PROTOCOL: LJ501-CRH02

AN OPEN-LABEL, MULTI-CENTER STUDY OF LJPC-501 IN PEDIATRIC PATIENTS WHO REMAIN HYPOTENSIVE DESPITE RECEIVING FLUID THERAPY AND VASOPRESSOR THERAPY

Sponsor: La Jolla Pharmaceutical Company
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Sponsor Clinical Contact: [redacted]

Sponsor Medical Contact: [redacted]

Original Protocol

Version 2.0

FOR QUALIFIED INVESTIGATORS AND THEIR IRB ONLY

INVESTIGATOR'S AGREEMENT

I have read the LJ501-CRH02 protocol, Version 2.0, and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	E mail Address and Telephone Number
Clinical Study Lead	[redacted]	[redacted]
Responsible Physician	[redacted]	[redacted]

1. SYNOPSIS

Name of Sponsor/Company:
La Jolla Pharmaceutical Company (La Jolla)

Name of Investigational Product:
LJPC-501 (angiotensin II)

Name of Active Ingredient:
angiotensin II

Title of study:
An Open-label, Multi-Center Study of LJPC-501 in Pediatric Patients Who Remain Hypotensive Despite Receiving Fluid Therapy and Vasopressor Therapy

Number of study center(s): Approximately 10

Objectives:

Primary:

- To evaluate the effect of LJPC-501 infusion on mean arterial pressure (MAP) or reduction in sum norepinephrine-equivalent dose (NED), at Hour 2 after the start of LJPC-501, in pediatric patients who remain hypotensive despite receiving fluid therapy and vasopressor therapy.

Secondary:

- To establish the safety and tolerability of LJPC-501 in pediatric patients
- To evaluate the change in MAP over 24 hours after the start of LJPC-501
- To evaluate the change in serum lactate concentrations
- To evaluate change in Pediatric Logistic Organ Dysfunction (PELOD) scores

Methodology:

Screening

During Screening, there will be a titration period of standard of care (SOC) vasopressors (for a minimum of 2 hours to a maximum of 48 hours) to achieve an age-, size-, and disease-appropriate MAP (Appendix A, Dellinger 2013) at the discretion of the Investigator. Baseline MAP is defined as the average of 3 recorded MAP values documented within 15 minutes prior to initiation of LJPC-501 (ie, approximately -15 minutes, -5 minutes, and 0 minutes or just prior to initiation of LJPC-501 administration).

Administration and Assessments

Following informed consent/assent per institutional requirements, as age appropriate, and confirmation of eligibility, patients will begin LJPC-501 treatment at a dose rate of 5 ng/kg/min. To assess multiple possible improved outcomes for pediatric patients, the primary endpoint is a composite of improvement in MAP or reduction in sum NE equivalent dosing. The goal at Hour 2 of LJPC-501 administration is to increase the Baseline MAP by 25% or to decrease the sum NED by 25% at the 2-hour time point.

LJPC-501 dose rate will be titrated during the first 2 hours according to protocol guidelines and the Investigator's discretion, to achieve a MAP above baseline, but less than 90 mmHg. During the first 2 hours and throughout treatment, the LJPC-501 dose rate may be increased to a maximum rate of 40 ng/kg/min, and decreased to a minimum of 1.25 ng/kg/min. If MAP exceeds 90 mmHg, SOC vasopressors should be down-titrated first, then LJPC-501 should be down-titrated if MAP remains ≥ 90 mmHg. Any decision to increase the dose rate above 40 ng/kg/min must be made in consultation with Sponsor. With Sponsor approval, the dose rate may be increased to a maximum of 80 ng/kg/min. Unless adjustment is required for safety reasons, SOC vasopressor dosing may be decreased, but not increased, the first 2 hours of LJPC-501 treatment (ie, up to the Hour 2 time point). MAP should not be allowed to decrease below baseline.

During LJPC-501 dosing, MAP should be assessed once every 5 minutes during the first 15 minutes of treatment, then once every 15 minutes up to the Hour 2 time point and at least once hourly thereafter through the duration of LJPC-501 administration (a minimum 24 hours). Additionally, MAP should be assessed once prior to every dose rate titration.

Treatment will continue to Hour 24, with the goal of maintaining age-, size-, and disease-appropriate MAP, and sparing the use of SOC vasopressors. At Hour 24, LJPC-501 treatment may be stopped or continued up to Day 7 (168 hours) at the Investigator's discretion, and consultation with Sponsor. To stop treatment, LJPC-501 will be down-titrated in steps to avoid transient hypotension. If the Investigator determines that it is necessary to discontinue LJPC-501 prior to Hour 24, the Sponsor should be notified.

If LJPC-501 treatment has been stopped for 3 hours or less (after the Hour 24 assessments), the Investigator may reinitiate treatment after consultation with Sponsor; if treatment has been stopped for more than 3 hours it may not be reinitiated. All patients will be followed for a minimum of 7 days, or for 72 hours (3 days) ± 6 hours following discontinuation of LJPC-501, whichever is later, before the end of study (EOS) assessments are collected.

All components of the PELOD, PRISM, and PIM2 scores will be collected during Screening (no more than 6 hours prior to the initiation of LJPC-501 dosing) and at Hour 24. If possible, blood samples to determine the levels of endogenous angiotensin II and its precursor, angiotensin I, will be obtained at Screening prior to LJPC-501 administration.

Assessment of Safety

Safety will be addressed by assessing adverse events (AEs), blood pressure (BP), heart rate (HR), and routine clinical safety laboratory testing including blood chemistry, hematology, and urine output. A follow-up phone call or chart review will occur at approximately 28 days following initiation of LJPC-501 for safety.

This study will be overseen by an independent external Data Safety Monitoring Board (DSMB).

Number of patients (planned):

10 to 30

Diagnosis and main criteria for inclusion:

1. Pediatric patients 2-17 years of age and weighing ≥10 kg.
2. Patients requiring a sum norepinephrine-equivalent dose of > 0.1 µg/kg/min (see Appendix B for conversion) for a minimum of 2 hours and a maximum of 48 hours prior to initiation of LJPC-501 dosing.
3. Patients must have a clinical diagnosis of distributive shock in the opinion of the treating team and the Investigator.
4. Patients are required to have central venous access, which is expected to remain present for the duration of LJPC-501 treatment.
5. Patients are required to have an indwelling arterial line, which is expected to remain present for at least the first 24 hours of LJPC-501 treatment.
6. Patients must have received at least 40 mL/kg of crystalloid or colloid equivalent over the initial 24-hour resuscitation period, and are adequately volume resuscitated in the opinion of the Investigator.
7. Patients should receive venous thromboembolism (VTE) prophylaxis per institutional guidelines, if indicated, before beginning treatment with LJPC-501.
8. Parent or legal guardian is willing and able to provide informed consent and assist the patient in complying with all protocol requirements.

Exclusion Criteria:

1. Patients who are < 2 years of age or ≥ 18 years of age.
2. Patients who weigh < 10 kg.
3. Patients with a standing Do Not Resuscitate order.
4. Patients diagnosed with acute occlusive coronary syndrome requiring pending intervention.
5. Patients on veno-arterial (VA) extracorporeal membrane oxygenation (ECMO).
6. Patients who have been on veno-venous (VV) ECMO for less than 6 hours.
7. Patients with a clinical suspicion of cardiogenic shock
8. Patients who have a history of asthma or are currently experiencing bronchospasm requiring the use of inhaled bronchodilators and who are not mechanically ventilated.
9. Patients with acute mesenteric ischemia or a history of mesenteric ischemia.
10. Patients with active bleeding AND an anticipated need of multiple transfusions (within 48 hours of Screening).
11. Patients with active bleeding AND hemoglobin < 7 g/dL or any other condition that would contraindicate serial blood sampling.
12. Patients requiring more than 5 mg/kg daily of hydrocortisone or equivalent glucocorticoid medication as a standing dose.
13. Patients with an expected lifespan of < 12 hours or withdrawal of life support within 24 hours of Screening.
14. Patients with a known allergy to mannitol.
15. Patients who are currently receiving an investigational drug (active or placebo) as part of another clinical trial.

16. Patients of childbearing potential who are known to be pregnant at the time of Screening.

Investigational product, dosage and mode of administration:

LJPC-501 for intravenous (IV) infusion: 2.5 mg per mL

Patients will begin LJPC-501 treatment by IV infusion at a dose rate of 5 ng/kg/min. The dose rate may escalate up to 40 ng/kg/min in order to achieve and maintain an age-, size-, and disease-appropriate MAP greater than baseline (above baseline, but less than 90 mmHg, per Investigator discretion). Throughout treatment, LJPC-501 dose rate may be increased to a maximum rate of 40 ng/kg/min, and decreased to a minimum of 1.25 ng/kg/min. Any decision to increase the dose rate above 40 ng/kg/min must be made in consultation with Sponsor. With Sponsor approval, the dose rate may be increased to a maximum of 80 ng/kg/min. Dose administration for more than 24 hours, and for up to 7 days, is permitted with Sponsor consultation.

Duration of treatment:

The target minimum duration of treatment is 24 hours. Continued administration of LJPC-501 for up to 7 days is permitted after consultation with the Sponsor.

Criteria for evaluation:

Efficacy:

Primary composite endpoint:

- Proportion of patients with an increase of 25% over Baseline MAP (without an increase in sum NED from baseline) at 2 hours after the initiation of LJPC-501 OR a 25% reduction in sum NED (without a decrease in MAP from baseline) at 2 hours after the initiation of LJPC-501

Secondary endpoints:

- Adverse events, BP, HR, and routine clinical safety laboratory testing including blood chemistry, hematology, and urine output
- Change in MAP from baseline to 24 hours
- Change in concentration of serum lactate from baseline to 2 hours and to 24 hours
- Change in PELOD score from Screening to 24 hours

Exploratory endpoints:

- Change in tissue oxygenation from baseline to 2 hours and to 24 hours
- Change in HR from baseline to 2 hours
- Change in sum NED from baseline to 24 hours
- 28-day all-cause mortality
- Number of ventilator days
- Number of days on a vasopressor
- Change in PRISM and PIM2 scores from Screening to 24 hours

Statistical methods:

Data will be summarized and reported in a descriptive fashion. All patients who receive any amount of LJPC-501 will be included in the safety evaluation.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ABG	arterial blood gas
ACE	angiotensin converting-enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AT1R	angiotensin II type 1 receptor
BP	blood pressure
BUN	blood urea nitrogen
CRA	clinical research associate
CRF	case report form
DSMB	data safety monitoring board
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EOS	end of study
FiO_2	fractional inspired oxygen
GCP	good clinical practice
HR	heart rate
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous(ly)
MAP	mean arterial pressure
mEq	milliequivalent
mmHg	millimeter of mercury
NE	norepinephrine

NED	norepinephrine-equivalent dose
NIRS	near-infrared spectroscopy
$PaCO_2$	carbon dioxide partial pressure
PaO_2	arterial oxygen partial pressure
PE	physical exam
PELOD	Pediatric Logistic Organ Dysfunction
PIM2	Pediatric Index of Mortality 2
PRISM	Pediatric Risk of Mortality
PT	prothrombin time
PTT	partial thromboplastin time
RAAS	renin angiotensin aldosterone system
RR	respiratory rate
SAE	serious adverse event
SGOT	serum glutamic-oxaloacetic transaminase
SOC	standard of care
SOP	standard operating procedures
VA	veno-arterial
VV	veno-venous
WBC	white blood cell

4. INTRODUCTION

4.1. Pediatric Shock Etiology

Shock, a life-threatening condition, is the clinical expression of circulatory failure that results in inadequate cellular oxygen utilization. In one subtype of shock, distributive shock, cardiac output is typically high and the main deficit lies in the periphery, with decreased systemic vascular resistance and altered oxygen extraction. Sepsis is a common cause of distributive shock.

The progression of shock in pediatric patients is unique from adults. Younger children are unable to significantly increase stroke volume in the face of a stress response, augmenting cardiac output instead by increased chronotropy. Early compensatory mechanisms like tachycardia are inadequate, and uncompensated shock ensues and downstream micro- and macroscopic perturbations occur. Cellular ischemia and the release of vasoactive metabolites and inflammatory mediators start to affect the microcirculation. If not reversed, multi-organ system failure can occur. The vascular endothelium of these patients is also immature and can display marked heterogeneity to the effects of circulating catecholamines or vasopressor support, leading to rapid and sometimes unpredictable changes from vasodilated to vasoconstricted or vice versa.

4.2. Treatment and Unmet Medical Need

Treatment of shock and sepsis in children involves a progression of interventions, beginning with establishing adequate ventilation and administering fluids and antibiotics. If patients do not respond to fluids, vasopressor or inotropic support may be used, including epinephrine (for cold shock) or norepinephrine (NE; for warm shock) infusions. Hydrocortisone may be administered if adrenal insufficiency is suspected. Vasopressor use has been reported in 21% of pediatric patients with shock (Fisher 2010).

The use of high dose catecholamines, such as epinephrine and NE, in patients with severe hypotension is associated with poor outcomes. The only other approved vasopressor that is not a catecholamine is vasopressin, which may reduce NE requirements in adult patients with severe hypotension (Bassi 2013, Neto 2012). However, high-dose vasopressin has been associated with myocardial ischemia and mesenteric ischemia (Russell 2011, Sharman 2008). Vasopressin is not indicated for pediatric use because the safety and effectiveness in patients with vasodilatory shock have not been established. One placebo-controlled study of arginine vasopressin in pediatric patients showed that while there was a statistically significant increase in mean arterial pressure (MAP) from baseline after 1 hour, there were no significant differences in the time to hemodynamic stability, organ failure-free days or ventilator-free days, length of intensive care unit (ICU) stay, and adverse events (AEs). The authors concluded that low-dose vasopressin did not demonstrate any benefits in pediatric vasodilatory shock (Choong 2009).

No product has been shown to effectively and safely treat pediatric patients with distributive shock who remain hypotensive despite treatment with fluids and catecholamines. Thus, there is a significant unmet need in this patient population. Pediatric sepsis is a significant healthcare burden. Based on the incidence of sepsis in children (Watson 2003), and the proportion of pediatric patients with severe sepsis who are reported to develop septic shock (Kutko 2003), the

annual incidence of septic shock in pediatric patients is estimated to be 2,065 to 12,390 in the US. While the outcomes for pediatric patients who remain hypotensive despite receiving fluid therapy and vasopressor therapy are not specifically described, the mortality rate for pediatric severe sepsis has ranged from 8.9% to 14.4% in recent years (Hartman 2013, Ruth 2014).

This study (LJ501-CRH02) will evaluate the safety and efficacy of LJPC-501 in pediatric patients 2 to 17 years old who remain hypotensive despite receiving fluid therapy and vasopressor therapy, and will be conducted in compliance with the protocol, good clinical practice (GCP), and all applicable regulatory requirements(s).

4.3. Angiotensin II Mechanism of Action

The active ingredient in LJPC-501 is the acetate salt of synthetic angiotensin II, an octapeptide identical to endogenous human angiotensin II. Angiotensin II is the major bioactive component of the renin-angiotensin-aldosterone system (RAAS System), and serves as one of the body's central regulators of blood pressure (BP). The RAAS system along with the arginine-vasopressin system and the sympathetic nervous system make up the three major counter-regulatory systems the human body utilizes to manage BP. Angiotensin II is a naturally occurring peptide hormone that regulates BP through activation of the angiotensin II type 1 receptor (AT1R). Through the AT1R, angiotensin II induces peripheral vasoconstriction, increases sodium and water retention, aldosterone release, and vasopressin release leading to increase in BP (Harrison-Bernard 2009, Basso 2001).

4.4. Nonclinical Experience with Angiotensin II

Extensive nonclinical studies are reported in the literature on angiotensin II that provide a comprehensive understanding of its pharmacodynamic, safety pharmacology, pharmacokinetic, and toxicology profile; these studies are described in the Investigator's Brochure.

Briefly, intravenous (IV) infusion of angiotensin II produces a sustained increase in MAP in normotensive animals, including rats, dogs, and rabbits (Campbell 2013). In animal models of hypotension, there are two key studies:

- In a sepsis model in pigs, treated with either NE or angiotensin II for 48 hours after a 12-hour period of untreated sepsis, angiotensin II was as effective as NE in restoring arterial BP and increased cardiac output (Corrêa 2014).
- In a septicemia model in sheep, infusion of angiotensin II was effective in restoring arterial BP and increased urinary output and creatinine clearance, despite a marked decrease in renal blood flow. In this model, angiotensin II improved renal function without major adverse effects on blood flows to other vital organs, blood lactate, or other biochemical variables (Wan 2009).

Furthermore, the range of angiotensin II administered in these animal models of septic shock was similar to the range of angiotensin II that has been used in humans with hypotensive shock (Chawla 2014; Whiteley 1996).

Pharmacokinetic studies in rats indicate that angiotensin II equilibrates rapidly and has a half-life in blood of less than 60 seconds (Al-Merani 1978).

No studies have been conducted to assess the genotoxicity of LJPC-501 because it is a naturally occurring peptide. There have been no classical reproductive or developmental studies conducted with exogenously administered angiotensin II.

4.5. Clinical Experience with Angiotensin II

GIAPREZA™ (angiotensin II) injection for IV infusion (LJPC-501) is approved for use in the United States as a vasoconstrictor to increase blood pressure in adults with septic or other distributive shock.

In numerous clinical studies, angiotensin II has demonstrated significant effects on systemic and renal blood flow. Intravenous angiotensin II has been safely studied in patients with hypertension, aortic regurgitation, coronary artery disease, recent myocardial infarction, congestive heart failure, traumatic brain injury, chronic obstructive pulmonary disease, peripheral vascular disease, diabetes mellitus, congenital adrenal hyperplasia, primary hyperaldosteronism, renovascular hypertension, cirrhosis, and adrenal masses (Fraser 1980, Goldsmith 1993, Thomas 1991, Yunge 2000). Case reports support the use of angiotensin II to treat hypotension in patients suffering from vasopressor-resistant shock (Thomas 1991, Yunge 2000, Wray 1995). In addition, angiotensin II has been reported to successfully restore MAP in patients who have taken overdoses of angiotensin converting-enzyme (ACE) inhibitors and were refractory to catecholamines (Newby 1995, Trilli 1994).

In humans, infusion of 1.5-3.0 ng/kg/min angiotensin II was found to increase MAP (Campbell 2013, Nassif 1963). When synthetic angiotensin II was administered to 14 patients in hypotensive states, the drug was found to increase MAP to some degree in all patients, including those who were relatively unresponsive to other vasopressor agents (Nassif 1963). Data from a study by Chawla et al (Chawla 2014) support the safety and efficacy of angiotensin II in the treatment of patients who remain hypotensive despite receiving fluid therapy and vasopressor therapy. In that study, patients were randomized to receive angiotensin II acetate infusion or a placebo infusion plus the standard of care (SOC) treatment for severe hypotension. The titration protocol was designed to elucidate the dose of angiotensin II that was required (in conjunction with a NE dose of between 5-10 µg/min) to achieve a MAP goal of 65 mmHg. The dose rate of angiotensin II administered was between 5 and 40 ng/kg/min. Norepinephrine doses were significantly lower for the angiotensin II cohort than for the placebo cohort, and the effect reached statistical significance at Hour 2. Upon cessation of the angiotensin II infusion, the need for NE was reestablished.

La Jolla completed a double-blind, placebo-controlled Phase 3 clinical study (ATHOS-3) of LJPC-501 in patients ≥ 18 years old who remain hypotensive despite receiving fluid therapy and vasopressor therapy. Patients were randomized to receive LJPC-501 or a placebo infusion plus SOC treatment. A starting dose rate of 20 ng/kg/min was administered IV, and during the first 3 hours of administration could be titrated up to 200 ng/kg/min in order to achieve and maintain a MAP of 75 mmHg or higher. Results demonstrated a statistically significant improvement in MAP in LJPC-501-treated patients compared to placebo-treated patients. The percentage of patients obtaining a pre-specified target MAP was 70% with LJPC-501 compared to 23% with placebo (chi-square test $p < 0.00001$). In addition, LJPC-501 was generally safe and well tolerated in this population: 92% of placebo-treated patients compared to 87% of LJPC-501-treated patients experienced at least one AE, and 22% of placebo-treated patients compared to

14% of LJPC-501-treated patients discontinued treatment due to an AE. Although the study was not powered for a mortality endpoint, LJPC-501 showed a positive trend at Day 7 with 35% mortality in the placebo arm compared to 29% in the LJPC-501 arm (hazard ratio = 0.78; 95% CI: 0.53-1.16; p = 0.218, unstratified log-rank test) and at Day 28 with 54% mortality in the placebo arm compared to 46% in the LJPC-501 arm (hazard ratio = 0.78; 95% CI: 0.57-1.07; p = 0.123, unstratified log-rank test).

In a search of the literature, a single article was found on the use of angiotensin II in pediatric shock (Yunge 2000). The article reports on two children with severe septic shock. One had meningococcal septicemia and the other *Escherichia coli* septicemia. Both remained hypotensive despite high concentrations of conventional inotropes and vasopressors. The first child was given an infusion of angiotensin II that started at 100 ng/kg/min and increased to a maximum of 320 ng/kg/min over 24 hours. The second child was given an infusion of angiotensin II at 400 ng/kg/min and increased to a maximum of 800 ng/kg/min over 7 days. In both cases, there was significant improvement in clinical status, resulting in a rapid reduction in the concentration of inotropes required. Both patients successfully survived their septic episodes.

4.6. Summary of Known Risks

Forms of angiotensin II have been administered to patients and healthy subjects in multiple clinical studies since 1941. A systematic review of the literature identified more than 31,000 human subjects who were exposed to synthetic angiotensin II by IV infusion (Busse 2017). The most common symptoms reported in two or more studies were headache (including severe), sensation of chest pressure/tightness, dyspepsia/nausea, bradycardia, and orthostatic hypotension/dizziness.

In the Phase 3 study of LJPC-501 in critically ill adult patients(ATHOS-3), there was a higher incidence of venous and arterial thromboembolic events in patients who received GIAPREZA compared to placebo-treated patients (12.9% versus 5.1%). The major imbalance was in venous thromboses. Because of the risk of venous or arterial thrombotic or thromboembolic events, concurrent venous thromboembolism (VTE) prophylaxis is advised for adults treated with LJPC-501 (GIAPREZA™ [angiotensin II] Prescribing Information). The risk of thrombosis in children treated with LJPC-501 is unknown, and it is recommended to follow your institution's guidelines for VTE prophylaxis in pediatric patients.

Other adverse events occurring with an incidence of at least 4% among adult patients treated with GIAPREZA and with a rate of at least 1.5% higher with GIAPREZA than with placebo are listed in Table 3. Risk of these or other adverse events in pediatric patients is unknown.

Table 3: Adverse Reactions Occurring in ≥ 4% of Patients Treated with GIAPREZA and ≥ 1.5% More Often than in Placebo-treated Patients in ATHOS-3

Adverse Event	GIAPREZA (LJPC-501) N=163	Placebo N=158
Thromboembolic events[a]	21 (12.9%)	8 (5.1%)
Deep vein thrombosis	7 (4.3%)	0 (0.0%)
Thrombocytopenia	16 (9.8%)	11 (7.0%)
Tachycardia	14 (8.6%)	9 (5.7%)
Fungal infection	10 (6.1%)	2 (1.3%)
Delirium	9 (5.5%)	1 (0.6%)
Acidosis	9 (5.5%)	1 (0.6%)
Hyperglycemia	7 (4.3%)	4 (2.5%)
Peripheral ischemia	7 (4.3%)	4 (2.5%)

Source: GIAPREZA Prescribing Information
[a] Including arterial and venous thrombotic events

Consistent with the mechanism of action and short half-life of angiotensin II, transient hypertension and hypotension are known risks of LJPC-501 treatment that may be mitigated by frequent or continuous monitoring of hemodynamic variables and appropriate dose titration.

A summary of the AEs observed in the Phase 3 study and risks of LJPC-501 treatment are provided in the Investigator's Brochure.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

- To evaluate the effect of LJPC-501 infusion on MAP or reduction in sum NE equivalent dosing, at Hour 2 after the start of LJPC-501, in pediatric patients who remain hypotensive despite receiving fluid therapy and vasopressor therapy

5.2. Primary Endpoint

- Proportion of patients with
  - a 25% increase in MAP over baseline (without an increase in sum NE equivalent dose [NED] from baseline) at 2 hours after the initiation of LJPC-501
    OR
  - a 25% reduction in NED from baseline (without a decrease in MAP from baseline) at 2 hours after the initiation of LJPC-501

5.3. Secondary Objectives

- To establish the safety and tolerability of LJPC-501 in pediatric patients
- To evaluate the change in MAP over 24 hours after the start of LJPC-501
- To evaluate the change in serum lactate concentrations
- To evaluate change in Pediatric Logistic Organ Dysfunction (PELOD) scores

5.4. Secondary Endpoints

- Adverse events, blood pressure (BP), heart rate (HR), and routine clinical safety laboratory testing including blood chemistry, hematology, and urine output
- Change in MAP from baseline to 24 hours
- Change in concentration of serum lactate from baseline to 2 hours and to 24 hours
- Change in PELOD score from Screening to 24 hours

5.5. Exploratory Endpoints

- Change in tissue oxygenation from baseline to 2 hours and to 24 hours
- Change in HR from baseline to 2 hours
- Change in sum NED from baseline to 24 hours
- 28-day all-cause mortality
- Number of ventilator days
- Number of days on a vasopressor
- Change in PRISM and PIM2 scores from Screening to 24 hours

6. INVESTIGATIONAL PLAN

6.1. Study Rationale

Severe hypotension is associated with significant mortality, and the use of high doses of catecholamines in patients with severe hypotension is associated with poor outcomes. Given that LJPC-501 has recently been demonstrated to be efficacious and well-tolerated in adults with hypotension who do not respond to fluids and vasopressor therapy (Section 4.5), it is reasonable to hypothesize that LJPC-501 may also be efficacious and well-tolerated in pediatric patients with the same diagnosis.

This is an open-label, multi-center study. Pediatric patients, age 2 to 17 years, who remain hypotensive despite receiving fluid therapy and vasopressor therapy and are hospitalized in an ICU setting may be eligible to participate. Because severe hypotension is life threatening, and because the treatment options are limited for pediatric patients who remain hypotensive despite fluids and vasopressors, this study will examine a single LJPC-501 treatment arm, without a placebo-controlled arm. Efficacy of LJPC-501 will be measured by each patient's response over time. To assess multiple possible improved outcomes, the primary endpoint is a composite of the proportion of patients with an increase of 25% over Baseline MAP at Hour 2 after the initiation of LJPC-501, or with a 25% reduction in sum NED at Hour 2 after the initiation of LJPC-501.

Secondary endpoints will include the change in MAP at Hour 24, and the change in serum lactate concentrations. The risk of mortality will be assessed using the PELOD score at Hour 24. Safety and tolerability will be assessed throughout the study.

Exploratory endpoints will include tissue oxygen levels, HR, reduction in sum NED at Hour 24, all-cause mortality at 28 days, the number of days that patients spend on mechanical ventilation, and the number of days on vasopressors. Exploratory measures of the risk of mortality will include PRISM and PIM2 scores at Hour 24.

6.2. Overall Study Design

The overall sequence of study events is shown in Figure 1. During Screening, patients will have their SOC vasopressors titrated to an age-, size-, and disease-appropriate MAP (Appendix A, Dellinger 2013) at the discretion of the Investigator. A minimum titration period of 2 hours, and a maximum of 48 hours, is required. The Screening MAP is calculated as the average of at least two once-hourly MAP readings during SOC vasopressor titration, and within 24 hours prior to LJPC-501 treatment initiation.

In the 15 minutes prior to initiation of LJPC-501 dosing, a baseline MAP will be documented. The Baseline MAP is the average of 3 recorded MAP values documented within 15 minutes prior to initiation of LJPC-501 (ie, at approximately -15 minutes, -5 minutes, and 0 minutes or just prior to initiation of LJPC-501 administration).

After obtaining informed consent from the patients' parent(s) or legal guardian(s), assent from the patients (per institutional requirements, as age appropriate, if possible), and confirmation of eligibility, patients will begin LJPC-501 treatment at a dose rate of 5 ng/kg/min. The goal at Hour 2 of LJPC-501 administration is to increase the Baseline MAP by 25% or to decrease the

sum NED by 25%. The LJPC-501 dose will be titrated during this period according to the guidelines in Section 8.3, to achieve a MAP above baseline, but less than 90 mmHg. Throughout treatment, the LJPC-501 dose rate may be increased to a maximum rate of 40 ng/kg/min, and decreased to a minimum of 1.25 ng/kg/min. If MAP exceeds 90 mmHg, SOC vasopressors should be down-titrated first, then LJPC-501 should be down-titrated if MAP remains ≥ 90 mmHg. Any decision to increase the dose rate above 40 ng/kg/min must be made in consultation with Sponsor. With Sponsor approval, the dose rate may be increased to a maximum of 80 ng/kg/min. Unless adjustment is required for safety reasons, SOC vasopressor dosing should be decreased, but not increased, during the first 2 hours of LJPC-501 treatment (ie, up to the Hour 2 time point). MAP should not be allowed to decrease below baseline.

A schedule of study procedures is shown in Table 4. Patients will be monitored for hemodynamic vital signs (MAP, HR) at Screening and at approximately -15, -5 and 0 minutes (or just prior to initiation of LJPC-501 dosing) to establish the Baseline MAP value. MAP should be assessed once every 5 minutes during the first 15 minutes of LJPC-501 treatment, then once every 15 minutes up to the Hour 2 time point and at least once hourly thereafter through the duration of LJPC-501 administration (at minimum 24 hours). Additionally, MAP should be assessed just prior to every dose titration. If LJPC-501 administration is continued for longer than 24 hours, MAP should be assessed hourly and just prior to any dose adjustment until LJPC-501 is discontinued.

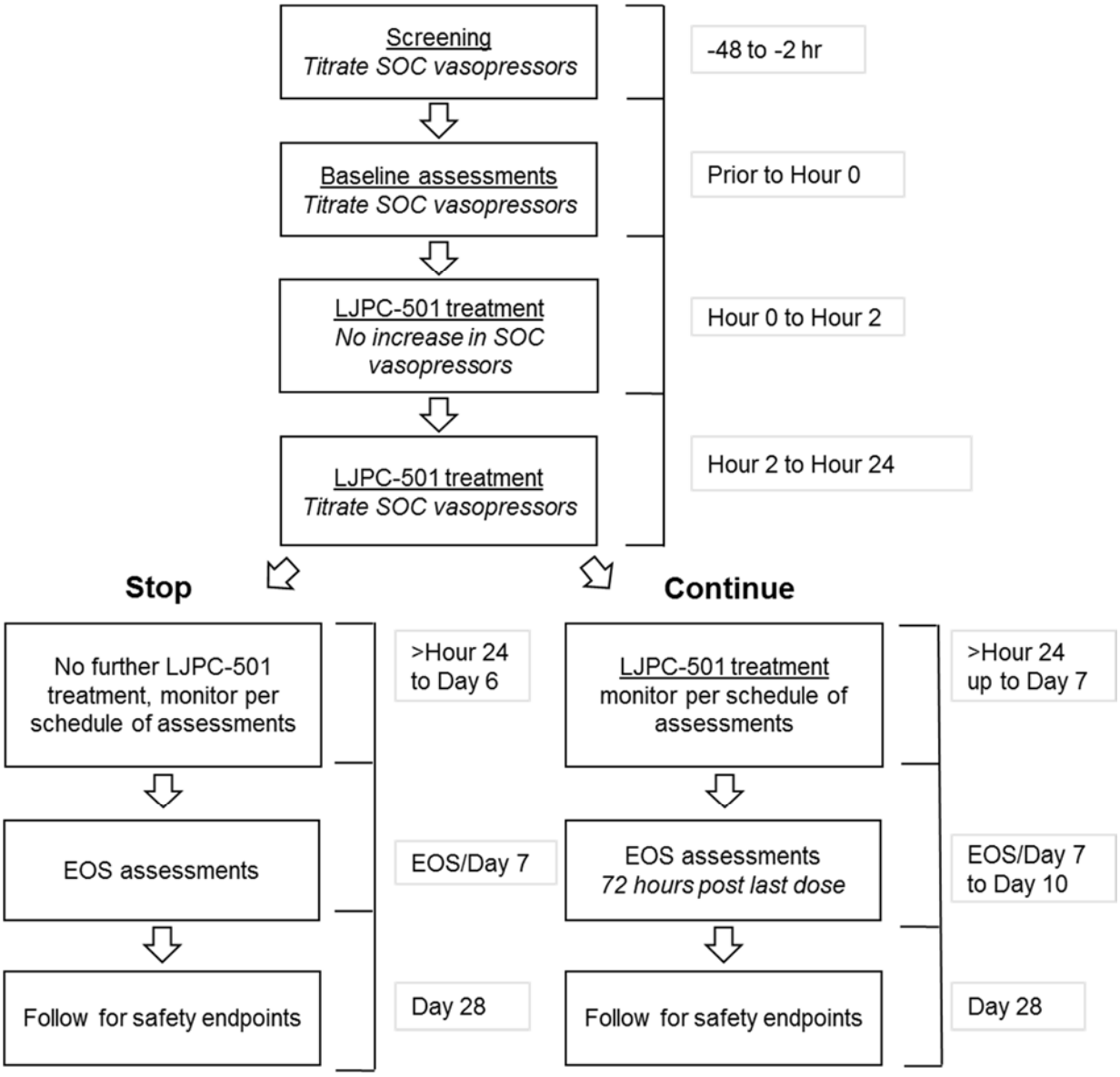
Treatment with LJPC-501 will continue to Hour 24, with the goal of maintaining age-, size-, and disease-appropriate MAP (Appendix A, Dellinger 2013), while reducing the reliance on SOC vasopressors. Down-titration of SOC vasopressors should be done according to individual institutional protocols and the Investigator's discretion.

After 24 hours, LJPC-501 treatment may be stopped or continued up to 7 days (168 hours) at the Investigator's discretion. It is recommended that the Investigator check in with the Sponsor's contact to continue treatment for more than 24 hours. If the Investigator determines that it is necessary to discontinue LJPC-501 prior to Hour 24, the Sponsor should also be consulted prior to discontinuation. To stop treatment, LJPC-501 will be titrated off by decreasing the dose at the Investigator's discretion and according to guidelines in Section 8.3.2. After Hour 24, if LJPC-501 treatment has been stopped for 3 hours or less, the Investigator may reinitiate treatment after consultation with Sponsor; if treatment has been stopped for more than 3 hours it may not be reinitiated. All patients will be followed for a minimum of 7 days, or for 72 hours (3 days) ± 6 hours following discontinuation of LJPC-501, whichever is later, before end-of-study (EOS) assessments.

All components of the PELOD, PRISM, and PIM2 scores will be collected during Screening (no more than 6 hours prior to the initiation of LJPC-501 dosing) and at Hour 24. If possible, blood samples to determine the levels of endogenous angiotensin II and its precursor, angiotensin I, will be obtained at Screening prior to LJPC-501 administration. Safety will be addressed by assessing AEs, BP, HR, and routine clinical safety laboratory testing including blood chemistry, hematology, and urine output. A follow-up phone call and/or chart review will occur at approximately 28 days following initiation of LJPC-501 for safety assessments.

This study will be overseen by an independent external Data Safety Monitoring Board (DSMB).

Figure 1: Study Design



Abbreviations: EOS=end of study; SOC=standard of care

6.3. Treatment Assignment

All patients will receive LJPC-501 in this single-arm, open-label study.

6.4. Number of Subjects

The study will include 10 to 30 pediatric patients.

6.5. Dose Rationale

Patients will receive an initial LJPC-501 dose rate of 5 ng/kg/min. Throughout treatment, the LJPC-501 dose rate may be increased to a maximum rate of 40 ng/kg/min, and decreased to a minimum of 1.25 ng/kg/min, to achieve an age-, size- and disease-appropriate MAP (Appendix A, Dellinger 2013). Any decision to increase the dose rate above 40 ng/kg/min must be made in consultation with Sponsor. With Sponsor approval, the dose rate may be increased to a maximum of 80 ng/kg/min.

In the recently completed double-blind, placebo-controlled Phase 3 clinical study, LJPC-501 was found to be efficacious in patients ≥ 18 years old with hypotension (Section 4.5). The starting dose was 20 ng/kg/min, and the dose rate range allowed per protocol was 2.5 ng/kg/min to 200 ng/kg/min during the first 3 hours 15 minutes of treatment. Thereafter, the allowed dose rate range was 2.5 to 40 ng/kg/min. A minimum dose rate of 1.25 ng/kg/min was allowed if MAP remained ≥ 70 mmHg without vasopressin and with NED as low as 0.03 µg/kg/min. Per protocol, the dose was titrated based on the observed MAP. By 30 minutes, 67% of patients in the LJPC-501 group were receiving doses below 20 ng/kg/min, including 48.4% with doses of 5 ng/kg/min or less and 23.9% with doses of 2.5 ng/kg/min or less, demonstrating that doses below 20 ng/kg/min were effective.

6.6. Dose Adjustment Criteria

LJPC-501 dose may be titrated to achieve an age-, size-, and disease-appropriate MAP, which should remain above baseline, but less than 90 mmHg. Throughout treatment, LJPC-501 dose may be decreased to a minimum of 1.25 ng/kg/min and increased to a maximum rate of 40 ng/kg/min. If MAP exceeds 90 mmHg, SOC vasopressors should be down-titrated first, then LJPC-501 should be down-titrated if MAP remains ≥ 90 mmHg. Any decision to increase the dose rate above 40 ng/kg/min must be made in consultation with Sponsor. With Sponsor approval, the dose rate may be increased to a maximum of 80 ng/kg/min. Dose titration guidelines are provided in Section 8.3.2.

6.6.1. Safety Criteria for Adjustment or Stopping Doses

LJPC-501 administration may continue through Day 7 to support an age- and disease-appropriate MAP. At any time during dosing, if clinically significant toxicities or worsening of symptoms of underlying disease is observed, treatment should be down-titrated and discontinued.

LJPC-501 infusion should not be stopped abruptly (see dose titration guidelines in Section 8.3.2). To discontinue, down titrate by 5 to 20 ng/kg/min every 15 minutes until a dose of 10 ng/kg/min is reached. After 15 minutes at 10 ng/kg/min, down titrate to 5 ng/kg/min. After 15 minutes at 5 ng/kg/min down titrate to 2.5 ng/kg/min. Discontinue LJPC-501 infusion after 15 minutes at 2.5 ng/kg/min.

6.7. Criteria for Study Termination

This study may be prematurely terminated by La Jolla for any reason. Written notification documenting the reason for study termination will be provided to the Investigator by La Jolla.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Unacceptable patient enrollment rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue development of LJPC-501

Table 4: Schedule of Assessments

Assessment	Screening[1] (-48 to -2 hr)	Baseline	Day 1 0 to 2 hours	Day 1 2 to < 24 hours	Hour 24 (± 1 hr)	Days 2 to 6	EOS[2] Day 7 to 10 (± 6 hr)	Day 28 Follow-up (± 2 days)
Informed Consent[3]	X							
Titrate SOC Vasopressors[4]	X	X		X		(X)	(X)[5]	
Inclusion/Exclusion Criteria	X							
Demographics	X							
Medical/Surgical History	X							
Limited Physical Exam[6]	X						X	
Chest X-ray[7]	X							
Hemodynamic Vital Signs (HR, MAP)[8]	X	X	X	X	X	X	X	
Other Vital Signs (BP, RR, Body Temperature)[9]	X	X	X		X	X	X	
12-Lead ECG[10]	X				X			
Urine Output[11]	X	X	X	X	X	X	X[5]	
Fluid Intake[12]	X	X	X	X	X	X	X[5]	
Tissue Oxygen Saturation[13]		X	X		X			
Arterial Blood Gas[14]	X				X			
Serum Lactate[15]		X	X		X			
Serum Pregnancy Test[16]	X							
Hematology and Serum Chemistry[17]	X				X			
Angiotensin I/II levels [18]	X							
LJPC-501 Administration[19]			X	X	X	(X)	(X)[5]	

1

Assessment	Screening[1] (-48 to -2 hr)	Baseline	Day 1 0 to 2 hours	Day 1 2 to < 24 hours	Hour 24 (± 1 hr)	Days 2 to 6	EOS[2] Day 7 to 10 (± 6 hr)	Day 28 Follow-up (± 2 days)
PELOD/PRISM/PIM2 Scoring, Including[20] Pupillary Reactions Glasgow Coma Score Diagnosis Ratings	X				X			
Concomitant Medications and Concomitant Procedures[21]	X	X	X	X	X	X	X	X
Safety Assessments (AEs/SAEs)[22]			X	X	X	X	X	X

Abbreviations: ABG=arterial blood gas; AE=adverse event; BP=blood pressure; ECG=electrocardiogram; EOS=End of Study; HR=heart rate; MAP=mean arterial pressure; PELOD=Pediatric Logistic Organ Dysfunction; PIM2=Pediatric Index of Mortality 2; PRISM=Pediatric Risk of Mortality; RR=respiratory rate; SAE=serious adverse event; SOC=standard of care.

[1] Screening procedures may be conducted up to 48 hours prior to anticipated initiation of LJPC-501 dosing. SOC procedures collected prior to informed consent may be used to qualify patients for the study.

[2] Patients will be followed for a minimum of 7 days, or for 72 hours (3 days) ± 6 hours following discontinuation of LJPC-501, whichever is later, before end of study (EOS) assessments are completed. Depending on the duration of treatment, EOS may occur on Day 7 through Day 10. If a patient is treated for the target minimum of 24 hours, EOS will occur on Day 7.

[3] Informed consent must be obtained before any study related activities can occur. SOC procedures conducted prior to informed consent may be used to qualify patients for the study, if performed within the specified time window for the procedure (Section 8.5).

[4] All patients will have their SOC vasopressors titrated (to a total sum NE equivalent dose of > 0.1 µg/kg/min to be eligible) for a minimum of 2 hours but not for longer than 48 hours prior to initiation of LJPC-501 dosing. During the first two hours of LJPC-501 treatment, SOC vasopressor dosing may be decreased, but not increased, unless adjustment is required for safety reasons. After Hour 2 and throughout LJPC-501 treatment, up to Day 7, titration of SOC vasopressors may continue with the goal of sparing the use of catecholamines. (X) indicates time periods during which LJPC-501 dose administration is optional. During treatment with LJPC-501, SOC vasopressor titration should be tracked.

[5] Do not continue administration for more than 7 days (168 hours).

[6] A limited physical exam (PE) focused on extremities, abdominal region and neurological system should be performed at Screening and at EOS. Screening PE will also document body weight and height.

[7] Chest X-ray is optional. SOC chest X-rays collected prior to informed consent but within 24 hours prior to LJPC-501 treatment initiation may be used.

[8] Patients will be continuously monitored during the first 24 hours following initiation of LJPC-501. Hemodynamic vital signs, (MAP, HR) must be documented hourly during Screening for a minimum of 2 hourly readings within 24 hours prior to LJPC-501 treatment initiation. The average of the 2 MAP readings will determine the Screening MAP. MAP must be measured during Baseline at approximately -15 min, -5 min, and 0 min (or just prior to initiation of LJPC-501). The average of these 3 MAP values will determine the Baseline MAP. MAP and HR will be recorded on Day 1 prior to every dose titration and minimally every 5 minutes during the first 15 minutes, every 15 minutes during the first 2 hours, and hourly thereafter through the duration of LJPC-501 administration (target minimum of 24 hours). If a patient remains on LJPC-501 beyond 24 hours, documentation of MAP and HR should continue as during Hours 2 to 24 (ie, just prior to any dose adjustment and a minimum of hourly through discontinuation of LJPC-501.) After LJPC-501 treatment, but before EOS, documentation of MAP and HR should occur once daily.

[9] Other vital signs should be assessed at Screening, just prior to initiation of dosing on Day 1, on Day 1 at Hour 2, at Hour 24, and once daily on Days 2-7.
[10] ECG assessments will be performed at Screening and at Hour 24 after initiation of LJPC-501, if possible.
[11] Urine output will be measured and recorded as appropriate for the patient's age, per local SOC, if possible. Assessments for the 24 hours prior to LJPC-501 administration will be recorded, if available. Urine output will be measured and recorded continuously through Day 7.
[12] IV fluid intake will be assessed for the 24-hour period prior to LJPC-501 administration, if available. IV fluid intake will be measured and recorded continuously through Day 7 per local practice.
[13] Tissue oxygen saturation will be measured non-invasively, if possible, at baseline, Hour 2, and Hour 24.
[14] An ABG sample will be collected during Screening (within 6 hours prior to LJPC-501 administration) and at Hour 24.
[15] Serum lactate (arterial or venous) will be collected at baseline, Hour 2, and Hour 24. Any measurements taken at other times will also be recorded in the electronic case report form (eCRF).
[16] Serum pregnancy tests are required for female patients of childbearing potential.
[17] Blood for clinical chemistry and hematology testing will be collected at Screening (within 6 hours prior to LJPC-501 administration), and at Hour 24 (Section 11.1.8).
[18] If total blood collection volume limits (per institutional guidelines) allow, blood samples will be collected for angiotensin I/II levels.
[19] See Section 6.2 and Section 6.6 for study periods and dose adjustment guidelines. (X) indicates time periods during which dose administration is optional.
[20] All parameters of the PELOD/PRISM/PIM2 scores should be performed at Screening and at Hour 24. The Screening PELOD/PRISM/PIM2 scores must be determined with data obtained no more than 6 hours prior to initiation of LJPC-501 dosing. See Appendix C, Appendix D, and Appendix E.
[21] Record all concomitant medications (including vasopressors) and any procedures performed through Day 28. In addition, record all vasopressors administered up to 2 days prior to beginning LJPC-501 administration. Total daily dose for each vasopressor administered through Day 28 may be recorded after completion of LJPC-501 administration.
[22] Safety will be evaluated at every time point. On Day 28, a phone call follow-up to the patient's parent(s) or legal guardian(s), the patient's primary care physician, and/or a chart review will be conducted to determine if reportable safety events occurred between EOS and Day 28.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Pediatric patients 2-17 years of age and weighing ≥ 10 kg.
2. Patients requiring a sum norepinephrine-equivalent dose of > 0.1 µg/kg/min (see Appendix B for conversion) for a minimum of 2 hours and a maximum of 48 hours prior to initiation of LJPC-501 dosing.
3. Patients must have a clinical diagnosis of distributive shock in the opinion of the treating team and the Investigator.
4. Patients are required to have central venous access, which is expected to remain present for the duration of LJPC-501 treatment.
5. Patients are required to have an indwelling arterial line, which is expected to remain present for at least the first 24 hours of LJPC-501 treatment.
6. Patients must have received at least 40 mL/kg of crystalloid or colloid equivalent over the initial 24-hour resuscitation period, and are adequately volume resuscitated in the opinion of the Investigator.
7. Patient should receive VTE prophylaxis per institutional guidelines, if indicated, before beginning treatment with LJPC-501.
8. Parent or legal guardian is willing and able to provide informed consent and assist the patient in complying with all protocol requirements.

7.2. Subject Exclusion Criteria

1. Patients who are < 2 years of age or ≥ 18 years of age.
2. Patients who weigh < 10 kg.
3. Patients with a standing Do Not Resuscitate order.
4. Patients diagnosed with acute occlusive coronary syndrome requiring pending intervention.
5. Patients on veno-arterial (VA) extracorporeal membrane oxygenation (ECMO).
6. Patients who have been on veno-venous (VV) ECMO for less than 6 hours.
7. Patients with a clinical suspicion of cardiogenic shock
8. Patients who have a history of asthma or are currently experiencing bronchospasm requiring the use of inhaled bronchodilators and who are not mechanically ventilated.
9. Patients with acute mesenteric ischemia or a history of mesenteric ischemia.
10. Patients with active bleeding AND an anticipated need of multiple transfusions (within 48 hours of Screening).

11. Patients with active bleeding AND hemoglobin < 7 g/dL or any other condition that would contraindicate serial blood sampling.
12. Patients requiring more than 5 mg/kg daily of hydrocortisone or equivalent glucocorticoid medication as a standing dose.
13. Patients with an expected lifespan of < 12 hours or withdrawal of life support within 24 hours of Screening.
14. Patients with a known allergy to mannitol.
15. Patients who are currently receiving an investigational drug (active or placebo) as part of another clinical trial.
16. Patients of childbearing potential who are known to be pregnant at the time of Screening.

7.3. Subject Withdrawal Criteria

Patients and their parent(s) or legal guardian(s) will be informed that they have the right to withdraw from the study at any time and for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Clinically significant concurrent illness
- Occurrence of an unacceptable AE
- Request of patient, parent(s), or legal guardian(s)
- Major protocol violations
- Non-compliance
- Administrative reasons
- General or specific changes in the patient's condition unacceptable for further treatment based upon the judgment of the Investigator

At the time of withdrawal, all study procedures for EOS are to be completed, if possible. The reason(s) for a patient's withdrawal from the study are to be recorded on the appropriate case report form (CRF).

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

LJPC-501 drug product is a sterile, aqueous solution for dilution prior to infusion that is supplied in single-dose vials (Table 5). Vials contain 2.5 mg/mL angiotensin II and 25 mg/mL mannitol as an excipient in water for injection. LJPC-501 is diluted in normal saline for continuous IV infusion administration. The infusion rate of LJPC-501 may be adjusted to maintain adequate MAP.

Table 5: Investigational Product

	Investigational Product
Product Name:	LJPC-501 (angiotensin II)
Dosage Form:	Injection
Unit Dose:	2.5 mg/mL
Route of Administration:	IV infusion
Physical Description:	aqueous solution
Manufacturer:	Emergent BioSolutions, Inc. (EBSI)

8.2. Concomitant Medications and Procedures

All patients should be given maximal supportive therapy during the course of the study. All medications and supportive therapies (including renal replacement therapy and ventilation support) that are administered from Screening through the Day 28 follow-up, including the dose and indication, must be recorded on the appropriate CRF and in the source documents. Supportive therapy that is ongoing at baseline will be permitted during the treatment phase of the study. No other experimental therapy is permitted. Concomitant medications for other medical conditions are permitted as clinically indicated. Concomitant procedures, such as dialysis, mechanical ventilation, and relevant procedures used to diagnose or treat a serious adverse event (SAE), will also be recorded from screening through Day 28.

Start and stop date(s)/time(s), dose, and amount administered will be recorded for vasopressors administered up to 48 hours prior to, during, and after LJPC-501 administration. Total daily dose for each vasopressor administered through Day 28 may be recorded after completion of LJPC-501 administration.

8.3. Titration of Standard-of-Care Vasopressors and LJPC-501

8.3.1. Titration of Standard-of-Care Vasopressors

During the Screening and baseline time periods, patients will have their SOC vasopressors titrated to an age-, size-, and disease-appropriate MAP (Appendix A, Dellinger 2013), per Investigator discretion. All patients will have their SOC vasopressors titrated (to a sum NED of > 0.1 μg/kg/min to be eligible) for a minimum of 2 hours but not for longer than 48 hours prior to initiation of LJPC-501 dosing. The Screening MAP is defined as the average of at least 2 once-hourly MAP measurements collected during SOC vasopressor titration (when NED is > 0.1 μg/kg/min), and within 24 hours prior to LJPC-501 treatment initiation.

During the first two hours of LJPC-501 treatment, SOC vasopressor dosing may be decreased, but not increased, unless adjustment is required for safety reasons. After Hour 2 and throughout LJPC-501 treatment, titration of SOC vasopressors may continue with the goal of sparing catecholamine and other vasopressor use.

Baseline MAP will be assessed by 3 measurements documented within 15 minutes prior to initiation of LJPC-501 (ie, approximately −15 minutes, −5 minutes, and 0 minutes [just prior to initiation of study drug administration]). Standard-of-care vasopressor doses should not be changed during measurement of baseline MAP. Baseline NED is the NED at the time of initiation of LJPC-501.

8.3.2. Titration of LJPC-501

LJPC-501 infusion will be started at 5 ng/kg/min. After 5 minutes, the LJPC-501 infusion rate (dose) may be increased to increase MAP and/or allow reduction in SOC vasopressor doses. The dose of LJPC-501 may be increased by 5 ng/kg/min as frequently as every 5 minutes up to a maximum of 40 ng/kg/min. Any decision to increase the dose rate above 40 ng/kg/min must be made in consultation with Sponsor. With Sponsor approval, the dose rate may be increased to > 40 ng/kg/min (to a maximum of 80 ng/kg/min) by increases of 5 to 10 ng/kg/min as frequently as every 5 minutes.

Some patients may be more sensitive to the pressor effects of angiotensin II, and the LJPC-501 dose may be decreased to 1.25 ng/kg/min to avoid hypertension. If MAP exceeds 90 mmHg, SOC vasopressors should be down-titrated first, then LJPC-501 should be down-titrated if MAP remains ≥ 90 mmHg.

LJPC-501 treatment should continue for at least 24 hours. Between Hour 2 and Hour 24, LJPC-501 may be titrated between 1.25 and 40 ng/kg/min (or up to 80 ng/kg/min with Sponsor approval). Treatment with LJPC-501 may continue up to 7 days (168 hours) with Sponsor approval.

Changes in LJPC-501 and SOC vasopressor doses should be avoided during MAP measurement at Hour 2 (for evaluation of primary endpoint) and at Hour 24 (for evaluation of secondary endpoint). Interruptions of LJPC-501 administration for longer than 5 minutes before Hour 24 should be avoided, unless required for patient safety, because they may interfere with efficacy assessments. For patients who have received LJPC-501 for the target 24-hour treatment period, treatment may be reinitiated if LJPC-501 treatment has been stopped for 3 hours or less; if treatment has been stopped for more than 3 hours it may not be reinitiated.

LJPC-501 infusion should not be stopped abruptly. To discontinue LJPC-501, down titrate by 5 to 20 ng/kg/min every 15 minutes until a dose of 10 ng/kg/min is reached. After 15 minutes at 10 ng/kg/min, down titrate to 5 ng/kg/min. After 15 minutes at 5 ng/kg/min down titrate to 2.5 ng/kg/min. Discontinue the LJPC-501 infusion after 15 minutes at 2.5 ng/kg/min.

8.4. Treatment Compliance

LJPC-501 will be administered to eligible patients by a qualified healthcare professional under the supervision of either the Investigator or Sub-Investigator(s).

The pharmacist will maintain records of LJPC-501 receipt, preparation, and dispensing, including the applicable lot numbers, and the patient's body weight.

8.5. Procedures

8.5.1. Screening

The following assessments will be performed during Screening:

- Obtain informed consent from patient's parent(s) or legal guardian(s). Assent will be obtained from the patient, if possible, per the institution's guidelines.
- Assess inclusion and exclusion criteria
- Obtain the patient's complete medical history, including the demographic information, diagnosis, surgical history, concurrent medical conditions, concomitant medications, and concomitant procedures
- Perform a limited physical examination, focusing on extremities, abdominal region, neurological system, body weight, and height.
- Titrate patient's SOC vasopressors to an age-, size-, and disease-appropriate MAP (Appendix A)
- Perform chest X-ray (optional)
- Assess vital signs: BP, respiratory rate (RR), and body temperature
- Assess HR and MAP hourly during Screening for a minimum of 2 hourly readings, within 24 hours prior to LJPC-501 treatment initiation. The average of 2 MAP readings (when total sum NED is > 0.1 µg/kg/min) will determine the Screening MAP.
- Perform 12-lead electrocardiogram (ECG), if possible
- Perform arterial blood gas (ABG) within 6 hours prior to LJPC-501 administration
- Collect blood samples for hematology and clinical chemistry within 6 hours prior to LJPC-501 administration
- Serum pregnancy test for females of childbearing potential
- Collect blood sample for angiotensin I and II, if possible

- Perform PELOD/PRISM/PIM2 assessments not completed in assessments above, within 6 hours prior to LJPC-501 administration (Section 10.4)
  - Pupillary reactions
  - Glasgow Coma Score
  - Diagnosis ratings for PIM2: high risk diagnosis score, low risk diagnosis score, elective admission, recovery post procedure, cardiac bypass
- Document urine output and fluid intake for the 24 hours prior to LJPC-501 administration, if available

8.5.2. Baseline

- Titrate patient's SOC vasopressors
- Assess vital signs: BP, RR, and body temperature
- Assess HR and MAP at approximately -15 min, -5 min and 0 min (or just prior to initiation of LJPC-501). The average of the 3 MAP values will determine the Baseline MAP.
- Monitor urine output and fluid intake
- Collect blood sample for serum lactate (arterial or venous)
- Record tissue oxygen saturation
- Record concomitant medications and procedures

8.5.3. Day 1 (0 to 2 hours)

- Administer LJPC-501
- Assess vital signs: HR, MAP, BP, RR, and body temperature
  - HR and MAP should be measured once every 5 minutes during the first 15 minutes of treatment, then once every 15 minutes up to the Hour 2 timepoint
  - At Hour 2, record HR and MAP without changing doses of LJPC-501 or other vasopressors (for assessment of primary endpoint)
- At Hour 2, collect blood sample for serum lactate (arterial or venous)
- At Hour 2, record tissue oxygen saturation
- Monitor urine output and fluid intake hourly
- Record concomitant medications and procedures
- Assess AEs and SAEs

8.5.4. Day 1 (2 to < 24 hours)

- Administer LJPC-501

- Assess vital signs: HR, MAP
  - HR and MAP should be measured at least once hourly and prior to any dose adjustment through the duration of LJPC-501 administration.
- Monitor urine output and fluid intake hourly
- Titrate SOC vasopressors, with the goal of reducing reliance on catecholamines
- Record concomitant medications and procedures
- Assess AEs and SAEs

8.5.5. Hour 24 (± 1 hour)

- Continue to administer LJPC-501 at Investigator's discretion. If continuing, notify Sponsor. If not continuing, complete all Hour 24 procedures before beginning to down-titrate LJPC-501 dose to stop administration (see Section 8.3.2 for down-titration guidance).
- Assess LJPC-501 dose.
- Assess MAP without changing doses of LJPC-501 or other vasopressors (for assessment of secondary endpoint)
- Assess HR
- Collect blood sample for serum lactate (arterial or venous)
- Record tissue oxygen saturation
- Assess other vital signs: BP, RR, and body temperature
- Perform 12-lead ECG, if possible
- Perform ABG
- Collect blood samples for hematology and clinical chemistry:
- Perform PELOD/PRISM/PIM2 assessments completed in assessments above (Section 10.4)
  - Pupillary reactions
  - Glasgow Coma Score
  - Diagnosis ratings for PIM2: high risk diagnosis score, low risk diagnosis score, elective admission, recovery post procedure, cardiac bypass
- Monitor urine output and fluid intake
- Assess AEs and SAEs
- Record concomitant medications and procedures

8.5.6. Day 2 to 6, if LJPC-501 Administered after Hour 24

- Continue to administer LJPC-501 at Investigator's discretion. To discontinue at any time after Hour 24, down-titrate LJPC-501 dose to stop administration after procedures for that day are completed (see Section 8.3.2 for down-titration guidance)
- Titrate SOC vasopressors, with the goal of reducing reliance on catecholamines
- Assess HR and MAP prior to any dose adjustment and a minimum of hourly through discontinuation of LJPC-501
- Assess BP, RR, and body temperature once daily
- Monitor urine output and fluid intake hourly
- Record concomitant medications and procedures
- Assess AEs and SAEs

8.5.7. Day 2 to 6, if LJPC-501 NOT Administered after Hour 24

- Assess vital signs: HR, MAP, BP, RR, and body temperature once daily
- Monitor urine output and fluid intake per local practice
- Record concomitant medications and procedures
- Assess AEs and SAEs

8.5.8. Day 7, if LJPC-501 Administered

- Continue to administer LJPC-501 at Investigator's discretion
- Assess HR and MAP prior to any dose adjustment and a minimum of hourly through discontinuation of LJPC-501
- Assess BP, RR, and body temperature once daily
- Monitor urine output and fluid intake hourly
- Record concomitant medications and procedures
- Assess AEs and SAEs
- Discontinue LJPC-501 administration by down titration after procedures are completed (see Section 8.3.2 for down-titration guidance)

8.5.9. Day 7, if LJPC-501 NOT Administered

- Monitor urine output and fluid intake per local practice
- Perform EOS procedures

8.5.10. EOS (Day 7 to 10, variable)

- Perform a limited physical examination, focusing on extremities, abdominal region, and neurological system

- Assess vital signs: HR, MAP, BP, RR, and body temperature
- Record concomitant medications and procedures
- Assess AEs and SAEs

8.5.11. Day 28 Follow-up

- Record concomitant medications and procedures administered between EOS and Day 28
- Assess SAEs via phone call to the patient's parent(s) or legal guardian(s), the patient's primary care physician, and/or a chart review

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

LJPC-501 is an aqueous solution for IV infusion supplied in single-dose clear glass vials containing 2.5 mg/mL of angiotensin II and 25 mg/mL mannitol as an excipient. LJPC-501 is to be diluted in normal saline (0.9% sodium chloride solution) prior to infusion. Please refer to the Pharmacy Manual for detailed instructions.

9.2. Study Drug Packaging and Labeling

Single-dose vials of LJPC-501 will be provided that are labeled for investigational use only, in accordance with governing regulations.

9.3. Study Drug Storage.

Vials should be stored at 2-8°C in a secure area with limited access.

9.4. Study Drug Preparation

A pharmacist or designee will remove the appropriate number of vials of LJPC-501 from the refrigerator and prepare the LJPC-501 under aseptic conditions. The amount of LJPC-501 to be administered will be determined based on the Screening body weight (measurement method by local SOC). Contents of single-dose vials of LJPC-501 will be added to normal saline (0.9% sodium chloride solution). Polyvinyl chloride (PVC) or non-PVC bags are acceptable. The solution should be clear and colorless with no visible particles. Please refer to the Pharmacy Manual for detailed instructions.

Discard prepared diluted solution of LJPC-501 after 24 hours at room temperature or under refrigeration.

9.5. Administration

LJPC-501 must be delivered as an IV infusion via a central venous line.

For dosing precision, a minimum flow rate of 2 mL/hour should be used. Normal saline should be used as the carrier fluid to accomplish this minimum flow rate.

9.6. Study Drug Accountability

All used (empty and partially empty) and unused LJPC-501 vials must be saved for reconciliation by the Study Monitor or Clinical Research Associate (CRA). Following final reconciliation, all used and unused vials of LJPC-501 are to be returned to La Jolla or its designee for destruction, or destroyed (if approved by La Jolla) at the site.

9.7. Study Drug Handling and Disposal

All material containing LJPC-501 will be treated and disposed of in accordance with governing regulations.

10. ASSESSMENT OF EFFICACY

10.1. Vital Signs

Patients will be monitored for hemodynamic vital signs (MAP, HR) at Screening, at baseline, and throughout LJPC-501 administration. The Screening MAP is defined as the average of at least 2 once-hourly MAP measurements collected during SOC vasopressor titration (when total sum NED is > 0.1 µg/kg/min), and within 24 hours prior to LJPC-501 treatment initiation. Baseline MAP is defined as the average of 3 recorded MAP values documented within 15 minutes prior to initiation of LJPC-501 (ie, approximately -15 minutes, -5 minutes, and 0 minutes or just prior to initiation of LJPC-501).

Patients will be continuously monitored during the first 24 hours following initiation of LJPC-501. Heart rate and MAP should be measured approximately once every 5 minutes during the first 15 minutes of treatment, then once approximately every 15 minutes through Hour 2 and at least once hourly thereafter through the duration of LJPC-501 administration (target minimum of 24 hours). Additionally, HR and MAP should be measured just prior to every dose titration. If LJPC-501 administration is continued for longer than 24 hours, HR and MAP should be measured hourly and just prior to any dose adjustment until LJPC-501 is discontinued.

10.2. Serum Lactate

Serum lactate (arterial or venous) measurements will be taken at baseline, at Hour 2, and at Hour 24 after LJPC-501 administration. Any other serum lactate measurements taken during the study period at the Investigator's discretion will be recorded in the electronic case report form (eCRF).

10.3. Arterial Blood Gas

ABG samples will be collected at Screening (within 6 hours prior to LJPC-501 administration) and at Hour 24.

10.4. PELOD/PRISM/PIM2 Scoring

Risk scoring indices will include the PELOD, PRISM, and PIM2 scores (Table 6).

All components of the PELOD, PRISM, and PIM2 scores will be collected during Screening, employing data obtained no more than 6 hours prior to initiation of LJPC-501 dosing. In addition, all components of PELOD, PRISM, and PIM2 scores will be collected at Hour 24 after the initiation of LJPC-501. The PELOD score is the sum of the 6 individual item scores (Appendix C). The PRISM score is the sum of the 14 individual item scores (Appendix D). The PIM2 score is the sum of the 10 individual item scores (Appendix E).

Table 6: Assessments Included in Each Pediatric Mortality Risk Score

PELOD	PRISM	PIM2
Common to All		
Systolic BP	Systolic BP	Systolic BP
Pupillary reactions	Pupillary reactions	Pupillary reactions
PaO_2/FiO_2	PaO_2/FiO_2	$FiO_2 \times 100/PaO_2$
Common to 2 Scores		
Heart rate	Heart rate	
PTT or INR	PT/PTT	
Glasgow score	Glasgow score	
$PaCO_2$	$PaCO_2$	
Mechanical ventilation		Mechanical ventilation during first hour in ICU
Unique		
AST/SGOT	Bicarbonate (mEq/L)	Base excess (mmol/L) in arterial or capillary blood
Creatinine	Total bilirubin	High risk diagnosis score
Platelets	Calcium	Low risk diagnosis score
WBC	Potassium	Elective admission
	Glucose	Recovery post procedure
	Diastolic BP	Cardiac bypass
	Respiratory rate	

Abbreviations: AST=aspartate transaminase; BP=blood pressure; FiO_2=fractional inspired oxygen; ICU=intensive care unit; INR=international normalized ratio; mEq=milliequivalent; PaO_2=arterial oxygen partial pressure; $PaCO_2$=carbon dioxide partial pressure; PELOD=Pediatric Logistic Organ Dysfunction; PIM2=Pediatric Index of Mortality 2; PRISM=Pediatric Risk of Mortality; PT=prothrombin time; PTT=partial thromboplastin time; SGOT= serum glutamic-oxaloacetic transaminase; WBC=white blood cells.

Assessments for PELOD, PRISM, and PIM2 scores are drawn from multiple sources, and Investigators should ensure all assessments are performed within the time windows for Screening (within 6 hours prior to LJPC-501 administration) and Hour 24 (±1 hour).

- Vital signs: systolic BP, diastolic BP, HR, RR
- Hematology and serum chemistry: PTT, INR, AST, creatinine, platelets, WBC, total bilirubin, calcium, potassium, glucose
- ABG: PaO_2/FiO_2, $PaCO_2$, bicarbonate, base excess
- Physician assessed: pupillary reactions, Glasgow Coma Score (Appendix F), mechanical ventilation, diagnosis ratings for PIM2 (high risk diagnosis score, low risk diagnosis score, elective admission, recovery post procedure, cardiac bypass [Appendix E]).

Scores should be calculated with the most recent values prior to the assessment time point. Missing values will be assigned the last observation carried forward if missing for reason other than death or treatment failure. Missing values at Hour 24, due to death or treatment failure, will be assigned the worst possible score.

The Glasgow Coma Score (Appendix F) should be completed during a sedation holiday, if possible. If not, then the most recent non-sedated value should be used.

10.5. Tissue Oxygen Saturation

Tissue oxygen saturation will be measured non-invasively with near-infrared spectroscopy (NIRS), if available, and if feasible for the patient, at baseline, Hour 2, and Hour 24.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Medical History and Concomitant Medications

A full medical history will be taken during Screening and should include the patient's demographic information, surgical history, concurrent medical conditions, concomitant medications and procedures.

All medications and supportive therapies that are administered during administration of LJPC-501 and up to Day 28, including the indication, must be recorded on the appropriate CRF and in the source documents. For vasopressor medications only, start and stop date(s), dose, and amount administered, including dose adjustments, will also be recorded for vasopressors administered up to 2 days prior to, during LJPC-501 administration, and through Day 28. The total daily dose of administered vasopressors may be recorded after completion of LJPC-501 administration. Concomitant procedures, such as dialysis, mechanical ventilation, and any procedures used to diagnose or treat an SAE, will also be recorded though Day 28.

11.1.2. Physical Exam

A limited physical examination, focusing on extremities, abdominal region and neurological system, will be performed at Screening and at EOS. Body weight and height will be measured or documented at Screening only. Standard of care procedures performed prior to informed consent may be used to qualify patients for the study.

11.1.3. Vital Signs

Blood pressure, respiratory rate, and body temperature should be assessed at Screening, just prior to initiation of dosing on Day 1, on Day 1 at Hour 2, at Hour 24, once daily on Days 2 to 7, and at EOS.

11.1.4. ECG

Electrocardiogram assessments will be performed at Screening and at Hour 24 after initiation of LJPC-501, if possible.

11.1.5. Chest X-Ray

An optional chest X-ray may be performed at Screening, if possible. Standard of care chest X-rays collected prior to informed consent but within 24 hours prior to LJPC-501 treatment initiation may be used.

11.1.6. Urine Output

Urine output will be measured and recorded as appropriate for the patient's age, per local SOC, if possible. Assessments for the 24 hours prior to LJPC-501 administration will be recorded, if available. Urine output will be measured and recorded continuously through Day 7.

11.1.7. Fluid Intake

IV fluid intake will be assessed for the 24 hours prior to LJPC-501 administration, if available. IV Fluid intake will be measured and recorded from the start of LJPC-501 administration through Day 7, per local practice.

11.1.8. Clinical Laboratory Assessments

Samples for hematology and clinical chemistry will be collected at Screening and at Hour 24. Screening assessments contributing to PELOD/PRISM/PIM2 scores must be collected within 6 hours prior to LJPC-501 administration (Section 10.4). All clinical laboratory assessments will be performed by the site's local laboratory.

Specific parameters to be measured are shown in Table 7. Refer to Table 4 for an outline of activities.

Table 7: Clinical Laboratory and Biomarker Parameters

Hematology	Hemoglobin, hematocrit, platelets, and WBC
Clinical Chemistry	ALT, AST, ALP, total bilirubin, direct bilirubin, creatinine, BUN, phosphorus, glucose, albumin, calcium, bicarbonate, chloride, sodium, potassium, magnesium, PT, PTT, and INR
Biomarkers	Blood sample for angiotensin I and angiotensin II
Pregnancy	Serum pregnancy

Abbreviations: ALP=alkaline phosphatase; ALT=alanine transaminase; ANC=absolute neutrophil count; AST=aspartate transaminase; BUN=blood urea nitrogen; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; WBC=white blood cell.

11.1.8.1. Pregnancy Screen

Serum pregnancy tests are required for female patients of childbearing potential.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness;

(3) intercurrent illness; and (4) drug interaction. For recording purposes, pregnancy is a medical condition and is not considered an AE (see Section 11.2.6).

The patient, or if applicable, parent(s) or guardian(s), should be questioned in a general way, without leading the patient/guardian or asking about the occurrence of any specific symptom.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a gastric ulcer, it would not be appropriate to record the AE by describing the symptoms "stomach pain, or indigestion, or appetite loss, etc." The AE medical term of "gastric ulcer" should be recorded as the AE.

11.2.1.2. Serious Adverse Event (SAE)

A serious adverse event (experience or reaction) is an AE that results in one or more of the following:

- Results in death - An adverse event that caused or contributed to a fatal outcome
- Is life-threatening - Refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or results in prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity
- Results in a congenital abnormality or birth defect
- Important medical events when based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2.2. Relationship to Investigational Product

The Investigator will document her/his opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 8. An AE for which there is a "reasonable possibility" that the investigational product caused the AE means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable," the event will be considered related to the investigational product.

Table 8: Relationship of Adverse Events to Investigational Product

Relationship	Description
Related	• A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the investigational product, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge); **or** • An event that could also be explained by concurrent disease or other drugs or chemicals where information on investigational product withdrawal may be lacking or unclear. • Re-challenge or de-challenge information is not required to fulfill this definition.
Not Related	• A clinical event, including laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to investigational product administration (eg, no temporal relationship to investigational product administration, because the investigational product was administered after onset of event; investigation shows that the drug was not administered; proof of other cause; etc.); **or** • An event with a temporal relationship to investigational product administration, which makes a causal relationship improbable, and other drugs, chemicals or underlying disease provide plausible explanations.

11.2.3. Severity

AEs must be graded for severity (ie, intensity) using Common Terminology Criteria for Adverse Events (CTCAE) (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). A severity category of mild, moderate, severe, life threatening, or death as defined in Table 9 , must be entered on the AE CRF. It should be noted that the term "severe" is used to grade intensity and is not synonymous with the term "serious." The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE. When reporting AEs, reference should be made to the CTCAE manual for guidance on appropriate grading.

Table 9: Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
2 = Moderate	Minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.

3 = Severe	Medically significant but not life threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living.
4 = Life-threatening	Urgent intervention indicated.
5 = Death	Death related to AE.

11.2.4. Reporting of Adverse Events and Serious Adverse Events

11.2.4.1. Reporting of Adverse Events

All AEs will be recorded from initiation of study drug treatment, during treatment, and through EOS, regardless of the causal relationship to the investigational product.

All AEs, whether believed by the Investigator to be related or unrelated to the investigational product, must be documented in the patient's medical records/source documents, in accordance with the Investigator's normal clinical practice and on the AE CRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

11.2.4.2. Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for immediately reporting of SAEs to La Jolla. Immediate reporting implies within 24 hours of becoming aware of the occurrence of a SAE.

All SAEs that occur from initiation of study drug treatment, during treatment, and through the Day 28 follow-up, regardless of the causal relationship to the investigational product, must be reported to La Jolla by following the instructions provided in this Section. Redacted medical record source documentation will be requested for all SAEs and emergency room visits.

The method for reporting a SAE is by completing and sending the Serious Adverse Event Report Form and completing the AE CRF. The Serious Adverse Event Report Form and if applicable, a copy of redacted source documents (such as hospital discharge summary, medical records, etc.) related to the SAE will be sent as:

- e-mail to: safety@ljpc.com; or
- fax to: +1 (858) 263-1593

The Investigator will assess whether the event is causally related to the investigational product. La Jolla will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. La Jolla will notify the appropriate regulatory authorities in accordance with country regulations. It is the Investigator's responsibility to notify the IRB or independent ethics committee (IEC) of all SAEs that occur at his or her site, according to local requirements. Investigators will be informed about SAEs according to applicable local regulations. Each site is responsible for notifying its IRB/IEC of these additional SAEs, per local policy.

Following the initial report, any additional information obtained by the Investigator about the SAE must be reported promptly to La Jolla in the same manner as described above for the initial SAE report.

11.2.5. Follow-up of AEs and SAEs

All AEs must be followed during the course of the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the patient is lost to follow-up.

AEs ongoing at the final visit or assessment that are deemed to be "related" to the investigational product or of other clinical significance, must be followed for as long as necessary to adequately evaluate the safety of the patient or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented in the CRF. The Investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, or consultation with other healthcare professionals, as considered clinically appropriate by the Investigator.

11.2.6. Pregnancy and Follow-up

The effects of the study drug, LJPC-501, or procedures performed during this study may pose some unknown risks to the reproductive system, developing fetus, or during breastfeeding. The effects of LJPC-501 on the female and male reproductive systems are unknown. Therefore, patients of child-bearing potential should be advised that they and their partners use a highly effective method of contraception (or abstinence) and avoid pregnancy or fathering a child for at least 30 days after completing or discontinuing study drug treatment. The effects of LJPC-501 on the effectiveness of hormonal contraception are unknown.

Pregnancies are not considered AEs in and of themselves; however, if a female study participant is discovered to be pregnant while in the clinical study, investigational product treatment should be discontinued by down-titration per Section 6.6.1. La Jolla should be notified within 24 hours of the Investigator's learning of the pregnancy by completing and sending the Pregnancy Report form to safety@ljpc.com (or alternatively, fax to +1 (858) 263-1593). The female patient and neonate must be followed for outcome information as considered appropriate by the Investigator and La Jolla.

In the situation when an AE/SAE has occurred in a pregnant subject, the AE/SAE reporting procedures described in Section 11.2.4 must also be followed.

12. STATISTICS

This study will treat 10 to 30 pediatric patients who remain hypotensive despite fluids and vasopressors. Data will be summarized and reported in a descriptive fashion, including the proportion of patients who meet the primary composite endpoint. All patients who receive any amount of LJPC-501 will be included in the safety evaluation. An external data safety monitoring board (DSMB) will periodically review safety data.

The study will be considered successful if the data suggest that at least 33.3% of the pediatric patients experience clinical benefit. For the purposes of this study, clinical benefit is defined as either;

- a 25% increase from baseline in MAP at hour 2 (without an increase in NED from baseline); **or**
- a 25% reduction from baseline in NED at hour 2 (without a decrease in MAP from baseline).

Conditions under which the clinical benefit rate will be considered to be ≥ 33.3% depend on the sample size and the number of observed responses (number of patients experiencing clinical benefit) and are described in Table 10.

Table 10: Sample Size Estimates Assuming Clinical Benefit Rate of ≥ 33.3%

Sample Size	Minimum number of responses to declare the trial a success	Probability of observing at least the minimum number of responses
10	7	0.020
15	9	0.031
20	11	0.037
25	13	0.041
30	15	0.043
10	7	0.020

A complete description of statistical considerations will be provided in a separate statistical analysis plan.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring, Audits and Inspections

Site visits will be conducted by an authorized La Jolla representative, who will inspect study data, patient's medical records, and eCRFs according to Good Clinical Practice (GCP) and FDA and ICH guidelines. In addition to monitoring by La Jolla or its designees, the study may be audited by representatives of the FDA or other regulatory authorities, who will also be allowed access to study documents. The Investigator should immediately notify La Jolla's Clinical Operations department of any proposed or scheduled audits by regulatory authorities.

The Investigator will permit authorized representatives of La Jolla and national or local health authorities to inspect facilities and records relevant to this study.

13.2. Institutional Review Board (IRB)

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

La Jolla or its designee will instruct the study site regarding the conduct of the study and data capture procedures on eCRFs. Logic and consistency checks will be performed on all data entered into the CRF or ultimately transferred into a database to ensure accuracy and completeness.

Training sessions, regular monitoring of the study at the study site by the La Jolla or designated personnel (eg, CRA), instruction manuals, data verification, cross checking, and data audits will be performed to ensure quality of all study data. Investigators' meetings and/or onsite study initiations will be performed to prepare Investigators and other study site personnel for appropriate conduct of the study and collection of study data.

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported for each patient. Source documentation supporting the data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete data entry as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries should be completed immediately after the final examination. An explanation should be given for all missing data. The Investigator must sign and date the Investigator's Statement that will be supplied to endorse the recorded data.

To ensure compliance with GCP and all applicable regulatory requirements, La Jolla may conduct a quality assurance audit.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the informed consent form, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. The Investigator must submit written approval to La Jolla before he or she can enroll any patient into the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study, if applicable. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. La Jolla will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

15.2. Protocol Compliance

The Investigator will conduct the trial in compliance with the protocol provided by La Jolla. Modifications to the protocol may not be made without agreement of both the Investigator and La Jolla. Changes to the protocol will require a written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact La Jolla and/or the Medical Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented on the appropriate CRF and in the source documentation.

15.3. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and La Jolla's applicable policies and standard operating procedures (SOPs).

15.4. Written Informed Consent

The Investigator(s) at each center will ensure that the patient (as age appropriate) and the patient's parent(s) or legal guardian(s) are given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients and their parent(s) or legal guardian(s) must also be notified that they are free to discontinue from the study at any time. The patients and their parent(s) or legal guardian(s) should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent form must be obtained before conducting any study procedures. Assent from patients will also be obtained at Screening or at any time during the study, if possible, in an age-appropriate manner, per federal regulations (*Code of Federal Regulations, Title 45, Part 46.408*) and local requirements.

The Investigator(s) must maintain the original, signed informed consent form. A copy of the signed informed consent form must be given to the patient and the patient's parent(s) or legal guardian(s).

16. RECORDKEEPING

16.1. Inspection of Records

La Jolla will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow La Jolla representatives to inspect the drug storage area, LJPC-501 inventory, drug accountability records, patient charts and study source documents, and other records relative to the study conduct.

16.2. Retention of Records

The Investigator will coordinate with the study site to ensure all documentations relating to the study for a period of 2 years after marketing application approval, or if not approved, 2 years following the notification to FDA of the discontinuance of the test article for investigation. If it becomes necessary for La Jolla or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17. PUBLICATION POLICY

All information regarding LJPC-501 supplied by La Jolla to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for any other purposes without written consent from La Jolla. It is understood that there is an obligation to provide La Jolla with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of La Jolla's LJPC-501 program and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, shareholders, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. Investigator publication rights will be provided in the clinical trial agreement.

18. LIST OF REFERENCES

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19. APPENDICES

APPENDIX A. MAP TARGET RANGES BY AGE

Age	**MAP range**
2 to 4 years	50-80 mmHg
5 to 9 years	60-90 mmHg
10 to 17 years	65-90 mmHg

APPENDIX B. CONVERSION TO NOREPINEPHRINE EQUIVALENT

Drug	Dose	Norepinephrine Equivalent
Epinephrine	0.1 µg/kg/min	0.1 µg/kg/min
Norepinephrine	0.1 µg/kg/min	0.1 µg/kg/min
Dopamine	15 µg/kg/min	0.1 µg/kg/min
Phenylephrine	1.0 µg/kg/min	0.1 µg/kg/min
Vasopressin	0.04 U/min	0.1 µg/kg/min

APPENDIX C. PELOD SCORING

Organ system and variable	Points assigned: 0	1	10	20
Neurologic*				
Glasgow coma score	12–15	7–11	4–6	3
	and		*or*	
Pupillary reaction	Both reactive		Both fixed	
Cardiovascular				
Heart rate, beats/min				
< 12 years	≤ 195		> 195	
≥ 12 years	≤ 150		> 150	
	and		*or*	
Systolic blood pressure, mm Hg				
< 1 mo	> 65		35–65	< 35
≥ 1 mo–< 1 yr	> 75		35–75	< 35
≥ 1 yr–< 12 yr	> 85		45–85	< 45
≥ 12 yr	> 95		55–95	< 55
Renal				
Creatinine, μmol/L (mg/dL)				
< 7 d	< 140 (< 1.59)		≥ 140 (≥ 1.59)	
≥ 7 d–< 1 yr	< 55 (< 0.62)		≥ 55 (≥ 0.62)	
≥ 1 yr–< 12 yr	< 100 (< 1.13)		≥ 100 (≥ 1.13)	
≥ 12 yr	< 140 (< 1.59)		≥ 140 (≥ 1.59)	
Respiratory				
PaO_2:FiO_2 ratio, mm Hg	> 70		≤ 70	
	and		*or*	
$PaCO_2$, mm Hg (kPa)	≤ 90 (≤ 11.7)		> 90 (> 11.7)	
	and			
Mechanical ventilation†	No ventilation	Ventilation		
Hematologic				
Leukocyte count, × 10^9/L	≥ 4.5	1.5–4.4	< 1.5	
	and	*or*		
Platelet count, × 10^9/L	≥ 35	< 35		
Hepatic				
Glutamic oxaloacetic transaminase, IU/L	< 950	≥ 950		
	and	*or*		
Prothrombin time, % of standard (international normalized ratio)	> 60 (< 1.40)	≤ 60 (≥ 1.40)		

Source: Leteurtre 2003
Abbreviations: PaO_2 arterial oxygen partial pressure; FiO_2=fractional inspired oxygen; $PaCO_2$=carbon dioxide partial pressure.
Note: For the Glasgow coma score, use the most recent, non-sedated value. For pupillary reactions, nonreactive pupils must be > 3 mm; do not assess after iatrogenic pupillary dilation. The use of mask ventilation is not considered to be mechanical ventilation.

APPENDIX D. PRISM SCORING

Parameter	Infants	Children	All ages	Score
Systolic Blood Pressure (mmHg)	130-160	150-200		2
	55-65	65-75		2
	> 160	> 200		6
	40-54	50-64		6
	< 40	< 50		7
Diastolic Blood Pressure (mmHg)			> 110	6
Heart Rate (beats/min)	> 160	> 150		4
	< 90	< 80		4
Respiratory Rate (breaths/min)	61-90	51-70		1
	> 90	> 70		5
	apnea	apnea		5
PaO_2 / FiO_2 (mmHg)[a]			200-300	2
			< 200	3
$PaCO_2$ (mmHg)			51-65	
			> 65	
Glasgow Coma Score[b]			< 8	6
Pupillary Reactions			unequal or dilated	4
			fixed and dilated	10
PT/PTT			1.5 × control	2
Total Bilirubin			> 3.5	6
Potassium (mEq/L)			3.0-3.5	1
			6.5-7.5	1
			< 3.0	5
			> 7.5	5
Calcium			7.0-8.0	2
			12.0-15.0	2
			< 7.0	6
			> 15.0	6
Glucose			40-60	4
			250-400	4
			< 40	8
			> 400	8
HCO_3 (mEq/L)[c]			< 16	3
			> 32	3

Source: Pollack 1988

Abbreviations: PaO_2 arterial oxygen partial pressure, FiO_2=fractional inspired oxygen, HCO_3=bicarbonate; PTT= partial thromboplastin time; PT=prothrombin time; $PaCO_2$=carbon dioxide partial pressure; mEq=milliequivalents.

[a] Cannot be assessed in patients with intracardiac shunts or chronic respiratory insufficiency; requires arterial blood sampling.

[b] Assessed only if there is known or suspected central nervous system dysfunction; cannot be assessed in patients during iatrogenic sedation, paralysis, anesthesia, etc. Scores < 8 correspond to coma or deep stupor.

[c] Use measured values.

APPENDIX E. PIM2 SCORING

Variable	Values	Beta
Elective admission	Yes =1 No = 0	-0.9282
Recovery post procedure	Yes =1 No = 0	-1.0244
Cardiac bypass	Yes =1 No = 0	0.7507
High risk diagnosis[a]	Yes =1 No = 0	1.6829
Low risk diagnosis[b]	Yes =1 No = 0	-1.5770
No response of pupils to bright light (> 3 mm and both fixed)	Yes =1 No = 0	3.0791
Mechanical ventilation	Yes =1 No = 0	1.3352
Systolic blood pressure (mmHg)		0.01395
Base excess (mmol/L) (arterial or capillary blood)		0.1040
$FiO_2 \times 100 / PaO_2$ (mmHg)		0.2888

Source: Slater 2003

Abbreviations: PaO_2=arterial oxygen partial pressure; FiO_2=fractional inspired oxygen.

Use the most recent values for the calculation of PIM2. If information is missing (eg, base excess is not measured) record 0, except for systolic blood pressure, which should be recorded as 120.

[a] High risk diagnoses. If in doubt record 0.
- Cardiac arrest preceding intensive care unit (ICU) admission
- Severe combined immune deficiency
- Leukemia or lymphoma after first induction
- Spontaneous cerebral hemorrhage
- Cardiomyopathy or myocarditis
- Hypoplastic left heart syndrome
- HIV infection
- Liver failure is the main reason for ICU admission
- Neurodegenerative disorder

[b] Low risk diagnoses. If in doubt record 0.
- Asthma is the main reason for ICU admission
- Bronchiolitis is the main reason for ICU admission
- Croup is the main reason for ICU admission
- Obstructive sleep apnea is the main reason for ICU admission
- Diabetic ketoacidosis is the main reason for ICU admission

Calculation:

Logit = (-4.8841) + (values × Beta) + (0.01395 × (absolute(SBP-120))) + (0.1040 × (absolute base excess)) + (0.2888 × ($100 \times FiO_2/PaO_2$))

PIM2 Score = Predicted death rate = eLogit/ (1+eLogit)

APPENDIX F. GLASGOW COMA SCORE

Best eye response (E)	Spontaneous – open with blinking at baseline	4
	Opens to verbal command, speech, or shout	3
	Opens to pain, not applied to face	2
	None	1
Best verbal response (V)	Oriented	5
	Confused conversation, but able to answer questions	4
	Inappropriate responses, words discernible	3
	Incomprehensible speech	2
	None	1
Best motor response (M)	Obeys commands for movement	6
	Purposeful movement to painful stimulus	5
	Withdraws from pain	4
	Abnormal (spastic) flexion, decorticate posture	3
	Extensor (rigid) response, decerebrate posture	2
	None	1

The Glasgow Coma Score should be completed during a sedation holiday, if possible. If not, then the most recent non-sedated value should be used.