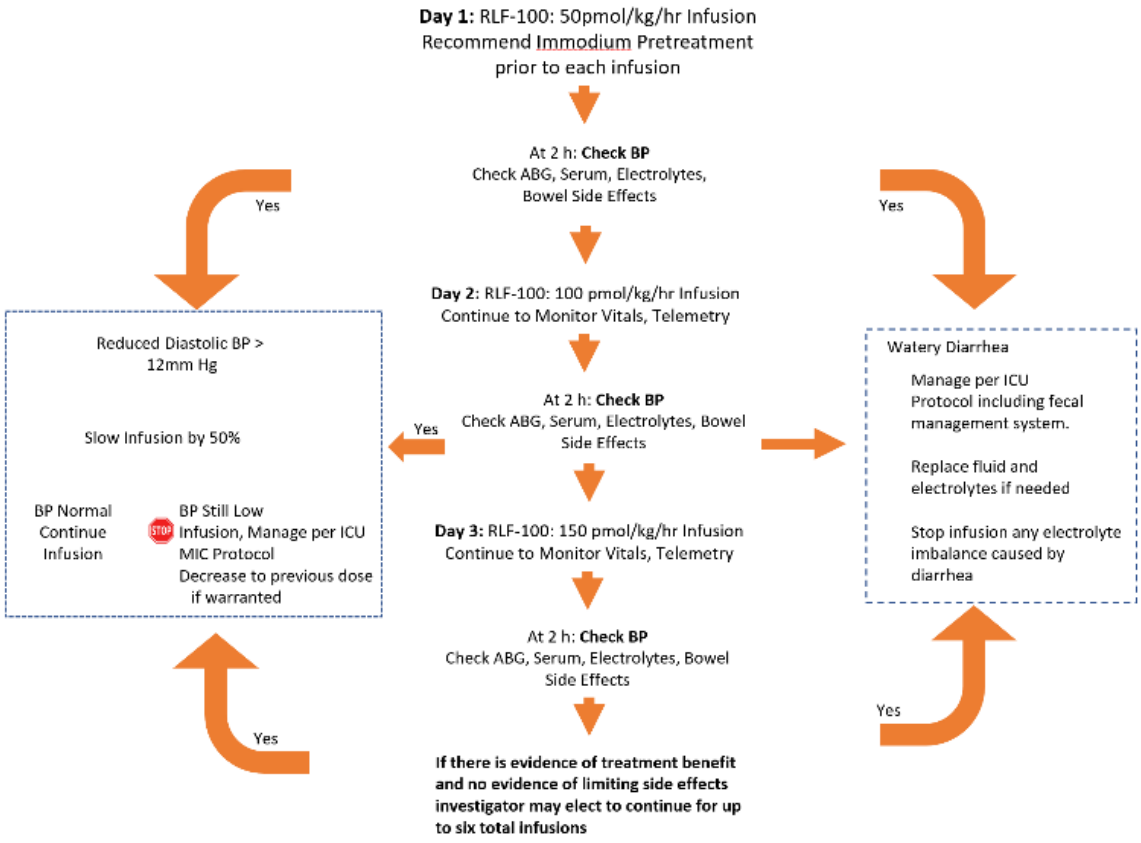


Figure 2: RLF-100 Expanded Access Study Flow Chart

7.5 RLF-100 Treatment Protocol

Figure 2 shows a graphical flow chart of the RLF100-001 protocol study design.

Note: If a determination is made to slow down the infusion rate by 50%, the next infusion would still be administered at the next 24-hour period, e.g., if infusion was started at 8:00 AM and it runs for 18 hours, the next infusion should still take place at 8:00 AM the following day.

7.6 Anticipated Risk

Reported adverse events for intravenous aviptadil include hypotension, tachycardia, facial flushing and watery diarrhea. Pretreatment with Immodium is recommended and the use of a fecal management system is recommended if diarrhea develops. Hypotension is routinely managed per ICU protocol with pressors and the infusion may be slowed by up to 50% or halted if pressors are not effective in managing hypotension. See Flow Chart (Figure 2 above).

8. SELECTION OF SUBJECTS

8.1 Study Population

The trial will be conducted in hospitalized patients with Critical COVID-19 by FDA/NIH criteria (section 6.2.) Subjects must either

- be ineligible for Protocol RLF-100-001 based on specific exclusion criteria or
- unable to access an active RLF-100-001 study site to participate in the study.

8.2 Inclusion Criteria

All patients entered this trial will have the diagnosis of Critical COVID-19. Subjects will be observed for a 1 to 24-hour period, during which time all inclusion criteria must be met. If all criteria are met once (not necessarily simultaneously), the patient will be enrolled and randomized to receive the study drug within 12 hours of the following entry criteria being fulfilled:

1) Critical COVID-19 with respiratory failure by NIH/FDA definition requiring either mechanical ventilation, non-invasive ventilation, or high flow rate nasal cannula at minimum 20L flow and 50% FIO_2.
2) Physician commitment to maximal Standard of Care treatment, as deemed necessary, i.e. patients on a "no code" status are not eligible.

8.3 Inclusion Criteria for Expanded Access Protocol

One or more of the below (which constitute exclusion criteria for Protocol RLF-100-001):

1) Pregnancy
2) Age <18 years
3) Mechanical ventilation for more than 7 days
4) Mean Arterial Pressure < 65 mm Hg with use of pressors per ICU protocol
5) Irreversible condition (other than COVID-19) with projected fatal course
6) ECMO
7) Current or recent (within 30 d) enrollment in another investigational trial of anti-IL6 drug
8) Active diagnosis of Acquired immune deficiency syndrome
9) Transplant patients currently immunosuppressed
10) Chemotherapy-induced neutropenia (granulocyte count <1000/mm3)
11) Cardiogenic shock; congestive heart failure – NYHA Class 3 or 4
12) Recent myocardial infarction, within last 6 months and current troponin > 0.5
13) Anuria (urine output < 50 ml/d) or other signs of multi-organ failure
14) Severe liver disease with portal hypertension
15) Recent stroke or head trauma within last 12 months
16) Increased intracranial pressure, or other serious neurologic disorder;

8.4 Exclusion Criteria

1) Eligible for enrollment in Protocol RLF-100-001.
2) Liquid Diarrhea more than 3x/day; defined as more than 3 non-bloody watery stools within a 24-hour period, requiring additional fluid and electrolyte supplementation

9. RECRUITMENT, CONSENT & ENROLLMENT

9.1 Recruitment & Consent Procedures

Prospective participants will be screened for fulfillment of inclusion criteria by the Principal Investigator. Patients are inherently unable to give consent in this setting. The PI or PI's

designee will seek consent from the patient's responsible party, after explaining the procedure and consent form, approved by all participating sites. It should be noted that one feature of the COVID-19 pandemic is that non-patients are barred from hospital premises. Therefore, informed consent from responsible parties will generally be obtained telephonically and signature will be obtained via an SMS text message or otherwise compliant consent systems (e.g. REDCAP). Consent will be documented by a witnessed, consent form, to be kept on file together with telephonic signature. This does not preclude a site from obtaining consent via paper, if such arrangements can be made, e.g. fax. Should the patient regain ability to consent, consent will be sought accordingly.

9.2 Obtaining Informed Consent

IRB-approved written informed consent forms (ICF) will be obtained from the responsible party of all subjects before any protocol-specified procedures are carried out. For entry into the study, all inclusion criteria must be met, and none of the exclusion criteria can be met. All signed ICF forms will be logged and kept in locked research cabinets under the supervision of the local Site PI and available for audit upon request.

9.3 Protecting Confidentiality

Any information obtained in this study will be treated as confidential and will be safeguarded. The data will be coded and kept in a secure location. When published, the results of the study will be in a form that does not identify any of the patients. In compliance with federal regulations, the records of the study will be available to representatives of the Food and Drug Administration.

9.4 HIPAA Compliance

The study will be compliant with the Health Insurance Portability and Accountability Act (HIPAA), which protects the privacy and security of healthcare information. All personal identifying information (PII) will be securely stored and only accessible to healthcare providers and authorized personnel only.

9.5 Standard of Care Support

Supportive treatment in the ICU, including antibiotics, oxygen, mechanical ventilation, blood pressure-supporting medications, and all other standard of care interventions as needed, will be continued, regardless of participation in the study.

9.6 Population Bias

For unknown reasons, males are affected by severe COVID-19 symptoms twice (2X) as often as are females. It is likely that the enrollment in this trial will be consistent with that gender difference. There is no evidence to suggest that RLF-100 will be differently tolerated based on race.

9.7 Enrollment

The initial total number of participants in the expanded access study will be 100. If the decision is made to continue the study beyond 100 patients, the amended protocol will be submitted to FDA.

There is no mathematical sample size calculation because no hypothesis tests are planned.

9.8 Charging for Investigational Product

Because sponsor is a small, venture-backed biotechnology company, sponsor plans to charge for investigational product. Consistent with § 312.315, Sponsor will charge for direct drug costs, costs of monitoring the expanded access protocol under § 312.320, complying with protocol reporting requirements, and other administrative costs directly associated with the expanded access use § 312.8(d)(2). Sponsor will further recover the fees paid to a third party for administering the intermediate-size patient population expanded access protocol, consistent with FDA's interpretation of § 312.8(d)(2).

Sponsor will provide to FDA documentation to show that its calculation is consistent with the requirements of § 312.8(d)(1), describing recovery of direct costs and, if applicable, the requirements of § 312.8(d)(2), describing certain additional costs that may be recovered for intermediate-size patient population expanded access uses or treatment INDs or protocols. This documentation must be accompanied by a statement that an independent, certified public accountant has reviewed and approved the calculations (§ 312.8(d)(3)).

10. TREATMENT OF SUBJECTS

10.1 Maximal Standard of Care

All patients entered in the trial receive Maximal Standard of Care treatment and support, including fluids, antibiotics, vasoactive agents, non-invasive or mechanical ventilation, hemodialysis, surgery and other supportive measures. Unlike care under Protocol RLF-100-001, treatment with extra-corporeal membrane oxygenation (ECMO) is not an exclusion criteria for this protocol and may in some cases be the basis for enrollment. Decisions regarding the use of intravenous fluids, cardiovascular and respiratory support, and surgical intervention are made by each patient's attending physician and are not dictated by the study protocol. At the completion of the three 12-hour infusions, patients are followed up for the 28 days or until discharged from the hospital, whichever comes sooner. An attempt will be made to follow all patients for 28 days even after discharge, but it will not be practical during the Corona Pandemic either to bring patients back for post-discharge visits or to make home visits. Death while on life support vs. death following discharge from mechanical ventilation will be tracked separately.

10.2 Proper Standard of Care (SOC) Management Principles

Management principles are similar despite different etiologies. Oxygenation must be maintained, and the underlying cause of acute lung injury corrected. Meticulous attention is necessary to prevent nutritional depletion, O_2 toxicity, superinfection, barotrauma, and renal failure, which may be worsened by intravascular volume depletion. While the diagnosis is

being considered, life-threatening hypoxemia must be treated with a high FiO_2 and monitored with repeated arterial blood gases or noninvasive oximetry. Prompt endotracheal intubation with mechanical ventilation and PEEP may be needed to deliver O_2 if hypoxemia is refractory to O_2 inhalation by face mask or nasal cannula. Despite the presence of alveolar edema, IV fluids should be given if needed to restore peripheral perfusion, urine output, and BP. Monitoring vascular volume is crucial because both hypovolemia and overhydration are deleterious. Physical findings and central venous pressure may be misleading in critically ill patients undergoing mechanical ventilation, and if severe hypoxemia persists, if skin perfusion is poor, if mentation is impaired, or if urinary output decreases (< 0.5 mL/kg/h), a reliable index of intravascular volume is needed immediately.

ECMO is a lifesaving modality that may be used when mechanical ventilation is unable to support life. Therefore, while ECMO is not an exclusion criterion for this study, ECMO is also not considered part of SOC for the purposes of this study based on its variable availability from one treatment facility to another.

10.3 Dosing Regimen

The escalating dosing regimen for RLF-100 is shown in Figure 2. Each infusion is planned for 12 hour duration, however, the infusion may be slowed by up to 50% (for an 18-hour total infusion time) at the discretion of the site personnel. Monitoring of vital signs and other safety measurements will be ongoing and decisions relating to dose-reduction or cessation will be based on the evaluation of these parameters.

10.4 Potential Side Effects of Drug Therapy

Signs and symptoms to look for: facial flushing, tachycardia, hypotension, diarrhea. These will be monitored for the duration of the infusion, and for 12 h afterward, by blood pressure and heart telemetry measurements and patient observation. One identified side-effect of Aviptadil infusion is watery diarrhea. As noted above, non-bloody watery diarrhea > 3x/day requiring additional fluids and electrolyte supplementation is an enrollment exclusion. Some investigators prefer to pretreat with Imodium. If watery diarrhea is observed during infusion, a fecal management system (i.e. rectal tube) should be used to monitor diarrhea and electrolyte content in order to ensure physiologic replacement of both fluid and electrolytes. Hypotension of >10mmHg that is not readily controlled with pressors is a basis for reducing the infusion rate by 50%. If hypotension persists, the dosage for subsequent infusions should be decreased to the prior, tolerated dose of RLF-100.

11. ASSESSMENT OF SAFETY

11.1 Serious Adverse Events

Sponsor provides medical monitoring/consultation as part of this expanded access protocol. Investigators will be provided with contact numbers to reach medical monitors who are board-certified critical care physicians on a 24/7/365 basis. Measurement of serious adverse events (SAE) will be the basis for assessing safety of RLF-100. All SAE's will be recoded on an IRB approved SAE Report Form. The SAE Report Form will include the exact nature of the event and the circumstances of the subject at the time of the event, in addition to the usual information required to document AEs or SAEs. Data on all the above will be collected on

separate eCRF pages. The latest version of the AE dictionary, MedDRA, will be used for the classification and analysis of AEs entered in the study database. For regulatory reporting, SAEs will be coded using MedDRA.

11.2 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH). AEs will be classified as expected/unexpected, drug-related, possibly drug-related, or non-drug related by the study safety monitor. Flushing, Diarrhea and hypotension are expected generally on-serious AEs that are known physiologic effects of Vasoactive Intestinal Peptide.

11.3 Definition of a Serious Adverse Event

The following criteria define a Serious Adverse Event:
1) Death
2) Life-threatening event
3) Persistent or significant disability/incapacity

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality). In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Explanation of seriousness of this AE
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to study drug
- Causality assessment in relation to other medication
- Description of AE

11.4 Relationship to Study Drugs

Adverse events and SAEs will be collected from the time of signature of informed consent throughout the treatment period. The investigator will assess the causal relationship (i.e., the relationship to study treatment) between the investigational product and the AEs and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the

event may have been caused by the investigational product?". For SAEs, causal relationship will also be assessed.

11.5 Recording of Adverse Events

Abnormal and clinically significant lab values will be reported as SAEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug. The principal investigator and the study biostatistician will establish the rules for what will constitute abnormal and clinically significant lab values based on established site-specific lab normal ranges. Adverse events, including abnormal lab values (clinically significant and clinically non-significant), will be review monthly for trends by the principal investigator and the medical monitor. Should any abnormal lab values exceed acceptable rates, the FDA will be notified within regulatory timelines. Wherever possible, the reporting investigator will use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

11.6 Reporting of Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated Informed Consent Form (ICF) is obtained until completion of the subject's last study-related procedure. All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses will be given when signs and symptoms are due to a common etiology. The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities.

11.7 Reporting of Serious Adverse Events

Reportable SAEs will be sent to the FDA by the sponsor. When a SAE is discovered, it will be reported immediately (within 24 business hours) to the Medical Monitor. Serious adverse events will be reported within 24 business hours of the site's knowledge of the event to the IRB, Sponsor, Medical Monitor, and study site investigators.

12. ASSESSMENT OF EFFICACY

12.1 Data Collection

Data will be collected via the electronic medical record (EMR) or other hospital information system and ICU telemetry systems. Once collected, data will be transferred by study personnel to the IBM Watson electronic data capture system, which has been audited by FDA in connection with multiple drug approvals. GCP will be observed throughout, using sponsor's quality system. Extensive data not already defined in this protocol will be available for analysis via the EMR and telemetry systems.

12.2 Assessments of Endpoints

12.2.1 Recovery from Respiratory Failure in Critical COVID-19

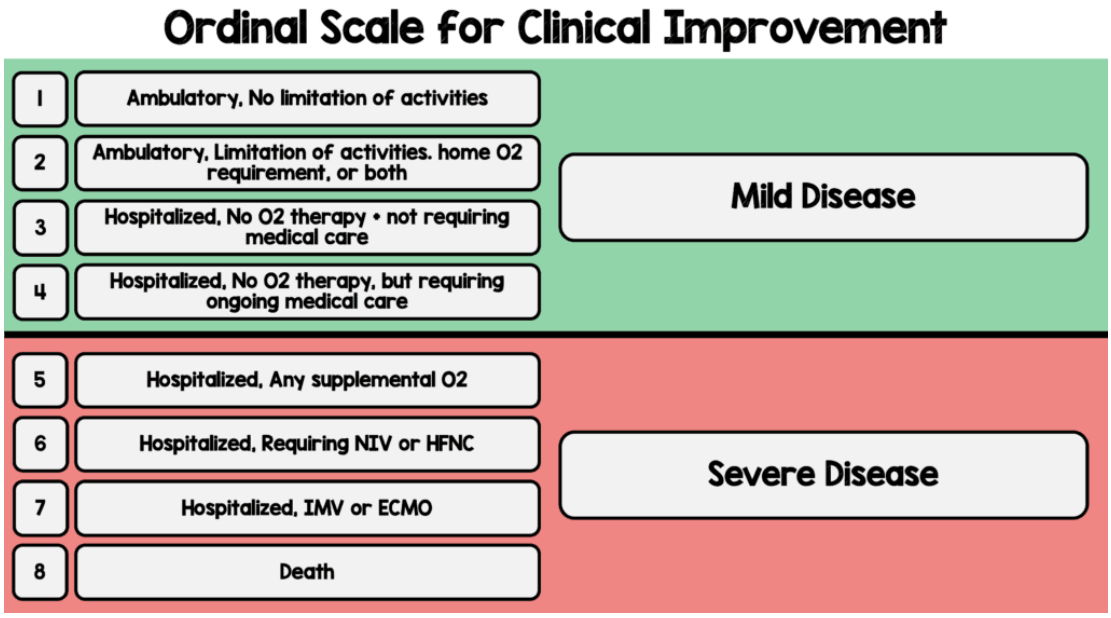
Recovery is defined as being able to maintain a physiologic oxygen saturation (SaO_2) without the need for mechanical ventilation, non-invasive ventilation, or high-flow Nasal Oxygen above 20L/min. As per FDA guidelines, the definition is resource consumption-based and not tied to a specific SaO_2

12.2.2 Improvement in SaO_2

The SaO_2 following cessation of ventilation will be compared to the SaO_2 that triggered the decision to institute ventilation.

12.2.3 Improvement on NIAID Scale

The NIAID 8 point scale is:



12.2.4 Chest x-ray

Investigators are requested to submit chest AP x-rays, which will generally be supine or sitting at day 0, 48-72 hours post first infusion, and day 7 or day of discharge, whichever comes sooner. Chest CT, if available should also be submitted

12.2.5 Inflammatory Markers

Cytokine studies will be performed by central lab. Note that these are not declared efficacy or safety endpoints

13. STATISTICAL ANALYSIS

13.1 Statistical Design and Analyses

Descriptive statistics only will be analyzed and reported

13.2 Data Analysis

All patient data will be collected via the electronic medical record and in -house ICU telemetry systems. Dedicated research personnel will extract data to a de-identified study database for statistical analysis.

13.3 Interim Safety Analysis

Upon completion of observations through Day 7 for the first 50 subjects, an analysis will be performed to assess safety. Safety determinations will entail a review of AEs and SAEs. Based on this evaluation, the sponsor will continue or expand the expanded access protocol.

Should the program be expanded, the next safety evaluation will occur at 100 patients.

14. HYPOTHESIS TESTS

14.1 Treatment Comparisons

Clinical outcomes will be compared both to historical controls and to published control groups from studies of other investigational agents.

14.2 Primary Hypothesis

We hypothesize that RLF-100 is of clinical benefit and poses no meaningful safety risk.

14.3 Primary Efficacy Endpoint: Recovery from Respiratory Failure

An informal comparison will be performed vs. historical controls. Should information be published that documents recovery in the drug and placebo groups of other agents, a comparison will be attempted.

14.4 Declared Secondary Efficacy Endpoint: SaO_2.

Descriptive statistics will be published

14.5 Secondary Efficacy Endpoint: NAIAD 8 point ordinal scale

Descriptive statistics will be published.

14.6 Secondary Laboratory Efficacy Endpoints: Inflammatory Markers

The secondary laboratory outcome measures are TNFα, IL6, and other inflammatory markers as measured in the central laboratory.

14.7 Overall Safety Endpoints

All safety results will be presented to FDA

15. SOURCE DATA & DOCUMENTS

15.1 Sources of Research Materials

The following source data and documents will be collected. All blood samples, except those taken for cytokine and arachidonate metabolite level monitoring, which would be part of this investigation, would be obtained in the normal course of clinical care of these patients as described above.

15.2 Patient Identification

Patient name, medical record number, age, gender, height, weight, ethnic background, residence address with zip code will be collected.

15.3 General Clinical Data

Primary diagnosis, coexisting diagnoses / conditions, hospital length of stay and outcome will be collected.

15.4 Data used to determine respiratory failure

Resource use (room air, low flow O2, High Flow O2, non-invasive ventilation, mechanical ventilation, or ECMO) together with SaO_2, PaO_2/FiO_2 ratio; PEEP/CPAP; must be entered into the IBM Cloud system in order for patient to be allowed to participate in the expanded access protocol

15.5 Radiology

Chest X-ray images in Dicom quality will be requested from treating physicians. Chest CT if performed will similarly be requested.

15.6 Laboratory Data

Arterial blood pH, PCO_2, PO_2; electrolytes (Na, K, Cl, HC03); renal function (BUN, serum creatinine); glucose, albumin & total plasma proteins; liver function tests; blood cell count; coagulation profile; lactic acid and serum osmolarity will be requested from treating physicians.

15.7 Vital Signs, Respiratory and Hemodynamic Data

Blood pressure (systolic, diastolic, mean), heart rate, respiratory rate must be entered in the IBM Watson Cloud system for ongoing participation.

16. STUDY MONITORING

16.1 Study Monitoring

Under expanded access, sponsor is unable to provide active study monitoring. However, sponsor is providing monitor support by a board-certified critical care physician available at all times.

16.2 Medical Monitor

The Medical Monitor will review all SAEs, assess the benefits and risks of protocols on an ongoing basis, and work in collaboration with the IRB and DMC to identify safety signals and trends. In addition, the Medical Monitor will be available for site questions regarding inclusion/exclusion criteria, protocol conduct, and safety. Trained and qualified physicians will be available to provide coverage during times when the medical monitor is unavailable. Sites will be provided with the Medical Monitor's cell phone number for emergency

situations. Otherwise, sites are instructed to contact the Medical Monitor through email. All conversations with sites will be documented by the Medical Monitor and reviewed periodically by the sponsor. Each month the Medical Monitor will receive a listing of protocol violations for review and identification of possible trends.

16.3 Audits and Inspections

Contracts with study sites will specify that sponsor or its representatives will have direct access to source data and documents for study monitoring. Additionally, the IRB and FDA may review source data following appropriate guidelines for this process.

16.4 Institutional Review Board

The study protocol and any amendments will be reviewed by the Advarra Institutional Review Board (IRB). The IRB will review the informed consent form, their updates (if any), and any written materials given to the participants. IRB approval will be obtained and documented prior to subject enrollment and screening. Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigators will provide the IRB with reports, updates, and other information (e.g., Safety Updates, Amendments, and Administrative Letters) according to regulatory requirements and Institution procedures. A detailed list of required regulatory documents, to be submitted to the sponsor, will be sent upon final approval of the protocol.

17. ETHICAL CONSIDERATIONS

17.1 Ethical Considerations

17.1.1 Anticipated benefits to participants and others

There are at present no satisfactory specific treatments Critical COVID-19 with Respiratory Failure. Based on early results in RLF-100-001 and in patients treated under named-patient emergency access INDs approved by FDA, there is the possibility that RLF-100 may prove effective in increasing the rate of recovery from Critical COVID-19 with respiratory failure.

17.1.2 Anticipated risks to participants and others

The only anticipated risks are due to the side-effects noted above of hypotension, tachycardia and watery diarrhea. Aviptadil has been evaluated in 4 species toxicology studies and the LD50 is more than 50x the exposure contemplated in this trial. Thus far, no drug-related SAEs have been reported either in Protocol RLF-100-001 or under name-patient emergency use INDs.

17.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with the approved protocol. Sponsor is not in a position to monitor and insure compliance with GCP at the sites that will participate in this protocol.

17.3 Informed Consent

The patient's legally authorized representative (LAR) must be capable of understanding the nature of this study and its potential risks, discomforts, and benefits. Study physicians will obtain consent after they have fully explained the study purpose and procedures, and the LAR has demonstrated an understanding of the protocol, willingness to participate, and competency to consent. The investigator must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the site-specific consent form is the responsibility of the site Principal investigator and must include all elements required by CFR 21 Part 50.25 and the IRB.

18. DATA HANDLING & RECORD KEEPING

18.1 Data Capture

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on everyone treated with the investigational product or entered as a control in the investigation.

18.2 Data Collection

No manual data collection is anticipated in the ICU. Data will be extracted from the EMR and other sources by hospital clinical research staff in a HIPAA-compliant, de-identified manner and transferred to the IBM Watson Cloud EDC.

18.3 Retention of Records

The investigator must retain investigational product disposition records and source documents for the maximum period required by applicable regulations and guidelines, or in accordance with institution procedures, and at least for 10 years. This is study practice in the study sites.

18.4 Use of Information and Publication Policy

All publications will be reviewed by the sponsor for accuracy before submission to peer-reviewed journals or scientific meetings. Abstracts will be submitted for review at least 10 days before submission, and publications should be submitted for review at least 30 days before submission. The study will be posted to Clinicaltrials.gov, and results will be reported in accordance with Clinicaltrials.gov guidelines.

19. APPENDIX A: SCHEDULE OF EVENTS

		Day 1		Day 2		Day 3		Day 4 and each day until discharge	DIscharge Day	EofS
Procedures	**Screening**	**1st Dose[a]**	**During infusion**	**2nd Dose[a]**	**During infusion**	**3rd Dose[a]**	**During infusion**	**Follow-Up**	**Follow-Up**	**D28 or day of discharge**
Informed Consent Process	X									
Evaluation of Exclusion & Inclusion Criteria	X									
Medical History/Demographics	X									
Confirm Eligibility and Randomization		X								
Vital Signs (Pulse, Respirations)[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X	
Blood Pressure[c]	X	X		X		X				
Weight	X	X		X		X		X	X	X
CNS Assessment	X	X				X		X	X	X
IV Administration of Study Drug		X	X	X	X	X	X			
Chest X-ray	X			X (between 48-72 hr)				Day 7	X	
ICU Telemetry: ECG		X		X		X		X	X	
PaO2/FiO2 Ratio	X	X		X		X		X	X	X
CBC (Complete Blood Count with Differential & Platelets)	X	X		X		X		X	X	X
CMP (Complete Metabolic Panel)	X	X		X		X		X	X	X
ABG (for PaO2/FiO2 ratio): pH, pCO2, pO2, CO2, HCO3 per ICU protocol		X	X	X	X	X	X	X	X	X
Study Drug Pharmacy Dispensing		X		X		X				

		Day 1		Day 2		Day 3		Day 4 and each day until discharge	DIscharge Day	EofS
Procedures	**Screening**	**1st Dose[a]**	**During infusion**	**2nd Dose[a]**	**During infusion**	**3rd Dose[a]**	**During infusion**	**Follow-Up**	**Follow-Up**	**D28 or day of discharge**
Assess for Adverse Events[d]		X	X[d]	X	X[d]	X	X[d]	X	X	X
NIAID Ordinal Scale for Clinical Improvement		X		X		X		X	X	X

Footnotes

a	Each dose is administered over 12 hours at the same time each day. Date and time of start and end of infusion will be recorded.
b	Pulse and respirations will be continuously monitored but will be recorded prior to and at 2, 4, 6, 8, 10 and 12-hour timepoints after each dose escalation
c	Blood pressure will be recorded prior to infusion and at 2, 4, 6, 8 and 12 hour timepoints throughout the infusion.
d	Infusion reactions/adverse events check at 2 hours, and then continuously throughout the 12-hour infusion period.
e	Collected pre-dose and at 1, 2, 12 hours for each infusion over 3 days, then daily on day 5 and 7 and day 28 / or day of discharge if sooner.