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RESEARCH**

APPLICATION NUMBER:

209360Orig1s000

CLINICAL REVIEW(S)

I refer to two CDTL memos (main review and addendum) by Dr. Martin Rose for NDA 209360 (angiotensin II; La Jolla Pharmaceutical). I concur with these memos and support approval of (human) angiotensin II as a pressor for use in distributive shock.

Shock is a syndrome in which the blood pressure is inadequate to prevent harm to critical organs. Keeping the blood pressure above a minimum level is a self-evident surrogate, preserving organs to enable interventions to treat the specific causes of hypotension. The risk of a pressor in this setting is of improving circulation in one vascular bed at the expense of another. The safety database for angiotensin II, particularly the study done by the sponsor to support approval, uncovered no evidence that it inappropriately diverts circulation from critical organs.

Other safety findings did appear in the development program. Efforts were made to distinguish which adverse events were likely to be actual adverse reactions to angiotensin II, but the small safety database makes this process imperfect. I and the review team were largely reassured by a favorable trend in mortality.

Several reviews make reference to literature or material to which the sponsor did not assert right of reference. As documented in Dr. Rose's CDTL addendum, reviewers, Dr. Rose, and I have concluded that the information external to the application was not necessary to support the safety or effectiveness of the sponsor's product, which means that it should be approved under 505b(1).

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/s/

NORMAN L STOCKBRIDGE
12/21/2017

Clinical Review
Fred Senatore MD, PhD, FACC; Tzu-Yun McDowell PhD
505(b)(2) NDA 209360
Angiotensin II

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	209360
Priority or Standard	Priority
Submit Date(s)	29 June 2017
Received Date(s)	19 July 2017
PDUFA Goal Date	28 February 2018
Division/Office	Cardiovascular and Renal Products / ODE-1
Reviewer Name(s)	Fred Senatore MD, PhD, FACC; Tzu-Yun McDowell PhD
Review Completion Date	29 Nov 2017
Established Name	LJPC-501 (Angiotensin II)
(Proposed) Trade Name	None (two proposed names have been rejected)
Applicant	La Jolla Pharmaceutical
Formulation(s)	Intravenous
Dosing Regimen	20 ng/kg/min and titrated to effect. Dose range: (b) (4) ng/kg/min.
Proposed Indication(s)	Treatment of hypotension in adults with distributive shock.
Intended Population(s)	Patients in the intensive care unit with distributive shock.
Recommendation on Regulatory Action	Approve
Recommended Indication(s)	Increase blood pressure in adults with distributive shock.

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Glossary

AC	advisory committee
ADH	Anti Diuretic Hormone
AE	adverse event
APACHE II	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BIMO	<u>Bi</u> oresearch <u>M</u> onitoring
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAMP	cyclic adenosine monophosphate
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHO	Chinese Hamster Ovary (cell line)
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRH	Catecholamine Resistant Hypotension
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CVP	Central Venous Pressure
DSMB	Data Safety Monitoring Board
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

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GRMP	good review management practice
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
mITT	modified-intent to treat
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NED	Norepinephrine Equivalent Dose
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RAAS	Renin Angiotensin Aldosterone System
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEALD	Study Endpoints and Labeling Development
SGE	special government employee
SOC	standard of care
SOFA	Sequential Organ Failure Assessment
SPA	Special Protocol Assessment

Clinical Review

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Angiotensin II

SVR Systemic Vascular Resistance

TEAE treatment emergent adverse event

TR-FRET time-resolved fluorescence resonance energy transfer

1 Executive Summary

1.1. Product Introduction

LJPC-501 (proposed proprietary name: (b) (4), is a chemically synthesized peptide with 8 amino acids, and has the identical sequence as endogenous human angiotensin II.

La Jolla Pharmaceuticals developed LJPC-501 to increase blood pressure in adults with distributive shock who remain hypotensive despite fluid resuscitation and vasopressor therapy. The starting dose is 20 ng/kg/min administered intravenously with instruction to titrate as frequently as every 5 minutes by increments of 5-15 ng/kg/min as needed to maintain a target mean arterial pressure (MAP) $\geq$ 75 mmHg or an increase in the MAP by at least 10 mmHg from baseline.

LJPC-501 qualifies as a new molecular entity (NME) because the 8 amino acid synthetic peptide LJPC-501 has not been previously marketed as a drug. Another form of angiotensin II (Hypertensin[®]) was approved on 23 Feb 1961 (NDA 012791, Novartis) for the treatment of patients in “states of shock and collapse in which blood pressure must be restored with a minimum of delay to permit perfusion of vital tissues & during anesthesia /surgery /hemodialysis”. It was withdrawn effective 18 June 2009. The Division of Cardiovascular and Renal Products (Medical Officer Dr. Avi Karkowsky) determined that there was no reason to believe the withdrawal was a consequence of safety issues. The amino acid sequence of Hypertensin[®] differs from LJPC-501 at the 1st and 5th positions. The amino acid in the 1st position is asparagine for Hypertensin[®] and aspartic acid for LJPC-501. The amino acid in the 5th position is valine for Hypertensin[®] and isoleucine for LJPC-501.

1.2. Conclusions on the Substantial Evidence of Effectiveness

LJPC-501 was shown to be efficacious in raising the MAP to target levels: $\geq$ 75 mmHg or a 10 mmHg increase in baseline MAP. Efficacy appeared to be consistent across all subgroups, including critically high-risk subjects whose baseline MAP was < 65 mmHg (38% of the mITT population).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

LJPC-501 (proposed proprietary name (b) (4)), a synthetic human sequence angiotensin II, is a peptide of 8 amino acids. The proposed indication is for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy. LJPC-501 successfully improved the mean arterial pressure (MAP) from a level associated with adversarial outcome to the target level in the management of shock. We recommend approval of LJPC-501 for the proposed indication.

Current treatment for distributive shock includes massive fluid administration followed by vasopressor treatment (i.e., catecholamines, vasopressin). Catecholamines include epinephrine, norepinephrine and dopamine. Treatment goals for hemodynamic stability are to raise the MAP above 65 mmHg, maintain the central venous pressure between 8-12 mmHg, maintain the mixed/central venous oxygenation above 70%, maintain hemoglobin between 7-9 g/dL, maintain arterial oxygen saturation above 92%, and maintain urinary output at 0.5 mL/mg/hour. Norepinephrine doses exceeding 0.1 ug/kg/min or the need for vasopressin rescue therapy is generally associated with a mortality rate exceeding 50%. Patients requiring doses greater than 100 ug/min of norepinephrine or epinephrine have a 94% mortality rate. Mortality rates increase with increasing numbers of concomitant vasopressor agents required to raise the MAP (i.e., 92% mortality when 3 different pressors were infused at full doses). Most patients respond to volume replacement or volume replacement plus vasopressor treatment. However, 6% of the patients develop refractory shock. Distributive shock refractory to massive fluid administration and maximally tolerated catecholamine treatment is an unmet medical need.

In the pivotal trial supporting the LJPC-501 NDA, LJPC-501 increased the mean MAP to at least 75 mmHg or increased the mean MAP by 10 mmHg from baseline in the overall patient population with refractory distributive shock where the mean baseline MAP was 65 mmHg. Of this population, 38% had a mean baseline MAP below 65 mmHg. The results were significant compared to placebo. This objective was achieved at 3 hours from the start of study drug treatment during a period in which the doses of catecholamines remained constant. The dose at which the benefit was achieved in most of the subjects was 20 ng/kg/min. The Sequential Organ Failure Assessment (SOFA) score, a tool that follows the status of the patient over time in the intensive care unit, worsened over 48 hours equally for both the placebo and the LJPC-501 arms of the study, rendering LJPC-501 no better than placebo for sequential organ failure. The subgroup cardiovascular SOFA score significantly improved for LJPC-501 over placebo at both 3 and 48 hours. This improvement was based on increasing the blood pressure and substituting a catecholamine listed as a variable determining the cardiovascular SOFA score with angiotensin II that is not listed in its determination. There is no evidence that angiotensin II is a safer and/or more efficacious vasoconstrictor than catecholamines. However, there was a statistically

insignificant but notable trend for decreased mortality favoring LJPC-501 over placebo that was consistent for up to 28 days and across all demographic, regional, and baseline disease subgroups.

The safety profile of LJPC-501 was mostly like that of placebo. The major safety concern was an excess of venous and arterial thromboembolic events with active treatment (12.9% vs. 5.1% of subjects in the LJPC 501 and placebo arms, respectively). Most of the imbalance arose from a higher frequency of thrombotic-related events in the LJPC-501 arm; there were 7 deep vein thrombosis (DVTs), 2 jugular vein thrombosis & 2 peripheral artery thrombosis in the LJPC-501 arm vs. none in the placebo arm. Both arms had similar background risk and baseline DVT prophylaxis treatment (heparin and related drugs), although such prophylaxis was not required by the protocol and was not provided to all subjects. This risk is very plausible, considering the preclinical evidence showing that angiotensin II enhanced the development of thrombosis. In addition, the population for which LJPC-501 is proposed to treat is at high risk for DVT. Hence, this potential risk should be adequately addressed in the labeling and monitored in the post-marketing setting.

Increasing the MAP to the extent demonstrated in the pivotal trial was consistent with standard-of-care treatment goals for hemodynamic stability in patients with distributive shock. However, there was uncertainty about whether this conferred a clinical benefit based on no improvement of SOFA scores over placebo, lack of a statistically significant mortality benefit, or any other objective assessment that indicates clinical benefit other than increased blood pressure. Despite this uncertainty, achieving target blood pressure goals in patients with distributive shock outweighed the risk of thrombotic events that could be routinely managed in the intensive care setting by standard prophylactic anticoagulation therapy. The starting dose should be 20 ng/kg/min and could be titrated to doses ranging from 10 to 90 ng/kg/min. The label should contain a caution about venous thrombosis and require standard prophylactic anticoagulation therapy while receiving LJPC-501 during the treatment of distributive shock. A risk evaluation and mitigation strategy is not necessary.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Distributive Shock is a condition of hypotension and reflex tachycardia due to systemic inflammation of the vasculature not responsive to endogenous catecholamines or vasopressin. • There are three types of Distributive Shock: septic shock (bacteria,	Distributive Shock is a critical condition where patients are at significant risk of mortality depending on their baseline physiological function and baseline hemodynamics. The risk

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	bacterial toxins), anaphylactic shock (massive histamine release due to an allergic reaction), and neurogenic shock (injury to the sympathetic nervous system or vagal over-activation from peritonitis or other GI disorders). • The hemodynamic presentation of distributive shock is an increased cardiac output, normal or decreased filling pressures, and a decreased systemic vascular resistance responsible for the low Mean Arterial Pressure. • Severity of shock and association with in-hospital mortality are based on intensive care unit tools: Acute Physiological and Chronic Health Care Evaluation (APACHE), Model for End-Stage Liver Disease (MELD) and Sequential Organ Failure Assessment (SOFA). APACHE and MELD are calculated upon admission to the ICU. SOFA scores can be followed over the duration of ICU care. • Mean Arterial Pressures < 55 mg Hg for greater than 10 minutes are associated with heart and kidney injury and increasing mortality. • Patients who are refractory to maximum treatment (see below) and therefore remain hypotensive are at significant risk of mortality.	of mortality is made worse if the patient is refractory to maximum treatment.
<u>Current Treatment Options</u>	• Treatment goals for hemodynamic stability are to raise the Mean Arterial Pressure > 65 mmHg, maintain the central venous pressure between 8-12 mmHg, the mixed/central venous oxygenation >70%, hemoglobin 7-9 g/dL, arterial oxygen saturation >92%, and urinary output at 0.5 mL/mg/hour. • Current treatment for distributive shock includes massive fluids followed by vasopressors (i.e., catecholamines, vasopressin). Catecholamines include epinephrine, norepinephrine and dopamine.	Uncertainties about the current treatment options are the risk of organ failure and death when increasing the dose of vasopressors and increasing the number of concomitant vasopressors to maintain sufficient blood pressure to adequately perfuse vital organs. The current treatment paradigm therefore has limitations. Patients refractory to the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Norepinephrine doses exceeding 0.1 ug/kg/min or the need for vasopressin rescue therapy is generally associated with a mortality rate exceeding 50%. Patients requiring doses greater than 100 ug/min of norepinephrine or epinephrine have a 94% mortality rate. Mortality rates increase with increasing numbers of concomitant vasopressor agents required increase the mean arterial pressure (i.e., 92% mortality when 3 different pressors were infused at full doses). - Most patients respond to either volume replacement or vasopressor treatment. However, 6% of critically ill patients develop refractory shock (aka catecholamine resistant hypotension).	current standard of care have an unmet medical need. The therapeutic context of this NDA is to treat patients with refractory distributive shock.
<u>Benefit</u>	Overview: The NDA was supported by a phase 3, randomized, double-blind, placebo-controlled, multicenter study of LJPC-501 in patients with catecholamine-resistant hypotension. The initial dose of LJPC-501 was 20 ng/kg/min and was subsequently titrated up-or-down as frequently as every 5 minutes by increments of 5-15 ng/kg/min as needed to maintain a target mean arterial pressure (MAP) $\geq$ 75 mmHg or an increase in the MAP by at least 10 mmHg from baseline. The dose range was 10-200 ng/kg/min, but all the efficacy was observed doses ranging from 10-90 ng/kg/min. There were 163 subjects in the LJPC-501 arm and 158 subjects in the placebo arm. The primary endpoint was achieving a mean arterial pressure of $\geq$ 75 mmHg or a 10 mmHg increase in baseline mean arterial pressure at 3 hours following initiation of study drug. In the modified intention-to-treat population, the primary endpoint was achieved in 114 of 163 subjects (70%) in the LJPC-501 arm and in 37 of 158 subjects (23%) in the placebo arm. Statistical significance was met (Odds Ratio 8, 95%	Subjects in the pivotal trial were in critical condition with a high mortality risk based on indices of ICU tools: baseline APACHE, baseline MELD, baseline total SOFA, and baseline mean arterial pressure. The catecholamine doses exceeded the amount associated with end-organ damage and did not yield an improvement in the mean arterial blood pressure, thus characterizing the subjects as refractory to catecholamine therapy. LJPC-501 successfully improved the mean arterial pressure from a level associated with adverse outcomes to the target level in the management of shock.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Confidence Interval 5—13, $p < 0.00001$). • Severity of patients with distributive shock from which benefit was assessed: The mean baseline APACHE and MELD scores were 28 (approximately 50% in-hospital mortality) and 21 (approximately 20% mortality), respectively. The mean baseline total SOFA score was 12.7 in the placebo arm and 11.8 in the LJPC-501 arm (> 11 portends a 95% mortality risk: Ferreria et al, 2001, Journal of the American Medical Association, 286 (14): 1754-1758). The mean catecholamine dose in both the placebo and the LJPC-501 arms was 0.5 ug/kg/min, representing $> 50\%$ mortality. The mean baseline mean arterial pressure, equal in both arms, was 66 mmHg with 35% of the blood pressures in the placebo arm and 41% of the blood pressures in the LJPC-501 arm below 65 mmHg thus representing an enhanced risk for organ failure and mortality. • Benefit based on Primary Endpoint: The primary endpoint was defined as an increase in mean arterial pressure to ≥ 75 mmHg Hg or a 10 mmHg increase in baseline MAP. The pivotal trial demonstrated a significant response compared to placebo in meeting the primary endpoint, each over an equal and non-changing dose of background catecholamines over a 3-hour time-period (Odds Ratio 7.95, 95% CI 4.76-13.3, $p < 0.00001$). These results were consistent over a variety of demographic, regional, and disease characteristic subgroups. • Benefit based on Clinical Endpoints: ○ The secondary endpoint of cardiovascular SOFA, with a baseline value of 4 in each arm (i.e., worst score in the cardiovascular domain), was significantly reduced in the	Increasing the MAP to the extent demonstrated in the pivotal trial was consistent with standard-of-care treatment goals for hemodynamic stability in patients with distributive shock. However, there was uncertainty about whether this conferred a clinical benefit based on no improvement of SOFA scores over placebo, lack of a statistically significant mortality benefit, or any other objective assessment that indicates clinical benefit other than increased blood pressure.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	LJPC-501 arm (-0.13) compared to the placebo arm (-0.01) (p 0.002) at hour 3. Similarly, there was a significant reduction in the cardiovascular SOFA score from baseline for the LJPC-501 arm (-1.75) compared to placebo (-1.28) at hour 48 (p=0.013). There was no clinical meaning associated with the decrease in the cardiovascular SOFA scores. This score is calculated by the mean arterial pressure and the doses of catecholamines that were required to elevate the blood pressure. The decrease in cardiovascular SOFA represented an elevation of mean arterial blood pressure and substitution of a catecholamine listed on the cardiovascular SOFA calculation with angiotensin II, which is not listed on the cardiovascular SOFA score calculation. This substitution occurred during the catecholamine sparing part of the protocol (i.e., beyond the 3-hour primary endpoint). There is no evidence that angiotensin II is a more efficacious or safer vasoconstrictor than catecholamine. ○ The other secondary endpoint of total SOFA showed no difference between the arms at hour 3 and hour 48. The total SOFA scores increased by a +0.5 in the placebo arm and by +0.8 in the LJPC-501 arm at hour 3, and by +1.0 in each arm at hour 48. An increase in total SOFA by a value of +1 increases in-hospital mortality (Jones et al, 2009, Critical Care Medicine, 37 (5): 1649-1654). ○ Exploratory mortality endpoints showed a non-significant trend towards decreased mortality in the LJPC-501 arm	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to the placebo arm at both day 7 (n= 47 [29%] vs n=55 [35%]) and day 28 [75 46%] vs 85 [54%]). This trend was consistent for all demographic, regional, and disease characteristic subgroups.	
<u>Risk</u>	• The clinical safety of LJPC-501 in patients with CRH was evaluated primarily using the safety data from the phase 3 trial, LJ501-CRH01. The safety dataset contains a total of 321 subjects who were received at least one dose of the study drug (n = 163 and 158 in the LJPC-501 and placebo arm, respectively). The size and quality of safety database is acceptable and the characteristics of patients in the phase 3 trial are generally adequate to represent the indicated US patient population. • Overall safety profile of LJPC-501 was similar to that of the placebo arm: ○ The incidence of AEs, SAEs, fatal SAEs and discontinuation due to AEs was similar in the two treatment arms ○ The incidence of known toxicities for vasopressors, such as arrhythmia and ischemia/vasoconstriction events was similar between the LJPC-501 arm and the placebo arm (cardiac arrhythmias 31% vs. 34%; ischemia / vasoconstriction 10% vs. 10%) ▪ There were 4 ischemia events in the central nervous system (CNS) in the LJPC-501 arm and 3 had a fatal outcome compared to 1 non-fatal ischemia CNS event in the placebo arm. • The major safety concern for LJPC-501 is the risk of thrombosis: ○ There was a higher incidence of venous and arterial	The safety profile of LJPC-501 was similar to placebo in subjects with distributive shock being managed in the intensive care unit. The incidence of ischemia/vasoconstriction AEs was similar in the two arms. There was a slightly higher incidence of these AEs in the central nervous system in the LJPC-501 arm compared to placebo (4 vs. 1). Ischemia events in the CNS could result in serious and fatal outcomes. However, the small numbers of these events limit interpretation of the data. It is reassuring that the overall mortality trend in the phase 3 study benefiting LJPC-501 arm. The totality of evidence suggests that the risk of thrombosis could be drug-related. Moreover, the population for which LJPC-501 is proposed to treat is at high risk for thrombosis and some of the thrombotic events could result in serious and irreversible

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	thromboembolic events in the LJPC-501 arm compared to the placebo arm (12.9% vs. 5.1%). The major imbalance arose from a higher frequency of thrombotic events in the LJPC-501 arm; there were 7 DVTs, 2 jugular vein thrombosis & 2 peripheral artery thrombosis in the LJPC-501 arm vs. none in the placebo arm. The occurrences of these events were distributed throughout the course of the study from Day 0 to Day 18. Based on reported medical history, there was a similar background rate of embolic and thrombotic events between the two arms (52% in the LJPC-501 arm and 49% in the placebo arm). Subjects in both arms also had similar DVT prophylaxis treatment (heparin and related drugs) at baseline. ○ Prothrombotic effect of angiotensin II has been demonstrated in animals and healthy volunteers. ● Other safety topics of interest ○ Safety concern about withdrawal of LJPC-501: ▪ Hypotension may occur in some patients during down-titration and/or following withdrawal of LJPC-501 ○ Other potential risks may be associated with LJPC-501: ▪ Thrombocytopenia: Angiotensin II has tendency to promote adhesion and aggregation of platelets. Thus, it is plausible that the free platelet count may appear depressed due to this indirect phenomenon. The incidence of thrombocytopenia was 9.8% vs. 7.0% in the LJPC-501 arm vs. the placebo arm. There was a higher percentage of subjects who had > 50% decrease in platelet count from baseline in the LJPC-501	outcomes. Hence, the safety concern about the risk of thrombosis should be adequately addressed in the labeling and carefully monitored in the post-market setting. The safety concern about withdrawal of LJPC-501 can be mitigated and managed through proper titration. The evidence from the phase 3 study is not strong enough to conclude the association between LJPC-501 and the risk of thrombocytopenia, hyperglycemia and renal toxicities. However, there are some mechanistic bases for these risks. These potential risks can be medically managed in the ICU setting where careful monitoring laboratory parameters is required. The safety concern about the consequences of these potential risks is alleviated considering the observed mortality trend benefiting the LJPC-501 arm. Current labeling recommends that the maximum dose should not exceed (b) (4) which could mitigate the potential risk of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	arm compared to the placebo arm (26.3% vs.19.1%). However, similar numbers of subjects had platelet count < 50,000 per microliter in the two arms. ▪ Hyperglycemia: Pre-clinical studies indicate that angiotensin II causes hyperglycemia and insulin resistance. The incidence of hyperglycemia was 4.3% vs. 2.5% in the LJPC-501 arm vs. the placebo arm. ▪ Renal toxicity: LJPC-501 could have excessive vasoconstrictive effects on kidney thus impact renal function. The incidence of renal toxicity related AEs was lower in the LJPC-501 arm vs. the placebo arm (8.6% vs. 11.4%). However, it should be noted that the initiation of renal replacement therapy was not included in the AE dataset. Dialysis was initiated during the study in ~30% of subjects in the LJPC-501 compared to ~24% of subjects in the placebo arm. The outlier analysis on serum creatinine shows that the LJPC-501 arm had slightly more subjects with creatinine increased greater than 50% from baseline compared to the placebo arm (12.2% vs. 9.5%). It is possible that these small differences could be due to chance or attributed by other confounding factors. ○ LJPC-501 is developed for short term use with titrations to the target blood pressure in the ICU setting. There is limited evidence to suggest any dose-related toxicity.	dose-related toxicity
<u>Risk Management</u>	• We believe the key toxicities of LJPC-501 and safety concerns (b) (4) of the drug can be managed through proper labeling. Specifically, the risk of thrombosis can be managed medically in the ICU setting where it is the standard practice to administer subcutaneous heparin or subcutaneous low molecular	Patients with refractory distributive shock who are at risk for thrombosis when treated with LJPC-501 can be managed with adequate prophylactic anticoagulation as per the standard clinical practice in bed-ridden

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	weight heparin for DVT prophylaxis, unless contraindicated as per clinical judgement. • This risk can be managed through labelling.	patients. A risk evaluation and mitigation strategy is not necessary.

2 Therapeutic Context

Analysis of Condition

Shock is a condition where there is insufficient oxygen-delivery to meet the metabolic needs of body organs. There are 4 types of shock: hypovolemic shock (excess loss of fluid, usually hemorrhagic), cardiogenic shock (related to severe heart failure), extra-cardiac obstructive shock (pericardial tamponade, acute pulmonary embolism, air embolism), and distributive shock.

The hallmark clinical presentation of shock is hypotension and reflex tachycardia. The cause of hypotension in hypovolemic, cardiogenic, and obstructive shock are, respectively, insufficient systemic fluid, pump failure, and inadequate blood flow beyond the obstruction.

Distributive shock occurs despite normal cardiac function and despite a euvoletic state. The cause of distributive shock is systemic inflammation that renders blood vessels unresponsive to endogenous vasoconstrictive agents. This causes redistribution of blood flow out of the arterial space and into the venous system, resulting in pseudo-hypovolemia. The hemodynamic profile in distributive shock is an increased cardiac output, normal or decreased filling pressures, and a decreased systemic vascular resistance (SVR). The decreased SVR is directly responsible for lowering the MAP that consequently precipitates organ hypoperfusion and associated morbidity and mortality. In this scenario, the cardiac output is elevated because the heart is pumping against a low-resistance environment.

There are 3 types of distributive shock: septic shock, anaphylactic shock, and neurogenic shock. Septic shock is the most common type of distributive shock and is most frequently caused by bacteria. Infection sites most likely to lead to septic shock are the chest, abdomen and genitourinary tract. Anaphylactic shock is triggered primarily by a massive release of histamine from mast cells activated by antigen-bound immunoglobulin E and by increased production and release of prostaglandins. Neurogenic shock is caused by the loss of vascular tone normally supported by the sympathetic nervous system, from injury to the central nervous system, especially the spinal cord. GI rupture with subsequent evacuation of contents in the peritoneal cavity could also precipitate neurogenic shock due widespread peritoneal irritation and consequent vagal activation, extensive peripheral vasodilation and bradycardia.

Shock is a life-threatening condition that requires immediate treatment in the intensive care environment.

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Prognostic indicators in the intensive care setting are the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score, and the Model of End-Stage Liver Disease (MELD) score. In the literature for the SOFA score, the term “sequential” is sometimes interchangeable with the term “sepsis”.

The APACHE II score, developed in 1982, is a simplified version of the original score developed in 1978. APACHE II is based on 12 of the most commonly measured physiological variables (i.e., temperature, MAP, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white blood cell count, and serum bicarbonate). Age and Glasgow Coma Scale (GCS) also form part of the APACHE II score.

The GCS scores range from 3 (worst) to 15 (best) and measures:

- eye opening (spontaneous = 4; to voice command = 3; to pain = 2; none = 1)
- verbal response (normal = 5; disoriented conversation = 4; incoherent words = 3; only sounds = 2; nothing = 1)
- motor response (normal = 6; localized to pain = 5; withdraws to pain = 4; decorticate posture = 3; decerebrate posture = 2; no response = 1)

The APACHE score is based on the first 24 hours in the intensive care unit (ICU). The APACHE II score ranges from 0 to 48 excluding age and GCS. Points are added to the APACHE II score based on GCS and age. The points added to the APACHE II score range from 0 for a GCS of 15 to 12 for a GCS of 3. The points added to the APACHE II score range from 0 for ages < 44 years to 6 for ages $\geq$ 75 years. The APACHE II scoring system is illustrated in Table 1. The hospital mortality rate increases exponentially with increasing values of the APACHE II score ranging from negligible at the APACHE II score of 0, to approximately 75% at the APACHE II score of 30-36, to > 90% for APACHE II scores $\geq$ 42 as illustrated in Figure 1 (Wong, 1991).

SOFA is a sepsis-related scoring system introduced in 1994. The objective of SOFA is to quantify the severity of patients' illness based on the degree of organ dysfunction serially over time. Unlike the APACHE score, the SOFA scoring system considers the time course of a patient's condition during the entire ICU stay. This enables physicians to follow the evolving disease process. The total SOFA score is composed of sub-scores from 6 organ systems (i.e., respiratory- PaO_2/FiO_2 , nervous system- *Glasgow coma scale*, cardiovascular- *MAP or vasopressors required*, hepatic- *bilirubin*, coagulation- *platelets*, and renal- *creatinine or urinary output*), each graded from 0 to 4. The total SOFA score ranges from 0 to 24. The total SOFA score assessment is shown in Table 2.

There is a non-linear rise in the mortality rate with increasing values of the mean total SOFA score ranging from 1% at the mean total SOFA score of 0-1 to approximately 85% at mean total SOFA score > 5.1 (Ferreria, 2001) for the first 48 hours in the ICU as shown in Table 3. There is

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also an association between the change in total SOFA score (i.e., *delta SOFA*) and mortality (Jones, 2009) as shown in Figure 2. The data in this figure showed that a reduction in SOFA by at least 2 can reduce the mortality from 19% (n=11 of 57) to 9% (n = 5 of 54). An increase in SOFA by at least 2 can increase the mortality from 19% to 42% (n=22 of 53).

Cardiovascular SOFA scoring is based on the following

- No hypotension: score 0
- MAP < 70 mmHg: score +1
- On vasopressors, dopamine < 5 ug/kg/min or dobutamine (any dose): score +2
- Dopamine > 5 ug/kg/min or epinephrine or norepinephrine < 0.1 ug/kg/min: score +3
- Dopamine > 15 ug/kg/min or epinephrine or norepinephrine > 0.1 ug/kg/min: score +4

The Cardiovascular SOFA score was identified as a secondary endpoint. Its reduction was emphasized as a clinical benefit associated with the drug effect of increasing the MAP. The cardiovascular SOFA score will be lowered if angiotensin II replaces a vasopressor listed as a contributor to the cardiovascular SOFA score (i.e., catecholamines). The clinical meaningfulness of replacing one vasoconstrictor listed in the cardiovascular SOFA scoring system by another not listed in the cardiovascular SOFA scoring system will be discussed during the review of the secondary endpoints.

The MELD score provides an estimate of the 3-month mortality risk and it is generally used to allocate available livers for transplantation. The MELD score is a mathematical equation involving 3 laboratory values: bilirubin, INR, and creatinine:

$$\mathbf{MELD = (0.957 \times \log (creatinine) + 0.378 \times \log (bilirubin) + 1.12 \times \log (INR) + 0.643) \times 10}$$

In a study of patients with chronic liver disease on a liver transplant waiting list (Wiesner, 2003), the 3-month mortality of 3437 patients as a function of MELD score is shown in Table 4. The mortality rate ranged from 2% for MELD scores < 9 to 71% for MELD scores > 40. In the Phase-3 trial supporting this NDA, patients with MELD scores ≥ 30 were excluded from the study.

Table 1: The APACHE II Scoring System

The APACHE II Score

Physiologic Variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal Temp (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥100	140-179	110-139		70-109		50-69	40-54	≤39
Respiratory Rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation a) FIO ₂ ≥ 0.5 record A-aDO ₂ b) FIO ₂ < 0.5 record PaO ₂	≥500	350-499	200-349		<200 PO ₂ > 70	PO ₂ 61-70		PO ₂ 55-60	PO ₂ < 55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
HCO₃ (mEq/l)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
K (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Na (mEq/l)	≥100	160-179	155-159	150-154	130-149		120-129	111-119	≤110
S. Creat (mgm/dl)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
TLC (10³/cc)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS									

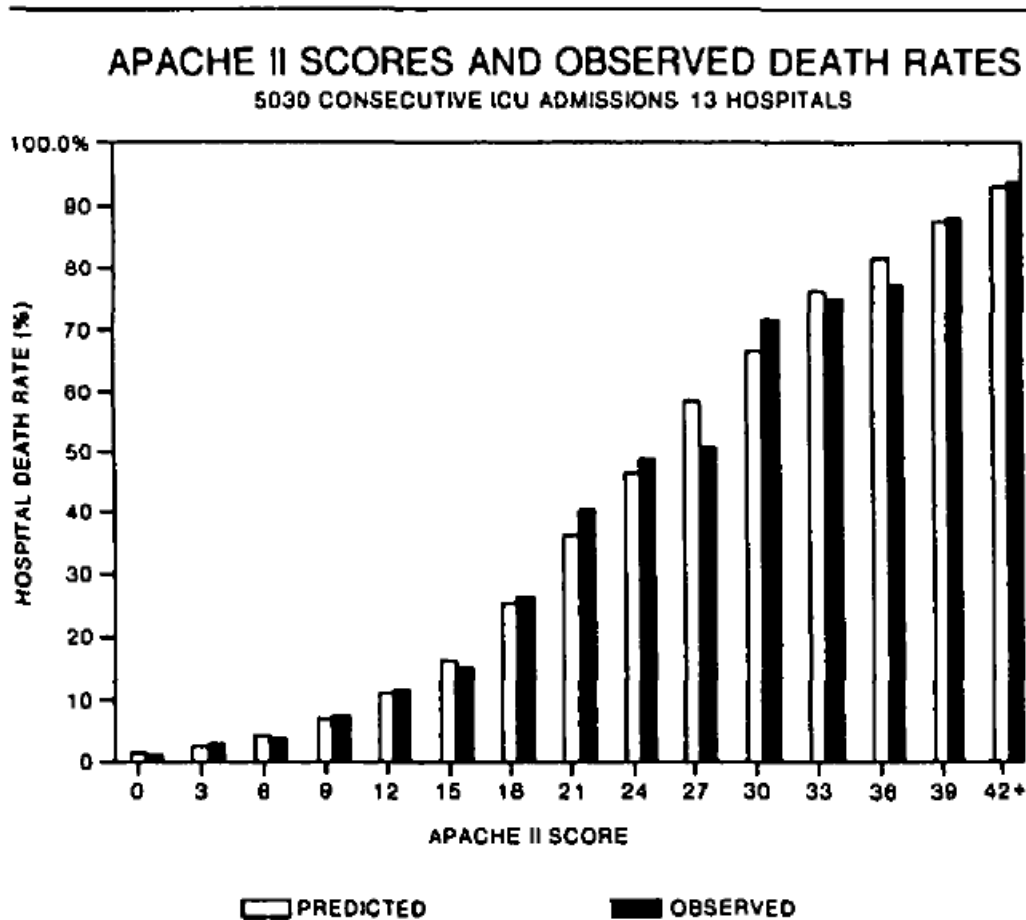
Age -score
<44 → 0
45-54 → 2
55-64 → 3
65-74 → 5
≥75 → 6

GCS:
15 → 0 14 → 1 13 → 2
12 → 3 11 → 4 10 → 5
9 → 6 8 → 7 7 → 8
6 → 9 5 → 10 4 → 11
3 → 12

JAMA 1993;270(24):2957-2963
fppl.com

Source: Le Gall, 1993

Figure 1: APACHE II Scores and Observed Death Rates



Source: Wong, 1991

Table 2: Total SOFA Score

SOFA score	1	2	3	4
<i>Respiration</i>				
PaO ₂ /FiO ₂ , mmHg	< 400	< 300	< 200 —— with respiratory support ——	< 100
<i>Coagulation</i>				
Platelets × 10 ³ /mm ³	< 150	< 100	< 50	< 20
<i>Liver</i>				
Bilirubin, mg/dl (μmol/l)	1.2 – 1.9 (20 – 32)	2.0 – 5.9 (33 – 101)	6.0 – 11.9 (102 – 204)	> 12.0 (> 204)
<i>Cardiovascular</i>				
Hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose) ^a	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
<i>Central nervous system</i>				
Glasgow Coma Score	13 – 14	10 – 12	6 – 9	< 6
<i>Renal</i>				
Creatinine, mg/dl (μmol/l) or urine output	1.2 – 1.9 (110 – 170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 440) or < 500 ml/day	> 5.0 (> 440) or < 200 ml/day

^a Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

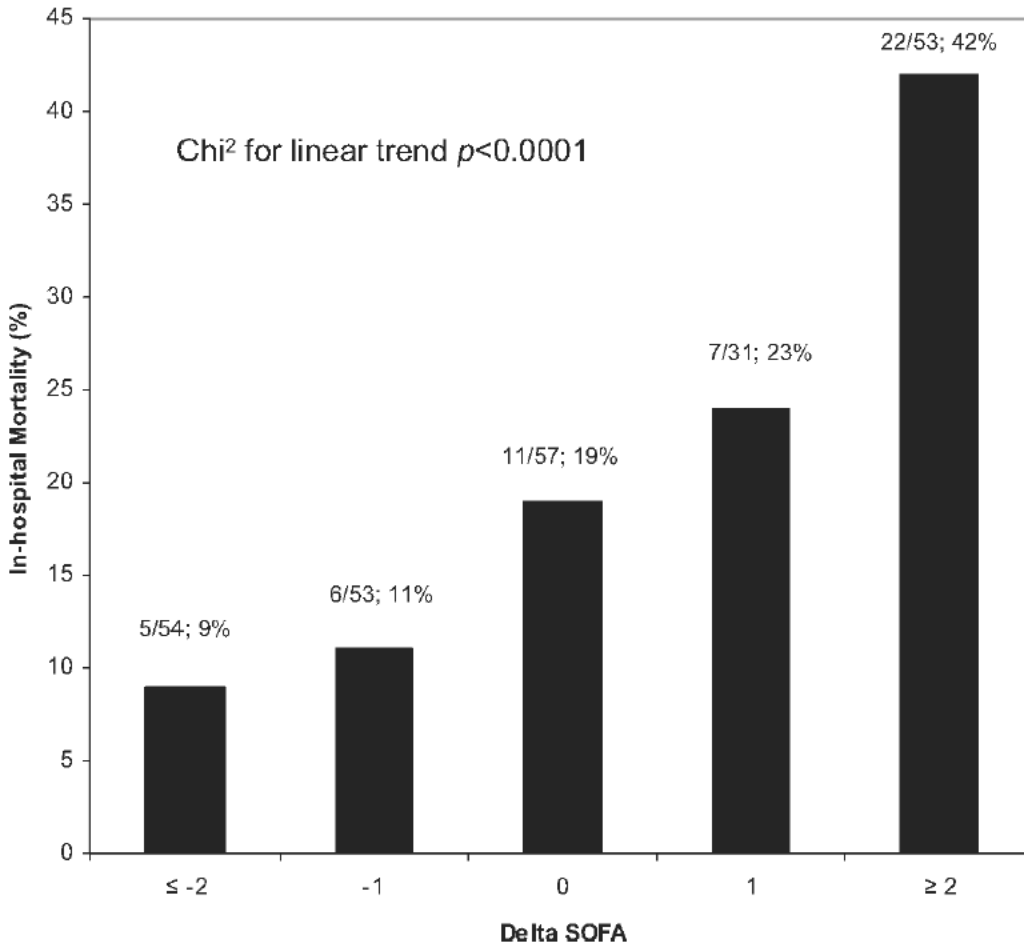
Source: Vincent, 1996

Table 3: Mean Total SOFA Score and Mortality (1st 48 hours in ICU)

Mean Total SOFA	Mortality (%)
0–1	1
1.1–2	5
2.1–3	20
3.1–4	37
4.1–5	75
> 5.1	85

Source: Ferreira, 2001

Figure 2: In-Hospital Mortality vs Delta SOFA



Source: Jones, 2009

Table 4: Three-month mortality based on MELD score

	MELD				
	<9	10-19	20-29	30-39	>40
Number	124	1800	1098	295	120
Mortality %	1.9	6.0	19.6	52.6	71.3
Mortality + Too Sick %	2.9	7.7	23.5	60.2	79.3

Source: Wiesner, 2003

2.2. Analysis of Current Treatment Options

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The clinical management objective for patients with shock, including distributive shock, is to maintain adequate oxygen delivery to body organs via restoration of adequate hemodynamics, restoration of sufficient oxygen-carrying hemoglobin, and restoration of adequate ventilation. In order to meet this objective, the immediate treatment goals are to restore the MAP to > 65 mmHg and central venous pressure (CVP) between 8-12 mmHg (Rhodes, 2017). The central venous oxygen saturation should be maintained > 70%. The hemoglobin should be maintained between 7-9 g/dL. Arterial oxygen saturation should be > 92%. These treatment goals should be met by rapid fluid replacement as well as vasopressor therapy, blood transfusion and mechanical ventilation when clinically indicated. In the case of septic shock, treatment of the infection (i.e., drainage and antibiotics) is necessary.

When rapid fluid replacement fails to increase the MAP to > 65 mmHg, exogenous vasopressors are introduced (catecholamines and non-catecholamines). The most widely used catecholamines include epinephrine and norepinephrine. Dopamine, phenylephrine, and dexmedetomidine are less often used. Vasopressin, a non-catecholamine vasoconstrictor that also acts to promote retention of water by the kidneys, has been approved by the FDA to increase blood pressure in patients with severe hypotension. A compilation of drugs used to treat septic shock is located in Table 5.

Most patients will respond to either volume replacement or vasopressor treatment. However, approximately 6% of critically ill patients will develop refractory shock. From a review of multiple studies, norepinephrine doses exceeding 0.1 ug/kg/min or need for rescue therapy with vasopressin is generally associated with mortality rates greater than 50%, while 94% of patients requiring doses above 100 ug/min of norepinephrine or epinephrine die (Bassi, 2013). The greater the peak number of vasopressors required, the higher the death rate which reached 92% when 3 different pressors were infused at full dose (Brand, 2017). Short durations of intraoperative hypotension in non-cardiac surgeries (i.e., MAP < 55 mmHg for $\geq$ 10 minutes) led to kidney and cardiac injury (Walsh, 2013).

Refractory septic shock, referred to as catecholamine resistant hypotension (CRH) by the applicant, is a life-threatening condition with significant mortality. This condition represents an unmet medical need and is the therapeutic context addressed by this NDA.

Table 5: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Epinephrine/ NDA 205029	Hypotension and Shock	2014	0.05 to 2.0 mcg/kg/min	Achieves MAP goal > 70 mmHg	Cardiac arrhythmias, renal impairment, caution with narrow- angle glaucoma, heart disease, diabetes	Hyperglycemia, impaired insulin sensitivity, lactic acidosis, worsening symptoms of Parkinson Disease
Nor- epinephrine/ NDA 007513	Hypotension and Shock	1950	8 to 12 mcg/min initial, then 2-4 mcg/min maintenance	Maintains MAP 80-100 mmHg	Ischemic injury due to potent vasoconstrictor action and tissue hypoxia. Reflex bradycardia. Respiratory difficulty. Extravasation necrosis.	Transient headache. Anxiety
Phenyl- ephrine/ NDA 203826	Hypotension and Shock	2012	0.5 to 6 mcg/kg/min	Increase MAP via titration to effect	Exacerbation of heart failure, heart failure and pulmonary hypertension. Skin and subcutaneous necrosis. Peripheral and visceral ischemia.	Headache, vomiting, reflex bradycardia, AV block, ventricular extrasystoles.
Vasopressin /NDA204485	Vasodilatory Shock	2014	0.01-0.07 units/minute	Increases MAP in septic shock	Decreased cardiac output, bradycardia, tachycardia, tachy- arrhythmia, coronary, mesenteric, and digital ischemia.	Increased bilirubin and liver transaminase, decreased platelets
Dopamine /NDA019099	Shock syndrome	Originally 1982; NDA 019099 approved 1996	Initial: 2-5 mcg/kg/min. Titrate to effect. If > 50 mcg/kg/ min is required, check urine output.	MAP requirements met at 20 mcg/kg/min in > 50% subjects	Hypovolemia, hypoxia, ventricular arrhythmia, occlusive vascular disease, local necrosis	Nausea, vomiting, dyspnea, cardiac conduction defects, headache

Source: Drug Labels for FDA approved drugs.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LPC-501 is an NME and does not have antecedent regulatory actions or a marketing history.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre-IND (IND 122708): A pre-IND meeting took place on 30 June 2014. At this meeting we clarified that citation of literature references to support safety was insufficient for the proposed indication, but that a Phase 3 study, properly designed, could be sufficient. The proposed phase 3 design was considered adequate, and showing that angiotensin II can raise blood pressure would be an acceptable endpoint. The Division also agreed that a sample size of 200-300 patients would be sufficient.

IPSP: The Division agreed with the initial pediatric study plan (iPSP) on 01 June 2015 as well as with the amended iPSP on 30 January 2017 where the date of the pediatric study initiation was changed from “no later than Dec 2016” to “no later than Feb 2017”.

EOP2: The end-of-phase 2 meeting held on 16 August 2016 led to the following agreements or understandings:

- Regulatory: the 505(b)(2) pathway appeared acceptable but would be based on the Phase 3 trial outcome and the appropriateness of bridging scientific information demonstrating comparability between LJPC-501 and the (b)(4) product.
- CMC: Comparability between LJPC-501 and the (b)(4) angiotensin II drug product has been sufficiently demonstrated to support reliance on studies from the literature using the (b)(4) product.
- Safety Pharmacology: No further safety pharmacology studies were required.
- Toxicology: No additional non-toxicology studies were required.
- Clinical Pharmacology: Additional PK/PD studies may not be required. The data collected from the Phase 3 study will inform the PK/PD response of angiotensin II.
- Clinical: Renal and hepatic studies were not necessary. No QT studies were required. QT prolongation or arrhythmias should be collected as adverse events of specific interest and a separate safety review and analysis should be performed.

SPA: A special protocol assessment (SPA) was performed and agreement was reached 02 February 2015. Notably, we explicitly agreed with the sponsor’s proposed primary endpoint, an increase in MAP to ≥ 75 mmHg Hg or a 10 mmHg increase from the baseline MAP, assessed on Day 1, 3 hours after the initiation of study drug. This primary endpoint by itself, independent of corroborative clinical benefits such as mortality or SOFA score, achieved a target standard-of-care treatment goal for hemodynamic stability in patients with distributive shock. Also, Clinical Pharmacology encouraged the Applicant to titrate the dose quickly in order to raise MAP above 60 mmHg as soon as possible if there was no expectation of serious adverse events with such titration. . The Applicant was also strongly encouraged to analyze PK samples within the established timeframe for which analytes are deemed stable

Pre-NDA: The pre-NDA meeting was held on 09 May 2017. At this meeting, the following

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agreements were achieved:

- Regulatory:
 - A waiver was granted for submitting case report forms for patients who died during the study or did not complete the study because of an adverse event. The Applicant agreed to provide case report forms expeditiously if requested during the NDA review.
 - A Risk Evaluation & Mitigation Strategy was unlikely to be required.
 - A 120-day safety update was not required.
- CMC: The applicant agreed to ensure that the two proposed packaging configurations meet USP <1151> for excess volume. The applicant also agreed to submit a minimum of 3 executed batches to determine if the executed batches were representative of proposed commercial scale manufacturing capability.
- Non-clinical: The Agency agreed that cellular function studies demonstrating similar potency between LJPC-501 and the bovine form of angiotensin II were sufficient to satisfy the request by the FDA to provide these data as part of the LJPC-501 bridging justification to Hypertensin and bovine forms of angiotensin II.
- Clinical:
 - The applicant agreed to apply CDISC standards in the creation of datasets and generation of tables, listings, and figures for the pivotal study. The CRF datasets were converted to SDTM datasets and the SDTM datasets were used to generate the ADaM datasets.
 - An ISE was not required. The applicant agreed to prepare an ISS to include data from the Phase-3 study and published data from the submitted literature in accordance to our instructions.
 - The Division agreed that a rationale for use of foreign data would be to demonstrate similarity of medical practice by comparing vasopressors used prior to and during study drug administration across regions by drug name and percentage of patients.

NDA/Filing:

- Priority Designation: The NDA was given a priority designation.
- NME: LJPC-501 was considered a new molecular entity (NME) because of an amino acid difference from Hypertensin® and an amino acid difference in bovine angiotensin II. These structural differences qualified LJPC-501 as an NME.

3.3. Foreign Regulatory Actions and Marketing History

No reported foreign regulatory action.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

There are no significant issues. A Bioresearch Monitoring (BIMO) site selection meeting was conducted with OSI on 26 July 2017 to determine the need for specific site audits based on outliers, enrollment, and site impact on the overall trial data. We concluded that no participating site was assessed as a notable outlier and that no participating site drove the overall results of the trial. Therefore, an OSI audit was not requested.

4.2. Product Quality

There are no significant issues pertinent to the clinical review. At the pre-NDA meeting, the information presented to CMC was not sufficient to comment on the adequacy of the scale-up strategy.

4.3. Clinical Microbiology

There were no issues pertinent to the clinical review.

4.4. Nonclinical Pharmacology/Toxicology

Preclinical findings related to potentiation of thrombosis are discussed in the safety section of this review. Otherwise, there were no issues pertinent to the clinical review.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Angiotensin II is part of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II stimulates the release of aldosterone from the adrenal cortex. Aldosterone promotes sodium retention in the distal nephron and consequent fluid retention. Angiotensin II also acts on the central nervous system (CNS) to increase anti-diuretic hormone (ADH) production. Angiotensin II also acts directly on the vessel wall by binding to the G-protein-coupled angiotensin II receptor-type 1 on vascular smooth muscle cells which stimulates calcium²⁺/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction. At the therapeutic dose, exogenous angiotensin II acts directly on the vascular smooth muscle as described and is therefore a potent vasoconstrictor.

The human body leverages 3 systems to maintain blood pressure: the sympathetic nervous

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system, the arginine-vasopressin system, and the renin-angiotensin-aldosterone system (RAAS). The current available therapies to raise MAP are those that leverage the sympathetic nervous system (catecholamines) and the arginine-vasopressin system (vasopressin).

The Applicant's rationale for adding angiotensin II as a treatment for patients with refractory distributive shock is based on the finding that mortality rate increased as the dose and number of exogenous vasopressors increased in an attempt to normalize MAP in patients with septic shock (Brand, 2017). The Applicant's overall objective was to use the RAAS via angiotensin II and spare the use of excess catecholamines that are associated with a high risk for toxicity and mortality. However, the mechanism of angiotensin II as a potent vasoconstrictor similar to the vasoconstrictive effects in the cardiovascular system mediated by catecholamines raises an uncertainty about the Applicant's rationale.

4.5.2. Pharmacodynamics

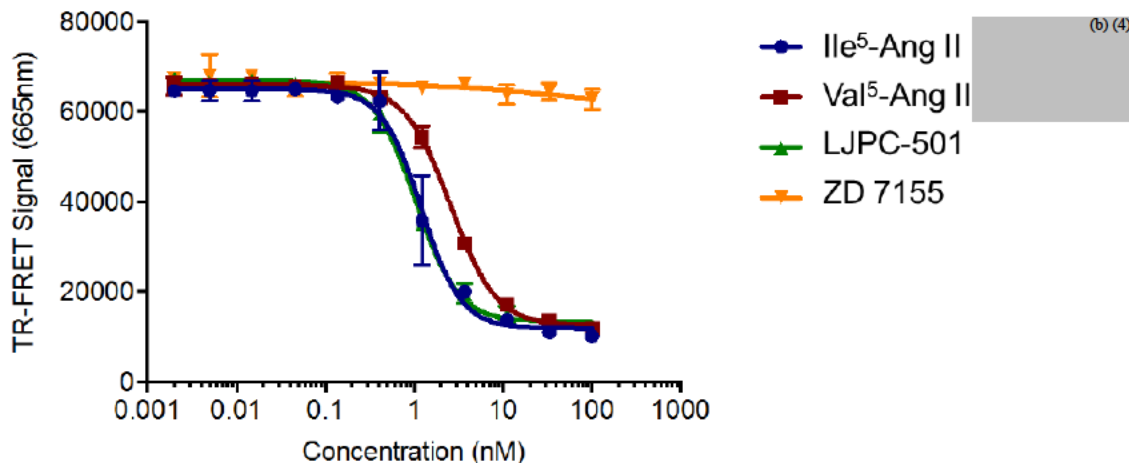
The pharmacodynamic effect of angiotensin II is the activation of the AT1 receptor and was used to assess comparability of LJPC-501 to the (b) (4) products.

Cyclic adenosine monophosphate (cAMP) is produced when the AT1 receptor is activated. cAMP can be measured by a time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassay. This assay is based on the transfer of energy between two fluorophores, a donor and an acceptor when in close proximity. Excitation of the donor by an energy source (i.e., laser) triggers the energy transfer to the acceptor which in turn emits a specific fluorescence at a specific wavelength. This assay can be interfered with by transient (nanoseconds) background fluorescence coming from buffers, proteins, or cell lysate. This can be eliminated by introducing a time delay of 50-150 microseconds between donor excitation and fluorescence measurement. This time delay is the basis of the assay name: time-resolved assay.

Free cAMP produced by angiotensin II-stimulated cells interferes with the donor-acceptor process thus causing a decrease in the TR-FRET signal that is proportional to the amount of cAMP.

Chinese Hamster Ovary (CHO) cells were transfected with human AT1 receptors and incubated with either isoleucine⁵-angiotensin II ((b) (4)), valine⁵-angiotensin II ((b) (4)), LJPC-501, and an antagonist specific for the AT1 receptor (ZD 7155) serving as the negative control. The results are shown in Figure 3. The data showed that the negative control appropriately did not interfere with the assay. The three angiotensin II moieties decreased the signal with similar dose-response curves. This suggested that LJPC-501 had similar functional activity as the (b) (4) products. I defer to clinical pharmacology for a full review.

Figure 3: AT1 cAMP Dose Response Curve



Source: NDA Module 2.6.2- Pharmacology Written Summary

4.5.3. Pharmacokinetics

The pharmacokinetics of angiotensin II in preclinical species was characterized by a high clearance rate, short half-life, and a relatively low volume distribution. The preclinical pharmacokinetic parameters gleaned from module 2.6.4 are in Table 6. The data were not completely available for each species. From the published literature, administration of angiotensin I results in rapid appearance of angiotensin II that is subsequently rapidly metabolized with an apparent half-life of under 1 minute. The metabolic clearance rate was 952 mL/min/m² for Val⁵-angiotensin II amide, and 1117 mL/min/m² for Ile⁵-angiotensin II.

Table 6: Preclinical Pharmacokinetic Summary

	Rats	Dog	Sheep
Half=Life (seconds)	16	15	45
Volume of Distribution (mL/kg)	18	---	---
Clearance (L/hr)	---	---	105

Source: NDA Module 2.6.4- Pharmacokinetic Written Summary

4.6. Devices and Companion Diagnostic Issues

Not applicable.

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4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The list of clinical trials relevant to this NDA is located in Table 7. There were 10 studies comprising the safety database, including the pivotal Phase-3 trial supporting both efficacy and safety. The remaining 9 studies supporting safety included the pilot randomized placebo controlled double-blind study performed by Chawla (2014) in patients with catecholamine resistant hypotension, an old randomized active comparator controlled trial in patients with hypotensive shock (Singh, 1966), a Phase 1-2 single arm open label safety study in patients with hepatorenal syndrome (performed by Applicant-no reference publication, no Case Study Report {CSR}), 5 Phase-1 studies in healthy subjects in which adverse events were prospectively collected and systematically reported, and a comprehensive review of 31, 281 subjects.

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Table 7: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
LJ501-CRH01	Phase 3 randomized, placebo controlled, double-blind, multicenter study	20 ng/kg/min IV, titrated q 5 minutes to achieve target MAP. Dose range (ng/kg/min) 2.5-200 from hour 0-3.; 2.5-40 from hours 3 -48.	<u>Primary:</u> proportion of patients with an average MAP > 75 mmHg or with a > 10 mmHg increase in MAP above baseline MAP at hour 3.	<u>Duration:</u> 3 hours <u>Follow Up:</u> hour 3 to hour 48.	321	Subjects in distributive shock with catecholamine resistant hypotension (requiring norepinephrine equivalent dose >0.2ug/kg/min to maintain MAP between 55-70 mmHg).	Centers: 128. Countries: 10.
Studies to Support Safety							
Chawla-2014	Pilot randomized, placebo-controlled, double-blind, parallel group comparing Isoleucine ⁵ -angiotensin II to placebo over norepinephrine +/- other vasopressors	5-40 ng/kg/min IV. Titrated to effect while reducing nor-epinephrine dose.	<u>Primary:</u> the effect of angiotensin II on standing dose of nor-epinephrine required to maintain a MAP of 65 mmHg.	<u>Duration:</u> 6 hours and then titrated off.	20	Subjects in distributive shock with catecholamine resistant hypotension.	One site: GWU Hospital, Washington DC.
Singh 1966	Randomized, controlled, parallel group comparing Valine ⁵ -angiotensin II amide to norepinephrine	4-12 ug/min IV	Not stated in publication.	15-105 hours	50	Hypotensive shock.	One site: V.J. Hospital, Amritsar.
LJPC-501-CS-5001 (2014-	Phase 1-2 single-arm, open-label safety and tolerability	Starting dose 1 ng/kg/min IV for	Safety and tolerability.	12 days: 5 days	Entered: 6	Subjects with Hepato-renal syndrome.	Two sites in US.

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Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
2015)	study	min 8 hrs. IV dose titration at 4-hr intervals to 5, 15, 25 ng/kg/min, followed by increases in multiples of 25 ng/kg/min to max 100 ng/kg/min.		treatment, 7 days follow-up with option to extend treatment to 14 days.	Complete: 0 Study halted		
Brod 1969	2-sequence cross-over, to compare effects of valine ⁵ -angiotensin II amide to norepinephrine on hemodynamics	Valine ⁵ -angiotensin II amide: 3-61 ug/min IV. Nor-epinephrine: 10-45 ug/min IV.	Hemo-dynamics and Cardiac Output	30 minutes with 30 minute saline infusion between treatments during cross-over.	15	Healthy subjects but 2 had inactive glomerulonephritis.	Not explicitly stated but inferred one site (Institute for Cardiovascular research, Prague)
Broughton Pipkin 1981	2 case reports with valine ⁵ -angiotensin II amide	IV: 2, 4, 8 ng/kg/min, 10 minutes each; prostaglandin E2 (PGE2) at 5 ug/min, 30 minutes. Combination of Ang II + PGE2.	No endpoint: reports on complications	10 minutes each dose of valine ⁵ -angiotensin II amide.	2	Healthy subjects.	One site: City Hospital, Nottingham UK

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Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Hausdorf 1987	Single group/methoxamine-crossover 1 st 10 subjects to compare angiotensin and methoxamine as tools to assess left ventricular performance	Angiotensin II sequence not reported (0.5 to 3.5 ug/min) IV.	Titration to target MAP: + 30 mmHg end-systolic pressure	Not reported	30: all received Ang II, 10 received methoxamine	Healthy subjects	One site: University of Hamburg
Lim 2007	2 parallel groups by genotype. Ang II challenge before and at timepoints after a single dose of valsartan to evaluate the PK/PD effects of valsartan and effects of 1166A/C polymorphisms in the AT1 receptor.	Isoleucine ⁵ -angiotensin II IV: 5, 10, 15, 20 ng/kg/min 2 minutes each.	PK/PD	2 minutes each dose	13	Healthy subjects	One site: Seoul National University, South Korea.
Sluiter 1987	Single group crossover (placebo vs felodipine) to test effect of calcium blockade on Ang II systemic and renal effects.	Valine ⁵ -angiotensin II amide IV 0.3, 1.0, 3.0 ng/kg/min, 40 minutes each. Added to ongoing placebo vs felodipine infusion after 140 minutes.	PD	40 minutes each dose: 120 minutes total.	12	Healthy subjects	One site: Sint Radboud Hospital, Nijmegen, The Netherlands.
Busse 2017	Systemic literature search and review of safety	Any synthetic angiotensin II IV and any dose.	Safety	Minutes to several days	31,281	Non-specific	Global

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Source: ISS, Table 1

5.2. Review Strategy

There were 2 primary reviewers: Dr. Fred Senatore (efficacy) and Dr. Tzu-Yun McDowell (safety). The basis of the efficacy evaluation was the Phase-3 clinical trial LJ501-CRH01. The basis of the safety evaluation included the Phase-3 clinical trial LJ501-CRH01 and the remaining 9 studies listed in Table 7 that formed the ISS. The emphasis for the safety evaluation resided with the Phase-3 clinical trial. The remaining studies in the ISS were assessed as supportive.

The efficacy review was based on the mITT population. Using the JUMP tool, datasets were compared with data listings from the Applicant's CSR. The efficacy analysis involved collaboration with the FDA statistician to confirm or supplement the Applicant's analysis. The safety analysis was based on use of the Jump-Start tool.

Both reviewers collaborated in the risk-benefit analysis by evaluating the extent and clinical meaningfulness of the Odds Ratio (OR) for the primary endpoint relative to the extent of serious drug-related adverse events and severe drug-related adverse events experienced by the subjects in the Phase-3 pivotal trial.

6 Review of Relevant Individual Trials Used to Support Efficacy

LJ501-CRH01: A Phase 3, Placebo Controlled, Randomized, Double-Blind, Multicenter Study of LJPC-501 in Patients with Catecholamine-Resistant Hypotension (CRH)

6.1.1. Study Design

Overview and Objective

Primary Objective:

- Compare the effect of LJPC-501 infusion on MAP in patients with CRH.

Secondary Objectives:

- Compare changes in SOFA scores.
- Establish safety and tolerability of LJPC-501 in patients with CRH compared to placebo.

Exploratory Objectives:

- Change in heart rate.
- Change in non-study drug vasopressor dose.

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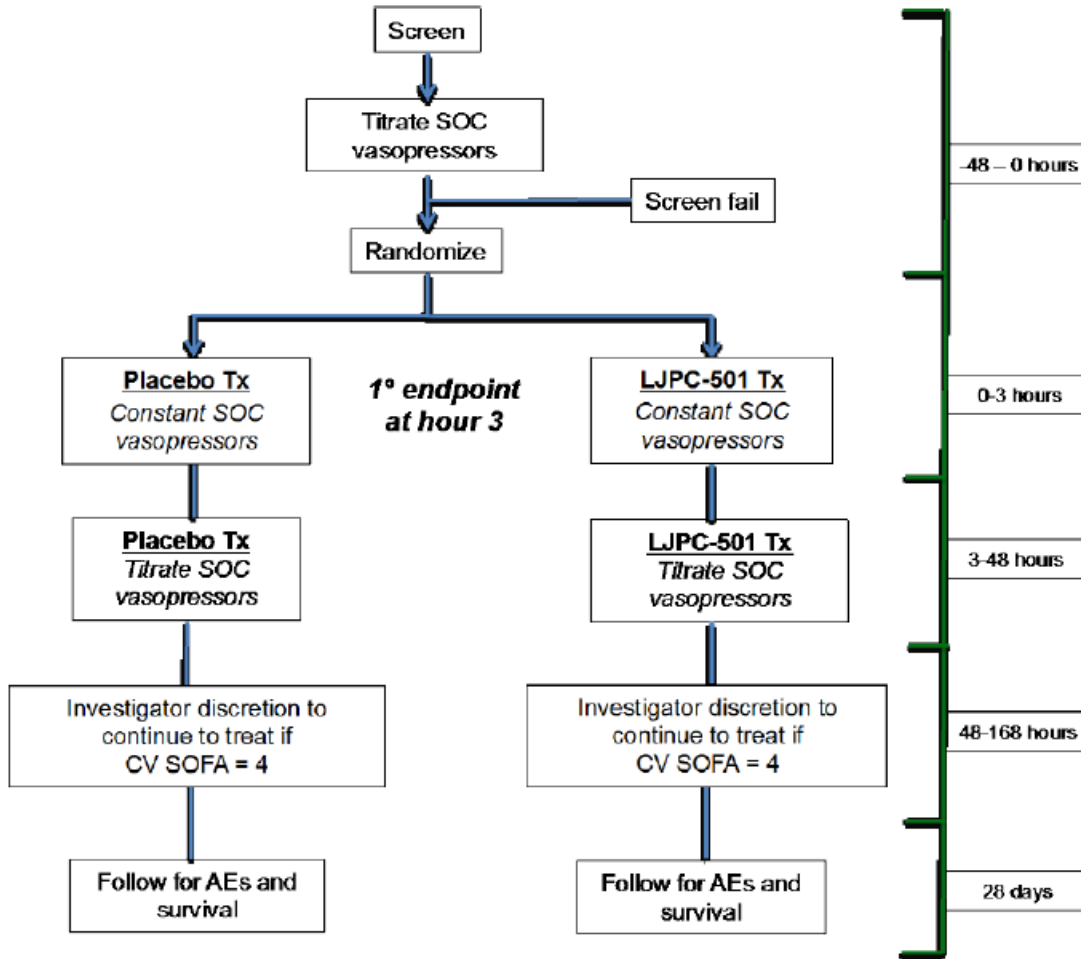
- Mortality at 7 and 28 days.

Trial Design

The study design compared LJPC-501 to placebo over standard of care in the CRH population and is illustrated in Figure 4.

CRH was defined as requiring a vasopressor dose, defined as the norepinephrine equivalent dose (NED), $> 0.2 \text{ ug/kg/min}$ because doses $> 0.1 \text{ ug/kg/min}$ in vasopressor dependent shock were associated with a mortality in excess of 50% (see Analysis of Current Treatment Options). The NED calculations are shown in Table 8.

Figure 4: Study Design



Abbreviations: AE = adverse event; CV = cardiovascular; SOC = standard-of-care; SOFA = sequential organ failure assessment; Tx = treatment.

Source: LJ501-CRH01 CSR

Table 8: Norepinephrine Equivalent Dose Definitions

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

Source: LJ501- CRH01 CSR

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Approximately 315 subjects were treated with study drug to assure that 300 evaluable subjects (150/arm) completed the study.

Each patient was required to meet all of the following inclusion criteria:

- Adult patients ≥ 18 years of age with CRH defined as those who require a total sum catecholamine dose of >0.2 ug/kg/min for a minimum of hours and a maximum of 48 hours, to maintain a MAP between 55-70 mmHg.
- Have central venous access and an arterial line present for at least the initial 48 hours of the study.
- Have an indwelling urinary catheter present in at least the initial 48 hours of the study.
- Received at least 25 mL/kg of crystalloid or colloid equivalent over the previous 24 hour period, and be adequately volume resuscitated in the opinion of the treating investigator.
- Have clinical features of high-output shock by meeting the following criteria:
 - Central venous oxygen saturation $> 70\%$ either by oximetry or by central venous blood gas, and central venous pressure (CVP) > 8 mmHg, OR
 - Cardiac Index > 2.3 L/min/m².
- Patient or legal surrogate willing and able to provide written informed consent and comply with all protocol requirements.

Patients meeting any of the exclusion criteria:

- Patients < 18 years of age.
- Burns covering $> 20\%$ of total body surface area.
- Cardiovascular SOFA score ≤ 3 .
- Acute coronary syndrome requiring intervention.
- Patients on veno-veno extra-corporeal membrane oxygenation (ECMO).
- Patients who have been on ECMO within the last 12 hours.
- Patients in liver failure with a MELD score ≥ 30 .
- Patients with a history of asthma or who are currently experiencing bronchospasm requiring the use of inhaled bronchodilators, if not mechanically ventilated.
- Patients with or having a history of acute mesenteric ischemia.
- Patients with a history of, presence of, or highly suspected of having an aortic dissection or abdominal aortic aneurysm.
- Patients requiring more than 500 mg daily hydrocortisone or equivalent glucocorticoid medication as a standing dose.
- Patients with Raynaud's phenomenon, systemic sclerosis or vasospastic disease.
- Patients with an expected lifespan < 12 hour.
- Patients with active bleeding and an anticipated need (within 48 hours of initiation of

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study) for transfusion of > 4 units of packed red blood cells.

- Patients with active bleeding and hemoglobin < 7 g/dL or any other condition that would contraindicate serial blood sampling.
- Patients with an absolute neutrophil count of < 1000 cells/mm³.
- Patients with a known allergy to mannitol.
- Patients currently participating in another interventional clinical trial.
- Patients known to be pregnant at screening.

The study comprised 4 stages:

- Stage 1: Screening, fluid resuscitation, and optimization of standard-of-care vasopressors beginning at least 6 and up to 48 hours prior to enrollment.
- Stage 2: Initiation (Hour 0) and titration of study drug to restore MAP (from Hour 0 to Hour 3).
- Stage 3: Study drug administration from Hour 3 to Hour 48 with mandatory down-titration and discontinuation of study drug at Hour 48.
- Stage 4: Optional re-initiation of study drug administration and/or monitoring and follow-up (Hours 48 to 168 or end of study drug administration plus 3 days).

A safety assessment was performed at a follow-up phone call or chart review on Day 28.

In Stage 1 (48-6 hours prior to randomization), after obtaining informed consent, standard of care vasopressors of at least 0.2 ug/kg/min were titrated to achieve a target MAP of 65 mmHg (55-70 mmHg) and maintained for at least 6 hours but no longer than 48 hours before enrollment. Hourly MAP readings were taken to determine the Screening MAP (i.e., average of 6 hourly readings). Eligible subjects were stratified by Screening MAP (< 65 mmHg or ≥ 65 mmHg) and by the APACHE II score (≤30, 31-40, or ≥ 41). Block randomization within strata was used to assign subjects in a 1:1 ratio via Interactive Web Response System to treatment with LJPC-501 or placebo. Additional subjects were enrolled to replace those who withdrew from the study after randomization but before receiving study drug. The primary reason for not initiating study drug was rapid clinical improvement including hemodynamic parameters from the time of randomization to time of planned study drug administration (3 subjects in the placebo group and 6 subjects in the LJPC-501 group- CSR-page 50). An unblinded pharmacist at each study site prepared the study drug and an infusion worksheet for each randomized subject. The investigator and other study personnel remained blinded to study drug assignment.

In Stage 2 (Hour 0), subjects were administered 20 ng/kg/min blinded study drug (LJPC-501 or placebo). This dose was selected because of favorable results with this dose from the pilot study antecedent to the Phase-3 trial (Chawla, 2014). This initial dose was adjusted as often as every 5 minutes to achieve a target MAP of ≥ 75 mmHg. The dose titration scheme is shown in Table 9. The dose ranged from 2.5 to 200 ng/kg/min. The doses of catecholamines or

vasopressin remained constant during Hours 0-3 unless adjustments were required for safety. Keeping concurrent vasopressor therapy constant was based on agreement with the Division to ensure that the trial can demonstrate the effect of LJPC-501 on MAP independent of other vasopressors.

In Stage 3 (Hour 3-Hour 48), study drug could be titrated to a maximum rate of 40 ng/kg/min while attempting to reduce reliance on standard-of-care vasopressors. The dose titration scheme is shown in Table 10. Study drug was down-titrated beginning at Hour 48 and discontinued. This stage was designed to demonstrate durability of LJPC-501 effect by assessing a potential catecholamine-sparing effect while maintaining MAP between 65 and 70 mmHg.

In Stage 4 (Hour 48-Hour 168-Day 7), study drug could be re-initiated at investigator's discretion if discontinuation at Hour 48 resulted in a cardiovascular SOFA score of 4 or more. Study drug administration could only be re-instituted within 3 hours of Hour 48 discontinuation and could be titrated to a maximum dose rate of 40 ng/kg/min. Standard-of-care vasopressors at this stage in the protocol were titrated according to individual institutional guidelines. No subject received more than 168 hours of study drug treatment.

Table 9: Study Drug Dose Titration Procedure from Hour 0-Hour 3

Current MAP (mmHg)	Initial Study Drug Dose (ng/kg/min)	Study Drug Titration Interval (min)	Study Drug Dose Titration (ng/kg/min)	Study Drug Maximal Dose (ng/kg/min)	Study Drug Minimal Dose (ng/kg/min)
≤ 59	20	5	Increase to 80 then by increments of 20	200	2.5
60-74	20	15	Increase by 10	200	2.5
75-84	NA	15	Maintain Dose	200	2.5
≥ 85	NA	5	Decrease by 10	200	2.5

Source: LJ501-CRH01 CSR (page 29)-Note: dosing could be modified pending DSMB consensus

Table 10: Study Drug Dose Titration Procedure from Hour 3-Hour 48

Current MAP (mmHg)	Study Drug Titration Interval (min)	Study Drug Dose Titration (ng/kg/min)	Study Drug Maximal Dose (ng/kg/min)	Study Drug Minimal Dose (ng/kg/min)
≤ 59	5	Increase to 40	40	2.5
60-64	15	Increase by 10	40	2.5
65-70	15	Maintain Dose	40	2.5
≥ 70	15	Decrease by 10	40	2.5

Source: LJ501-CRH01 CSR (page 30)

The study procedures and all efficacy and safety assessments by study stage are illustrated in Table 11. The procedures and schedule of study activities were consistent with ICU practices.

The study was blinded using placebo saline infusion. An unblinded study pharmacist at each study site had access to the treatment randomization for each patient enrolled at that site. The study drug lot number on pharmacy source documents remained separate from clinical source documents. Specific blinding procedures and procedures for study drug preparation and labeling were provided to the unblinded pharmacist in the Pharmacy Manual. The tubing, bag, label, solution color, and all other properties of the final study drug product and delivery system were reported to be identical for both active and placebo treatments. Unblinding was to occur only in emergency situations concerning subject safety. Before unblinding, the investigator was required to contact the Applicant and complete an emergency unblinding authorization form. Unblinded safety datasets were provided by an independent unblinded statistician to an independent Data Safety Monitoring Board (DSMB) approximately 4 times per year. The DSMB also reviewed unblinded efficacy and safety data after 150 subjects had been treated and completed 28-day follow-up procedures. The Applicant remained blinded to treatment arm.

The administrative structure of the study included the following:

- Clinical Operations, Medical Monitoring, Statistics, Medical Writing: Applicant
- Contract Research Organization (CRO) (US): (b) (4)
- CRO (rest-of-world): (b) (4)
- Data Management: (b) (4)
- Institutional Review Board: (b) (4)
- Safety Monitoring: (b) (4)
- Chair, DSMB: (b) (4)
- Analytical Laboratory: (b) (4)

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The delegation of authority by the Applicant to the CROs was not described. There were no reports of a steering committee.

The DSMB met 4 times (i.e., 11 December 2015, 05 April 2016, 21 July 2016 and 18 October 2016) and each time recommended that enrollment continue without modifications to study conduct.

There was no analysis of treatment compliance because study drug was delivered as an IV infusion by site personnel per study drug titration schema that accounted for individual subject responses.

Table 11: Study Procedures and Schedules

Activity	Screening ^a	Day 1 (0 to 3 hours)	Day 1 (3 to 24 hours)	Day 2 (24 to 48 hours)	Days 3 to 6	Day 7 (EOS ^b)	Day 28 (Safety)
Informed Consent ^c	X						
Titrate Standard-of-care Vasopressors ^d	X						
Inclusion/Exclusion Criteria Evaluation	X						
Demographics	X						
Medical/Surgical History	X						
Concomitant Medications and Concomitant Procedures ^e	X	X	X	X	X	X	
Limited Physical Exam ^f	X					X	
Chest X-Ray	X						
Hemodynamic Vital Signs (HR, MAP) ^g	X	X	X	X	X	X	
Other Vital Signs (BP, RR, Body Temperature) ^h	X	X	X	X	X	X	
12-Lead ECG ⁱ	X			X			
Central Venous Pressure (CVP) ^j	X	X	X	X			
Cardiac Output ^k	X	X	X	X			
Urine Output ^l	X	X	X	X			
Arterial Blood Gas ^m	X	X					
SOFA Scoring ⁿ a. Respiratory System (PaO ₂ /FiO ₂) b. Nervous System (Glasgow Coma Scale) c. Cardiovascular System (MAP or vasopressors required) d. Liver (Bilirubin) e. Coagulation (Platelets) f. Renal (Creatinine or Urine Output)	X	X		X			
Hematology ^o	X	X		X			
Serum Chemistry ^p	X	X		X			
Blood for Serum Angiotensin I and II Levels	X	X					
Blood for Banked Storage Sample ^q	X						
Routine Urinalysis ^r	X						
Randomize to Study	X						
Pharmacy Study Drug Preparation	X						
LJPC-501 Administration / Titration ^s		X	X	X	(X)	(X)	
Safety Assessments (AEs/SAEs) ^t		X	X	X	X	X	X

Source: LJ501-CRH01 CSR (page 32)

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Study Endpoints

Primary efficacy Endpoint:

- An increased MAP, defined as achievement of a Day 1 MAP at 3 hours following initiation of study drug, of ≥ 75 mmHg or a 10 mmHg increase in baseline MAP.

Secondary Endpoint:

- Change in cardiovascular and total SOFA score at Hour 48.

Exploratory Endpoints:

- Mortality at 7 and 28 days.
- Achievement of MAP ≥ 75 mmHg obtained at Hour 1 and Hour 2.
- Change in heart rate between Hours 0 and 3, and Hours 3 and 48.
- Change in catecholamine dosing between Hours 3 and 48.

Statistical Analysis Plan (SAP)

Statistical Analysis Dataset Definitions:

- Intention to treat (ITT): All patients who were randomized regardless of whether study drug was received.
- Modified Intention-to-Treat (mITT): All patients randomized and received study drug regardless of quantity.
- Safety: All patients who received any study drug.
- Per Protocol (PP): All mITT patients who did not have a major protocol deviation.

Primary Efficacy Endpoint Analysis:

- The primary efficacy endpoint was analyzed using logistic regression. Pre-defined covariates were Baseline MAP, APACHE II score, vasopressin use over the 1st 6 hours prior to randomization (yes or no), and quantity of catecholamine use (average norepinephrine equivalents in ug/kg/min) over the 6 hours prior to randomization.
- Sensitivity analyses were performed for MAP response at Hour 3:
 - Site effect and site by treatment interaction using alpha 0.15 and calculation of odds ratio and 95% CI.
 - Comparison across treatment arms by randomization strata using the Cochran-Mantel-Haenszel method.
 - Comparison across treatment arms by unadjusted chi-squared test.
 - Stepwise multivariate logistical regression with covariates defined by subgroups of interest and treatment, age, gender, and stratification variables as fixed factors.

Secondary Efficacy Endpoint Analysis:

- Change in cardiovascular SOFA score at 48 hours using the van Elteren stratified Wilcoxon rank test with strata defined by randomization strata.
- Change in total SOFA score at 48 hours using a general linear model including all of the randomization strata.

Exploratory Endpoint Analysis:

- All-cause mortality at Day 7 and Day 28 was analyzed by the Kaplan-Meier formula.
- MAP response at Hour 1 and Hour 2 was analyzed as described for the primary efficacy endpoint analysis.
- Change in heart rate was analyzed by a 2-sample t-test.
- Change in catecholamine dosing between Hours 3 and 48 was analyzed by a 2-sample t-test.

Time on key ICU management features:

- Time on vasopressors (Hour 0 to the time all non-study vasopressors were discontinued), time on ventilator (Hour 0 to time ventilator removed), time in ICU (Hour 0 to ICU discharge), and time in hospital (Hour 0 to hospital discharge) were compared across treatment arms using the Kaplan-Meier formula and the log-rank test.

Electrocardiograms:

- Twelve-lead ECGs were collected at screening and on Day 2 (Hour 48). QTcF and QTcB were summarized by mean, standard deviation, median, and range. Assessments were categorized as follows:
 - ≤ 450 msec
 - > 450 msec to ≤ 480 msec
 - > 480 msec to ≤ 500 msec
 - > 500 msec
- The change from baseline in QTcF and QTcB were summarized and categorized as follows:
 - ≤ 30 msec
 - > 30 msec to ≤ 60 msec
 - > 60 msec

Handling of Missing Data:

- For the mITT and PP populations, missing primary endpoints due to death were imputed as failure for the primary endpoint. Missing secondary endpoints (i.e. SOFA) due to death were assigned a cardiovascular SOFA score of 4 and a total SOFA score of 24.
- For the mITT population (i.e., not the PP population) in cases of no death, the last

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observed MAP was carried forward as the primary imputation method. The Applicant used multiple imputation as a sensitivity analysis for the primary endpoint using baseline MAP, APACHE II score, vasopressin use over the 6 hours prior to randomization (yes or no), the quantity of catecholamine used over the 6 hours prior to randomization, age, and gender. Because there were no missing MAP values, the multiple imputation procedure was not performed.

- For time-to-event analyses (i.e., mortality at Day 7, mortality at Day 28, time on ventilator, and time on vasopressors), censored data techniques were utilized. For mortality analyses, subjects with missing data were censored on the last known survival date up to the specified endpoint (i.e. Day 7 and Day 28). If a subject was on a ventilator on the day of death, the event time was censored on that day.
- No imputation of values for missing data was performed for the safety endpoints.

Interim Analyses:

- An interim analysis was conducted after data for 150 evaluable patients through Day 28 were collected. Blinded data were pooled across the 2 treatment arms and were reviewed by open-session participants including Applicant representatives. Unblinded data analyzes were provided by an independent statistician to the DSMB for review of efficacy and safety according to the DSMB charter.

Sample Size Determination:

- The sample size was based on the hypothesis that the response rate for the primary efficacy endpoint was 60% for LJPC-501 and 40% for placebo. A 2-by-2 Chi-square test with a 2-sided alpha of 0.05 would have greater than 90% power to demonstrate superiority of LJPC-501 over placebo with a sample size of 150 evaluable subjects per treatment arm.

Protocol Amendments

There were no amendments to the original protocol dated 05 December 2014. There were two country-specific protocol addenda:

- Switzerland: the addendum to the protocol required an additional study visit at day 28 for subjects who received ≥ 48 hours of study drug treatment. At this visit, a physical examination and assessment for drug-related cardiovascular and renal adverse events were to be performed. However, study enrollment was completed before any subject was recruited in Switzerland.
- United Kingdom: the addendum to the protocol required a pregnancy test for all women of child-bearing potential before initiation of study drug and required immediate (≤ 24 hours) reporting of all SAEs to the applicant. The protocol listed pregnancy test as optional. The protocol also required SAE reporting within 1 working

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day of the investigator's knowledge of the event.

Data Quality and Integrity: Sponsor's Assurance

The Applicant provided assurance that the clinical trial was performed in accordance with the principles of Good Clinical Practice (GCP). Audits were performed by in-house or contracted auditors who operated independently of the trial monitors. The study was well-designed for the primary endpoint and conducted mostly in the US/Canada under a special protocol agreement.

6.1.2. Study Results

Compliance with Good Clinical Practices

QA audit certificates were provided in the CSR Appendix 16.1.8. Documentation of inter-laboratory standardization methods and QA procedures were provided in CSR Appendix 16.1.10. Patient information and informed consent were conducted in accordance with ICH E6 GCP. Independent ethics committees or institutional review boards at each study site reviewed the protocol, the informed consent, and all written documents provided to each subject (CSR-Appendix 16.1.1 for the protocol and Appendix 16.1.3 for a sample informed consent form).

Financial Disclosure

I conducted a financial disclosure review of all sites contacted by the Applicant or the Applicant's representatives in addition to those who ultimately participated in the trial.

A total of 171 sites were contacted to participate in this trial. Of these, 43 sites were not activated. Of the remaining 128 sites that were activated, 53 sites did not enroll any patients in the trial. The remaining 75 sites enrolled at least 1 subject into the trial.

Initial financial disclosures (i.e., prior to enrolling a patient) from each individual listed in form 1572 at each site were required from all 128 activated sites. Final financial disclosures (i.e., at the completion of the trial) were not required for the 53 sites that did not enroll a patient into the trial. The 75 enrolling sites were required to submit both initial and final financial disclosures from everyone listed in each site's form 1572.

From across the 128 activated sites, there were a total of 814 investigators / subinvestigators / nurses / coordinators listed as participants in the study. These participants were categorized as having nothing to financially disclose (statement 3 of FDA form 3454). There were 27 of the 814 participants (i.e., 3.3%) whose financial disclosures could not be collected from sites that enrolled patients. Three (3) of these 27 participants did not submit final financial disclosure forms but were not required to submit these forms because their site did not enroll a patient

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(Monash Medical Center, Clayton, VIC 3168). The Applicant made attempts to collect the financial disclosure information from the 27 investigative participants. Reasons for not being able to collect the requisite information included:

- Departed the institution: n=15
- Removed from the study: n=3
- Passed away: n=1
- Included as a site investigative staff but did not participate: n=6
- Maternity leave: n=1
- Out of the country and follow-up disclosure pending: n=1

There were 36 instances where initial financial disclosure forms were not submitted as required from sites that did not enroll patients. These instances occurred in 5 sites and are listed in Table 12. Bern University Hospital had the largest incidence of initial financial non-disclosure. There were no reported attempts to retrieve this requisite information from these non-enrolling sites.

Table 12: Staff not submitting initial financial forms from non-enrolling sites

Site Number	Site Name	Number of initial financial forms not disclosed	Total number of investigator staff
97	Royal Alexandria Hospital	1	12
101	Bern University Hospital	22	26
108	Kuopio University Hospital	5	6
117	Southampton General Hospital	3	15
131	Bordeaux Hospital University	5	6

Source: financial data SN0001 module 1/us

I have assessed the Applicant to have adequately obtained clinical investigator financial information pursuant to 21 CFR §§ 312.53(c) and as described in the *Guidance to Investigators, Industry, and FDA Staff-Financial Disclosure by Clinical Investigator, February 2013*. The attempts to retrieve financial information from deficient investigative staff from enrolling sites were adequate and the reasons for unsuccessful retrieval were acceptable. Non-retrieval of pre-enrollment financial information from active sites that ultimately did not enroll patients was non-consequential. Pursuant to 21 CFR § 54.4(b) requiring each clinical investigator participating in a clinical study to provide adequate financial information, the overall compliance by the investigator staff from all the sites was 97%.

I have concluded that data integrity was not affected by any finance-mediated potential conflict

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of interest.

Patient Disposition

The subject disposition is illustrated in Figure 5.

A total of 404 patients were screened after obtaining informed consent. Of these, 60 were excluded (i.e., 54 did not meet eligibility criteria, 3 withdrew consent, 1 died, 1 moved to hospice care, and 1 for reasons unknown). The remaining 344 patients underwent randomization (i.e., 172 subjects per arm) and were included in the ITT population.

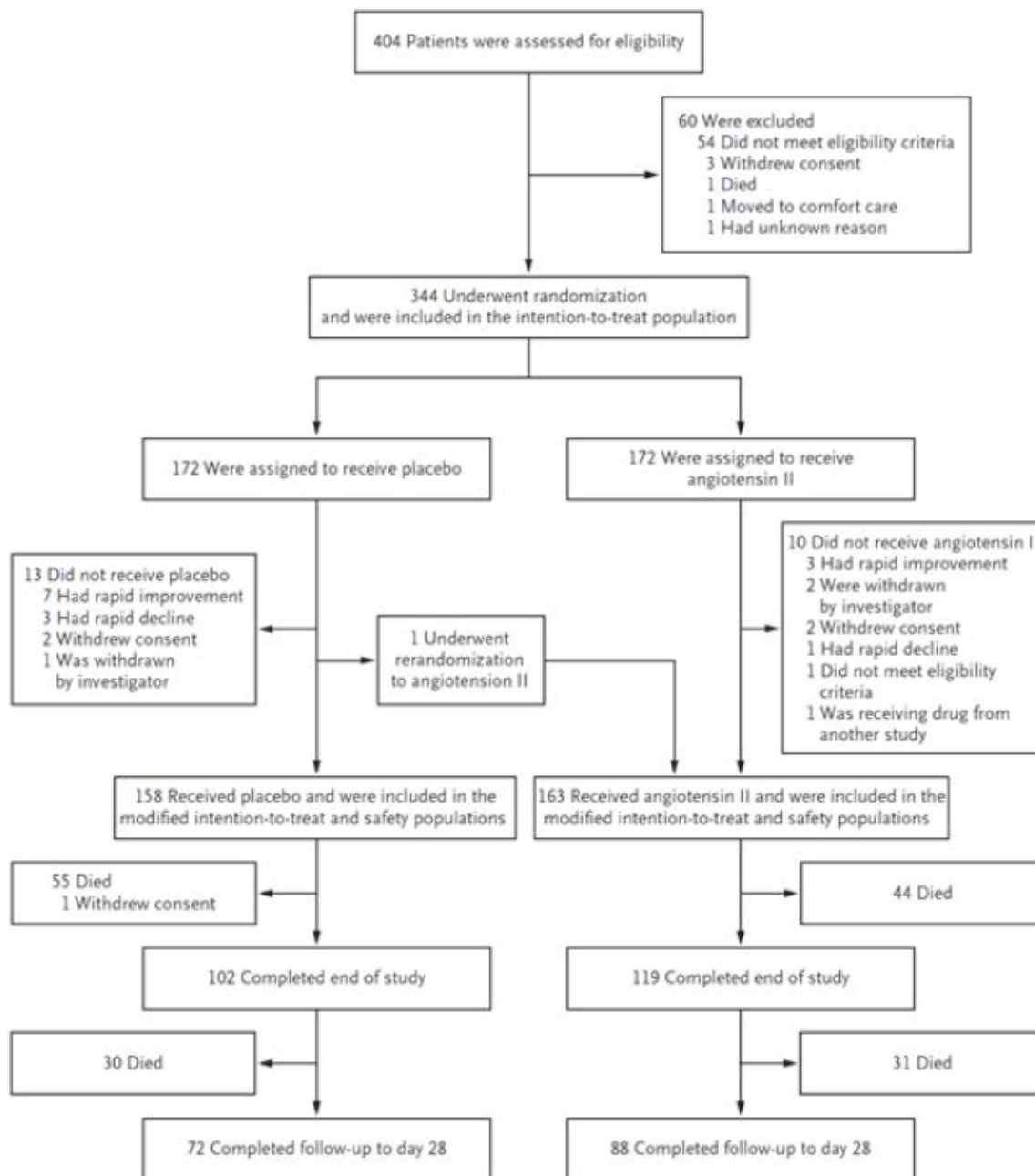
In the placebo arm, 13 of the 172 randomized subjects did not receive placebo (i.e., 7 had rapid improvement, 3 had rapid decline, 2 withdrew consent, and 1 was withdrawn via investigator discretion). In the LJPC-501 arm, 10 of the 172 randomized subjects did not receive active drug (i.e., 3 had rapid improvement, 1 had rapid decline, 2 withdrew consent, 2 were withdrawn via investigator discretion, 1 did not meet eligibility criteria, and 1 was receiving drug from another study).

One subject originally assigned to placebo had to be withdrawn from the study to undergo an operation. The subject was subsequently re-randomized to LJPC-501. Based on the SAP, this subject was included in the LJPC-501 group for the mITT and safety analyses, and in the placebo group for the ITT analyses.

One hundred and fifty eight (158) subjects received placebo and 163 subjects received LJPC-501. These subjects were included in the mITT and safety populations.

Of the 158 subjects receiving placebo, 55 died and 1 withdrew consent. Of the 163 subjects receiving LJPC-501, 44 died. Therefore, 102 subjects in the placebo arm completed the study but an additional 30 subjects died, resulting in 72 placebo subjects completing the Day 28 follow-up. Similarly, 119 subjects in the LJPC-501 arm completed the study but an additional 31 subjects died, resulting in 88 LJPC-501 subjects completing the Day 28 follow-up.

Figure 5: Subject Disposition



Source: LJ501-CRH01 CSR (page 52) with data source from CST Table 14.1.1.1.1, Table 14.1.1.1.2, and Table 14.1.1.5.2

Protocol Violations/Deviations

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There were a total of 28 protocol violations in the ITT population. The site and subject identifier, the subject age, gender, treatment arm, visit in which the violation occurred, the description of the violation and the action taken are described in Table 13. Most of the protocol violations occurred at screening and most of the actions taken were to continue the study. I re-arranged Table 13 by treatment arm and divided the protocol violation description into three categories: **1)** violations that may jeopardize data interpretation; **2)** protocol logistical errors that likely do not jeopardize data interpretation; and **3)** clinical conditions that precipitated a technical violation of the protocol (i.e., not a real protocol violation in my opinion). This is shown in Table 14.

Of the 28 protocol violations in the ITT population, 6 subjects were never dosed: 001-012, 015-018, 021-018, 042-002, 047-001, and 119-002. In 4 of these subjects, an inclusion criterion was not met, or an exclusion criterion was met. In the other 2 subjects, one was accidentally given the wrong product, presumably from another study not related to this trial (subject 042-002) and one had a non-patent central venous line (subject 119-002). There were therefore 22 protocol violations in the mITT population.

From Table 14, I determined that in the ITT population, there were 16 protocol violations in the LJPC-501 arm and 12 protocol violations in the placebo arm. These numbers were reduced to 12 and 10, respectively, in the mITT population.

Violations that may jeopardize data interpretation were screening MAP > 70 mmHg, NED $\leq$ 0.2 mcg/kg/min, MELD > 30, ANC < 1000 cells/mm³, insufficient CVP or ScVO₂, inadequate hydration, or accidental high dose not planned for the subject's hemodynamic presentation. A MAP in excess of the inclusion criteria range might disqualify the subject as catecholamine resistant because of potential responsiveness to catecholamines. Alternatively, fluid resuscitation might have been sufficient to ameliorate shock. Determination of drug efficacy in this setting might be jeopardized. A NED $\leq$ 0.2 mcg/kg/min would render the subject not qualified as truly catecholamine resistant based on the agreed definition. A MELD score > 30 would increase the mortality risk. An ANC count < 1000 cells/mm³ would have placed the subject at risk for infection and continued shock. Insufficient hydration based on CVP or clinical assessment prior to catecholamine administration would have been suboptimal management with enhanced morbidity.

In the mITT population, 4 subjects in the LJPC-501 group and 1 subject in the placebo group had a screening MAP > 70 mmHg. Two subjects in the placebo group, (0 in the LJPC group) did not meet the NED requirement for catecholamine resistance. Two additional subjects in the placebo group (0 in the LJPC group) had MELD scores exceeding 30. One subject in each group had an ANC < 1000 cells/mm³. One subject in the LJPC group (0 in the placebo group) was not sufficiently hydrated prior to catecholamine administration. In general, this group of protocol

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violations was equally balanced between the two treatment arms.

Protocol logistical errors not likely to jeopardize data interpretation (e.g., missing SOFA scores, missing ANC count, arterial rather than venous measurement for ScVO₂, ScVO₂ measured late, peripheral infusion rather than the requisite central infusion) were balanced between the two treatment groups (n= 4 each group).

The protocol violation rate in the mITT population randomized to LJPC-501 was 7%. The protocol violation rate in this population for those violations that may jeopardize data interpretation was 4%. Similarly, the protocol violation rate in the mITT population randomized to placebo was 6%, and the rate of protocol violations that may jeopardize data interpretation in the placebo population was 4%.

These violations were low in number, generally balanced, and unlikely to compromise data integrity.

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Table 13: Listing of All Protocol Deviations

Site/Pt/Age/G/Arm	Visit	Violation Description	Action Taken
001/005/55/M/501	Screening	MAP > 70 (extent unknown)	Caught retrospective
001/009/63/F/501	Screening	MAP > 70 (extent unknown)	Continued study
001/012/62/M/Pbo	Screening	CI < 2.3, ScVO ₂ <70	Drug never started
003/016/57/M/501	Screening	ScVO ₂ measured after protocol spec	Continued study
006/003/22/F/Pbo	Screening	WBC used instead of ANC	Continued study
015/015/63/F/501	Screening	Did not receive adequate hydration	Continued study
015/018/60/F/501	Day 1 (hr 0-3)	MELD > 30	Subject Discontinued
015/023/77/F/501	Day 1 (hr 3-24)	Received high dose (160 ng/kg/min)	Dose modified post 1 hr
017/002/57/M/501	Screening	MAP "little">70; reduced to meet IC	Continued study
018/003/42/M/Pbo	Screening	NED not > 0.2 ug/kg/min for 6 hrs	Continued study
021/003/70/M/Pbo	Screening	MELD>30; MAP<55; hx liver failure	Continued study-waiver
021/005/36/M/501	Screening	Already hypervolemic-no pre-fluids	Pt randomized
021/018/75/F/501	Screening	Screening ScVO ₂ was 70%, not>70%	"careful future screens"
036/002/60/F/Pbo	Day 2(hr 24-48)	Pharmacy error: given wrong arm	Continued study
041/002/67/M/501	Screening	Missing SOFA-no pre-dose bilirubin	Continued study
042/002/56/F/501	Not applicable	Pharmacy error: wrong product	Subject discontinued
044/002/50/M/Pbo	Screening	NED not > 0.2 ug/kg/min for 6 hrs	Already completed
047/001/47/M/Pbo	Screening	Inclusion criteria (CVP >8) not met	Subject never dosed
053/004/48/M/501	Screening	ANC not present during screening	Continued study
053/005/84/F/501	Screening	Met exclusion criteria (ANC<1000)	Continued study
082/001/50/M/Pbo	Screening	MAP>70 mmHg (MAP=74)	Continued study
087/004/68/M/501	Screening	ScVO ₂ 96 (probably arterial)	Continued study
087/005/51/M/Pbo	Screening	MELD > 30	Continued study
087/005/51/M/Pbo	Day 1 (hr 0-3)	Infusion was peripheral, not central	Continued study
119/002/78/F/501	Screening	Central line patency-no access	Discontinued
121/003/57/M/Pbo	Screening	ANC<1000 prior to enrollment	Continued study
125/001/53/M/Pbo	Screening	ANC not present during screening	Continued study
143/003/55/F/501	Screening	MAP>70 mmHg (MAP = 70.8)	Continued study

Arm= Placebo (Pbo) or Active Drug LJPC-501 (501); G=Gender; Pt=patient ID; IC=Inclusion Criteria; NED=norepinephrine equivalent dose

Source: LJ501-CRH01 CSR Protocol Deviation Listing, section 16.2.2

Table 14: Listing of All Protocol Violations by treatment group (ITT and mITT)

Protocol Violations	LJPC-501 (ITT n=172, mITT n=163)	Placebo (ITT n= 172; mITT n=158)
<i>Violations that may jeopardize data interpretation</i>		
MAP > 70 mmHg	4	1
NED ≤ 0.2 mcg/kg/min	---	2
MELD > 30	1 (not mITT)	2
ANC < 1000 cells/mm ³	1	1
ScVO ₂ not > 70%	1 (not mITT)	1 (not mITT)
CVP not > 8	---	1 (not mITT)
No adequate hydration	1	---
High Dose	1	---
<i>Protocol logistic errors that likely do not jeopardize data interpretation</i>		
ScVO ₂ measured late	1	
Missing SOFA score	1	
Missing ANC count	1	1
ScVO ₂ measurement arterial	1	
WBC rather than ANC		1
Wrong arm allocation		1
Peripheral not central infusion		1
Wrong drug product	1 (not mITT)	
<i>Clinical Condition-mediated technical violation</i>		
Hypervolemic prior to study	1	
No central access patency	1 (not mITT)	
TOTAL ITT	16	12
Total mITT	12	10

Source: reviewer derived from Table 13

Demographic Characteristics

Demographic characteristics of the mITT population are shown in Table 15. The mean age was 62 years; the median age was 64 years with a range from 22-89 years. Eighty-three subjects (26% of the mITT population) were 75 years old or greater.

Most the mITT population was white (81%). There were 33 black or African American subjects (10%). Most the subjects came from the United States/Canada (74%). Sixteen percent (16%) of the subjects came from Australia / New Zealand, and 10% of the subjects came from Europe.

Table 15: Demographic characteristics of the mITT population

Demographic Parameters	Placebo (N= 158) n (%)	LJPC-501 (N= 163) n (%)	Total (N= 321) n (%)
Gender			
Male	103 (65%)	92 (56%)	195 (61%)
Female	55 (35%)	71 (44%)	126 (39%)
Age			
Mean years (SD)	63 (15)	62 (16)	62 (15)
Median (years)	65	63	64
Min, max (years)	22-89	22-89	22-89
Age Group			
< 17 years	0	0	0
≥ 17 - < 65 years	77 (49%)	90 (55%)	167 (52%)
≥ 65 years	81 (51%)	73 (45%)	154 (48%)
≥ 65 - < 75 years	39 (25%)	32 (20%)	71 (22%)
≥ 75 years	42 (27%)	41 (25%)	83 (26%)
Race			
White	122 (77%)	135 (83%)	257 (81%)
Black or African American	19 (12%)	14 (9%)	33 (10%)
Asian	8 (5%)	5 (3%)	13 (4%)
American Indian or Alaska Native	0	1 (0.6%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)	0	1 (0.3%)
Other	8 (5%)	8 (5%)	16 (5%)
Ethnicity			
Hispanic or Latino	7 (4%)	10 (6%)	17 (5%)
Not Hispanic or Latino	151 (96%)	153 (94%)	304 (95%)
Region (optional)			
United States/Canada	120 (76%)	116 (71%)	236 (74%)
Rest of the World			
Europe	14 (9%)	19 (12%)	33 (10%)
Australia/New Zealand	24 (15%)	28 (17%)	52 (16%)

Source: JMP Datasets and listing 16.2.4.1 LJ501-CRH01 CSR

The demographic characteristics were balanced between the treatment arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The etiology of distributive shock is shown in Table 16. The major presentation was septic shock (n= 259) representing 81% of the mITT population. This was balanced between the two treatment arms (n=132 in the placebo arm and n= 127 in the LJPC-501 arm). Thirty-one subjects (10%) were diagnosed with potential sepsis (11 subjects in the placebo arm and 20 subjects in the LJPC-501 arm). Nineteen subjects (9 in the placebo arm and 10 in the LJPC-501 arm) were diagnosed with vasoplegia. Two subjects (both in the placebo arm) were diagnosed with pancreatitis as the cause of distributive shock. Ten subjects (4 in the placebo arm and 6 in the LJPC-501 arm) were diagnosed as “other”. In general, the causes of distributive shock were balanced between the two treatment arms.

Screening and baseline MAP are shown in Table 17. The mean screening MAP was 66 mmHg (SD 4). The mean baseline MAP after fluid resuscitation and catecholamine administration was 66 mmHg (SD 5). Both screening and baseline median MAPs were the same as the respective means. The screening MAPs ranged from 54-74 mmHg in both treatment arms. The baseline MAPs ranged from 43-92 mmHg and were similar between treatment arms. From the data, some subjects had baseline MAPs that were in the normal range and were therefore not hypotensive.

Screening and baseline MAP across the 3 regions are shown in Table 18. The mean and median screening MAPs were evenly distributed across the 3 regions. Similarly, the mean and median baseline MAPs were evenly distributed across the 3 regions. Both the USA/Canada and the European regions had a similar proportion of subjects with MAPs < and $\geq$ 65 mmHg at both screening and baseline. However in Australia and New Zealand, there was a greater proportion of subjects with a MAP $\geq$ 65 mmHg both at screening and at baseline.

Vasopressor usage for 6 hours pre-randomization and at baseline is shown in Table 19. During the 6 hours prior to randomization, the mean NED was 0.5 ug/kg/min. At baseline, the mean NED was also 0.5 ug/kg/min. Eight-nine percent (89%) of the subjects had a baseline NED dose $\geq$ 0.2 ug/kg/min. Forty-eight percent (48%) of the subjects had a baseline NED dose $\geq$ 0.35 ug/kg/min. Approximately 30% of the subjects had a baseline NED dose $\geq$ 0.5 ug/kg/min. The baseline NED doses ranged from 0.1-3.8 ug/kg/min. Seventy percent (70%) of the subjects were administered vasopressin. The baseline NED and the baseline vasopressin doses were equally distributed between the treatment arms. Across the 3 regions, the average NED during 6 hours prior to randomization and the baseline NED were higher in Europe compared to USA/Canada and Australia/New Zealand. There was a greater use of vasopressin in the US/Canada region compared to Europe and Australia/New Zealand (see Table 20). In general, the doses of catecholamines and vasopressin were sufficiently high enough to classify the subjects as catecholamine/vasopressin dependent in order to maintain a mean baseline MAP of 65 mmHg.

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The baseline APACHE II and MELD scores are shown in Table 21. The mean and median APACHE II scores for all mITT subjects were 28 and 28, respectively, with a range of 9-54. The mean and median MELD scores for all mITT subjects were 21 and 22, respectively, with a range of 4-41. Both the APACHE II and the MELD scores were evenly distributed between the two treatment arms. The baseline APACHE II and MELD scores across the regions are shown in Table 22. US/Canada had a higher mean baseline APACHE II score (29) compared to Australia/New Zealand (26) and compared to Europe (24). Based on the APACHE II-mortality profile (see Figure 1), the mortality risk was higher for US subjects compared to Europe and Australia/New Zealand. The mean baseline MELD scores were similar across the regions.

The baseline cardiac index, central venous pressure and central venous oxygenation saturation were similar between the two treatment arms (see Table 23) and across the regions (see Table 24). A normal central venous pressure is 3-8 mmHg. The higher than normal range of central venous pressure in these subjects with distributive shock likely reflected pre-randomization fluid resuscitation efforts and mechanical ventilation with the application of positive end-expiratory pressure in the setting where 185 of 321 subjects had respiratory failure.

The most frequent baseline medical histories are shown in Table 25. Ninety-two percent (92%) of the mITT subjects had an infection (septic shock, sepsis, pneumonia). Seventy-six percent (76%) of the mITT population had respiratory or acute respiratory failure or acute respiratory distress syndrome. Thirty-two percent (32%) of the mITT population had type II diabetes. Seventy-three percent (73%) had acute kidney injury. Seventy-six percent (76%) had cardiac disease. Sixty percent (60%) had blood dyscrasias (anemia, thrombocytopenia, and leukocytosis). Thirty-seven percent (37%) had a neoplasm, 34% injury/poisoning, 25% with a skin/subcutaneous disorder and 20% with an endocrine disorder. The incidences of baseline medical histories were similar between the two treatment arms.

In general, there were no significant differences between treatment arms and/or across regions in the baseline categories examined: causes of distributive shock, screening and baseline MAP, vasopressors, APACHE II and MELD scores, cardiac index, central venous pressure, venous oxygen saturation, and medical histories. One noticeable difference however between regions was the higher use of vasopressin in the US/Canada region (81%) compared to Europe (21%) and Australia/New Zealand (52%).

Table 16: Cause of Distributive Shock

Baseline Characteristic	Placebo (N=158)	LJPC-501 (N=163)	All Patients (N=321)
<i>Cause of Distributive Shock</i>	n (%)	n (%)	n (%)
Sepsis	132 (84%)	127 (78%)	259 (81%)
Potential Sepsis	11 (7%)	20 (12%)	31 (10%)
Vasoplegia	9 (6%)	10 (6%)	19 (6%)
Pancreatitis	2 (1%)	0	2 (0.6%)
Other	4 (3%)	6 (4%)	10 (3%)

Source: Table 14.1.2.2.2 and Table 14.2.4.1.3.1, LJ501-CRH01 CSR

Table 17: Screening and Baseline MAP

Characteristic	Placebo (N=158)	LJPC-501 (N=163)	All Patients (N=321)
<i>Screening MAP (mmHg)</i>	n (%)	n (%)	n (%)
< 65	55 (35%)	67 (41%)	122 (38%)
≥ 65	103 (65%)	96 (59%)	199 (62%)
Mean (SD)	65 (4)	66 (3)	66 (4)
Median (range)	67 (54-74)	66 (56-74)	66 (54-74)
<i>Baseline MAP (mmHg)</i>	n (%)	n (%)	n (%)
< 65	50 (32%)	52 (32%)	102 (32%)
≥ 65	108 (68%)	111 (68%)	219 (68%)
Mean (SD)	65 (6)	66 (5)	66 (5%)
Median (range)	66 (43-80)	66 (47-92)	66 (43-92)

Source: Table 14.1.2.2.2, LJ501-CRH01 CSR

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Table 18: Screening and Baseline MAP across Regions

Characteristic	USA/Can (n=236)	Europe (n=33)	AUS/NZL (n=52)
Screening MAP (mmHg)	n (%)	n (%)	n (%)
< 65	94 (40%)	14 (42%)	14 (27%)
≥ 65	142 (60%)	19 (58%)	38 (73%)
Mean (SD)	65 (4)	65 (4)	66 (4)
Median (range)	66 (54-74)	67 (57-71)	68 (56-74)
Baseline MAP (mmHg)			
	n (%)	n (%)	n (%)
< 65	77 (33%)	12 (36%)	13 (25%)
≥ 65	159 (67%)	21 (64%)	39 (75%)
Mean (SD)	66 (6)	65 (5)	67 (4)
Median (range)	66 (43-92)	65 (52-73)	67 (56-80)

Source: Table 14.1.2.2.5, LJ501-CRH01 CSR

Table 19: Pre-randomization and Baseline Vasopressors

Characteristic	Placebo (N=158)	LJPC-501 (N=163)	All Patients (N=321)
Average NED during 6 hours prior to randomization (ug/kg/min)			
Mean (SD)	0.5 (0.4)	0.5 (0.3)	0.5 (0.4)
Median (range)	0.4 (0.1-3.0)	0.4 (0.1-3.0)	0.4 (0.1-3.0)
Number of Vasopressors at Baseline			
Mean (SD)	2.0 (0.7)	1.9 (0.0)	2.0 (0.8)
Median (range)	2 (1-4)	2 (1-4)	2 (1-4)
Baseline NED (ug/kg/min)			
Mean (SD)	0.5 (0.5)	0.5 (0.4)	0.5 (0.4)
Median (range)	0.3 (0.1-3.8)	0.3 (0.1-2.6)	0.3 (0.1-3.8)
<0.2 ug/kg/min	15 (10%)	20 (12%)	35 (11%)
≥0.2--<0.35 ug/kg/min	68 (43%)	63 (39%)	131 (41%)
≥0.35--<0.50 ug/kg/min	27 (17%)	34 (21%)	61 (19%)
≥0.50 ug/kg/min	48 (30%)	46 (28%)	94 (29%)
Vasopressin during 6 hrs prior to randomization			
n (%)	111 (70%)	113 (69%)	224 (70%)

Source: Table 14.1.2.2.2 and Table 14.2.4.1.3.1, LJ501-CRH01 CSR

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Table 20: Pre-Randomization and Baseline Vasopressor Usage across Regions

Vasopressor Usage Prior to Study Drug	US/Canada (N=236)	Europe (N=33)	Australia/ New Zealand (N=52)
Average NED during 6 hours prior to randomization, mean (SD) (ug/kg/min)	0.5 (0.4)	0.7 (0.6)	0.5 (0.2)
Baseline NED, mean (SD) (ug/kg/min)	0.5 (0.4)	0.7 (0.5)	0.4 (0.3)
Vasopressin use during 6 hours prior to randomization, n(%)	190 (81%)	7 (21%)	27 (52%)

Source: Table 14.1.2.2.5, LJ501-CRH01 CSR

Table 21: Baseline APACHE II and MELD Score

Baseline Characteristic	Placebo (N=158)	LJPC-501 (N=163)	All Patients (N=321)
<i>APACHE II Score</i>	n (%)	n (%)	n (%)
< 30	93 (59%)	105 (64%)	198 (62%)
31-40	54 (34%)	50 (31%)	104 (32%)
≥ 41	11 (7%)	8 (5%)	19 (6%)
Mean (SD)	29 (8)	27 (8)	28 (8)
Median (range)	29 (12-51)	27 (9-54)	28 (9-54)
<i>MELD Score</i>			
< 30	138 (87%)	145 (89%)	283 (88%)
≥ 30	20 (13%)	18 (11%)	38 (12%)
Mean (SD)	22 (7)	20 (7)	21 (7)
Median (range)	23 (4-41)	21 (6-36)	22 (4-41)

Source: Table 14.1.2.2.2 and Table 14.2.4.1.3.1, LJ501-CRH01 CSR

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Table 22: Baseline APACHE II and MELD Score across Regions

Baseline Characteristic	USA/Can (n=236)	Europe (n=33)	AUS/NZL (n=52)
APACHE II Score	n (%)	n (%)	n (%)
< 30	134 (57%)	24 (73%)	40 (77%)
31-40	86 (36%)	9 (27%)	9 (17%)
> 41	16 (7%)	0	3 (6%)
Mean (SD)	29 (8)	24 (8)	27 (9)
Median (range)	29 (9-54)	24 (10-35)	26 (11-51)
MELD Score			
< 30	203 (86%)	33 (100%)	47 (90%)
≥ 30	33 (14%)	0	5 (10%)
Mean (SD)	22 (7)	19 (6)	20 (8)
Median (range)	23 (4-41)	20 (8-29)	22 (6-37)

Source: Table 14.1.2.2.5, LJ501-CRH CSR

Table 23: Baseline Cardiac Index, Central Venous Pressure and ScVO₂

Baseline Characteristic	Placebo (N=158)	LJPC-501 (N=163)	All Patients (N=321)
Cardiac Index (L/min/m²)	n=73	n=69	n=142
Mean (SD)	3.4 (1)	3.3 (1)	3.4 (1)
Median (range)	3.2 (2.4-6.6)	3.0 (2.1-6.4)	3.1 (2.1-6.6)
CVP (mmHg)	n=123	n=126	n=249
Mean (SD)	13 (5)	14 (5)	13 (5)
Median (range)	12 (1-28)	13 (5-35)	12 (2-7)
ScVO₂ (%)	n=117	n=120	n=237
Mean (SD)	77 (9)	78 (9)	77 (9)
Median (range)	77 (35-97)	77 (45-99)	77 (35-99)

Source: Table 14.1.2.2.2 and Table 14.2.4.1.3.1, LJ501-CRH01 CSR

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Table 24: Baseline Cardiac Index, Central Venous Pressure and ScVO₂ across Regions

Baseline Characteristic	USA/Can (n=236)	Europe (n=33)	AUS/NZL (n=52)
<i>Cardiac Index (L/min/m²)</i>	n=99	n=20	n=23
Mean (SD)	3.3 (0.9)	3.6 (1.2)	3.4 (1.0)
Median (range)	3.2 (2.1-6.4)	3.1 (2.4-6.6)	3.0 (2.4-5.9)
<i>CVP (mmHg)</i>	n=175	n=25	n=49
Mean (SD)	13 (5)	16 (7)	12 (4)
Median (range)	12 (1-30)	15 (6-35)	12 (1-24)
<i>ScVO₂ (%)</i>	n=171	n=22	n=44
Mean (SD)	78 (9)	76 (7)	76 (8)
Median (range)	77 (35-99)	79 (58-88)	76 (51-92)

Source: Table 14.1.2.2.5, LJ501-CRH CSR

Table 25: Most Frequent Baseline Medical Histories (mITT population)

System Organ Class Preferred Term	Placebo (N=158) n (%)	LJPC-501 (N=163) n (%)	All Patients (N=321) n (%)
Overall	158 (100%)	163 (100%)	321 (100%)
Infections	148 (94%)	148 (91%)	296 (92%)
-Septic Shock	89 (56%)	84 (52%)	173 (54%)
-Sepsis	51 (32%)	52 (32%)	103 (32%)
-Pneumonia	50 (32%)	42 (26%)	92 (29%)
Respiratory	141 (89%)	143 (88%)	284 (89%)
-Respiratory Failure	50 (32%)	46 (28%)	96 (30%)
-Acute Respiratory Failure	47 (30%)	42 (26%)	89 (28%)
-Pleural Effusion	31 (20%)	40 (25%)	71 (22%)
-Acute Respiratory Distress Syndrome	33 (21%)	27 (17%)	60 (19%)
Metabolic	139 (88%)	142 (87%)	281 (88%)
-Type 2 Diabetes Mellitus	56 (35%)	47 (29%)	103 (32%)
Renal and Urinary	136 (86%)	130 (80%)	266 (83%)
-Acute kidney injury	117 (74%)	116 (71%)	233 (73%)
Vascular	119 (75%)	129 (79%)	248 (77%)
-Hypertension	86 (54%)	97 (60%)	183 (57%)
-Hypotension	41 (26%)	47 (29%)	88 (27%)
Cardiac	117 (74%)	128 (79%)	245 (76%)
-Atrial fibrillation	55 (35%)	46 (28%)	101 (32%)
Gastrointestinal	103 (65%)	114 (70%)	217 (68%)
-Gastroesophageal Reflux Disease	41 (26%)	30 (18%)	71 (22%)
-Hepatobiliary	61 (39%)	49 (30%)	110 (34%)
Blood / Lymphatic	103 (65%)	91 (56%)	194 (60%)
-Anemia	53 (34%)	49 (30%)	102 (32%)
-Thrombocytopenia	36 (23%)	31 (19%)	67 (21%)
-Leukocytosis	32 (20%)	20 (12%)	52 (16%)
Neoplasm	58 (37%)	61 (37%)	119 (37%)
Injury / Poisoning	55 (35%)	53 (33%)	108 (34%)
Skin / Subcutaneous	31 (20%)	49 (30%)	80 (25%)
Endocrine	28 (18%)	36 (22%)	64 (20%)

Source: Table 14.1.3.1.2, LJ501-CRH CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

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The Applicant did not analyze treatment compliance because study drug was delivered as an IV infusion by site personnel participating in the trial.

Duration of study drug administration is shown in Table 26. A mean and median of 2 hours (ranging from 0.3—16 hours) transpired between randomization and initiation of study drug. This time duration was equal in both treatment arms. The mean duration of study drug exposure was 40 hours (range 1—60 hours) in the placebo arm and 47 hours (range 4—168 hours) in the LJPC-501 arm. The majority of subjects in both arms received study drug between 3 and 51 hours.

The mean and median placebo and LJPC-501 doses at each hour during the 3-hour primary endpoint time period are shown in Table 27. At baseline, both treatment arms began at the prespecified starting dose of 20 ng/kg/min. At Hour 1, 2, and 3, the mean placebo dose rose to 79→106→121 ng/kg/hour respectively. At Hour 1, the mean LJPC-501 dose was decreased to 19 ng/kg/min. At Hour 2, the dose increased to 29 ng/kg/min. At Hour 3, the dose increased to 36 ng/kg/min. The LJPC-501 dose decreased beyond Hour 3 to an average of 18—19 ng/kg/min. The placebo doses used beyond Hour 3 were approximately 27-30 ng/kg/min.

There were many dose titrations within the hourly intervals (Hour 0—1, Hour 1—2, Hour 2—3). The average dose within hourly intervals for the 3 hour primary efficacy endpoint testing period is shown in Table 28. The average hourly interval doses in this table were lower than the specific hourly doses for the initial 3 hours of study drug treatment but rose in proportion to the specific hourly doses. Doses are discussed in detail in the section entitled Dose and Dose-Response. The key information here is that the doses used in this study were compliant with the pre-specified protocol schema.

The list of concomitant vasopressors used during treatment is shown in Table 29. The overwhelming majority of the subjects were on norepinephrine (91% placebo, 94% LJPC-501). This was followed by vasopressin (41% placebo, 44% LJPC-501), epinephrine (15% placebo, 22% LJPC-501) and phenylephrine (19% placebo, 17% LJPC-501). The various vasopressors were generally balanced between the two arms. As agreed upon during the special protocol assessment, vasopressor doses were transformed into norepinephrine equivalent doses as described in Table 8.

The norepinephrine equivalent dose at baseline and by study period is shown in Table 30. The data shows that the NED remained constant between baseline and Hours 0- 3 as required in the protocol. Beyond Hour 3, the NED decreased as described in the protocol in order to explore the catecholamine sparing effect of LJPC-501. The norepinephrine equivalent doses at baseline and per hour for the initial 3 hours of study drug treatment are shown in Table 31. The key information from this table is the relative constancy of the NED within the crucial Hour 0-3

study period when the efficacy of LJPC-501 was tested.

In general, the data suggested that the conduct of the trial was compliant with the protocol. The study drug doses were within pre-specified dose ranges. There was no difference in the amount of time from randomization to initiation of treatment between the treatment arms. The background therapy of catecholamines/vasopressin remained constant throughout the 3 hour primary efficacy endpoint time period, thereby attenuating any concern that background vasoconstriction agents might have impacted the primary endpoint.

Table 26: Duration of Study Drug Administration

	Placebo (N=158)	LJPC-501 (N=163)
Time from randomization to study drug initiation, hours		
Mean (SD)	2 (2)	2 (1)
Median (Range)	2 (0.6—16)	2 (0.3—6)
Duration of Exposure, hours		
Mean (SD)	40 (14)	47 (27)
Median (Range)	48 (1—60)	48 (4—168)
Duration exposure by subgroups, hours	<i>n (%)</i>	<i>n (%)</i>
> 0--< 3hours	3 (2%)	0
3--< 45 hours	54 (34%)	62 (38%)
45--< 51 hours	96 (61%)	76 (47%)
51--< 72 hours	5 (3%)	12 (7%)
≥ 72 hours	0	13 (8%)

Source: Table 14.3.1.1, LJ501-CRH CSR

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Table 27: Study Drug Dose by Hour during 3-Hour Primary Endpoint Period

Dose (ng/kg/min)	Placebo (N=158)	LIPC-501 (N=163)
Baseline	N=158	N=163
Mean (SD)	20 (3)	20 (2)
Median (Range)	20 (1–40)	20 (5–40)
Hours 1	N=156	N=163
Mean (SD)	79 (54)	19 (25)
Median (Range)	60 (3–200)	10 (0–140)
Hours 2	N=154	N=162
Mean (SD)	106 (53)	29 (40)
Median (Range)	100 (1–200)	10 (0–183)
Hours 3	N=155	N=163
Mean (SD)	121 (58)	36 (50)
Median (Range)	130 (0–200)	10 (0–200)

Source: Table 14.3.1.3, LJ501-CRH CSR

Table 28: Study Drug Dose during Hourly Intervals in the 3-Hour Time Period

Dose (ng/kg/min)	Placebo (N=158)	LIPC-501 (N=163)
Overall	N=158	N=163
Mean (SD)	40 (21)	21 (21)
Median (Range)	42 (3–152)	14 (1–124)
Hours 0–1	N=158	N=163
Mean (SD)	51 (37)	16 (16)
Median (Range)	35 (13–171)	9 (2–92)
Hours 1–2	N=156	N=163
Mean (SD)	91 (53)	24 (32)
Median (Range)	75 (3–200)	10 (0–183)
Hours 2–3	N=156	N=163
Mean (SD)	113 (53)	32 (46)
Median (Range)	115 (0.3–200)	10 (0–200)

Source: Table 14.3.1.1, LJ501-CRH CSR

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Table 29: List of Vasopressors Used During Treatment

Vasopressors	Placebo (N=158)	LJPC-501 (N=163)
Norepinephrine	144 (91%)	154 (94%)
Vasopressin	64 (41%)	71 (44%)
Epinephrine	24 (15%)	36 (22%)
Phenylephrine	30 (19%)	28 (17%)
Dopamine	2 (1%)	4 (2%)
Ephedrine	0	2 (1%)
Terlipressin	0	1 (0.6%)
Argipressin	0	1 (0.6%)
Metaraminol	1 (0.6%)	0

Source: Reviewer Analysis of Database CMDECOD

Table 30: Norepinephrine Equivalent Dose by Study Period

NED (ug/kg/min)	Placebo (N=158)	LJPC-501 (N=163)
Baseline	<i>n=158</i>	<i>n=163</i>
Mean (SD)	0.48 (0.45)	0.45 (0.35)
Median (Range)	0.34 (0.05—3.80)	0.33 (0.08—2.58)
Hours 0-3	<i>n=158</i>	<i>n=163</i>
Mean (SD)	0.49 (0.48)	0.43 (0.37)
Median (Range)	0.34 (0.05—4.46)	0.31 (0.01—2.58)
Hours 3-48	<i>n=157</i>	<i>n=162</i>
Mean (SD)	0.43 (0.62)	0.34 (0.59)
Median (Range)	0.21 (0.02—3.92)	0.13 (0.00—4.43)

Source: Table 14.2.4.2.1, LJ501-CRH CSR

Table 31: Norepinephrine Equivalent Dose during Initial 3-hours Study Drug Treatment

NED (ug/kg/min)	Placebo (N=158)	LJPC-501 (N=163)
Baseline	<i>n=158</i>	<i>n=163</i>
Mean (SD)	0.48 (0.45)	0.45 (0.35)
Median (Range)	0.34 (0.05—3.80)	0.33 (0.08—2.58)
Hour 1	<i>n=158</i>	<i>n=161</i>
Mean (SD)	0.49 (0.44)	0.43 (0.37)
Median (Range)	0.34 (0.05—3.80)	0.30 (0.01—2.58)
Hour 2	<i>n=157</i>	<i>n=161</i>
Mean (SD)	0.49 (0.49)	0.42 (0.37)
Median (Range)	0.35 (0.05—4.80)	0.30 (0.1—2.58)
Hour 3	<i>n=157</i>	<i>n=160</i>
Mean (SD)	0.51 (0.53)	0.42 (0.38)
Median (Range)	0.35 (0.05—4.80)	0.29 (0.01—2.58)

Source: Table 14.2.4.1.3.2, LJ501-CRH CSR

Efficacy Results – Primary Endpoint

The primary efficacy results are shown in Table 32. In the mITT population, 70% of the subjects in the LJPC-501 arm achieved the primary efficacy endpoint and 23% of the subjects in the placebo arm achieved the primary efficacy endpoint (i.e., responder). The Odds Ratio was 8 (95% CI 5—13). This statistically significant result was also evident in the ITT population and the PP population (see Table 33).

The reasons for non-response (i.e., not achieving the primary efficacy endpoint) are shown in Table 34. The majority of non-responders in both arms of the study failed to reach the requisite $\text{MAP} \geq 75$ mmHg or an increase of 10 mmHg from baseline, or both. Ten percent (10%) of the subjects in the placebo arm and 14% of the subjects in the LJPC-501 arm had increases in the NED during the efficacy testing period (Hours 0—3), presumably reflecting non-response to LJPC-501. These results were consistent between the ITT, mITT and PP populations.

The MAP by study period is shown in Table 35. The mean baseline MAP was 65 mmHg in the placebo arm and 66 mmHg in the LJPC-501 arm. In the Hour 0-3 study period, the mean MAP was 68 mmHg in the placebo arm and 79 mmHg in the LJPC-501 arm. Between Hours > 3—48, the mean MAP was 70 mmHg in the placebo arm and 72 mmHg in the LJPC-501 arm. These mean MAP values in Stage 3 of the study (Hours >3—48) were maintained by reducing the dose of catecholamines (i.e., catecholamine sparing) and substituting LJPC-501 in its place. This strategy was based on the original intent of the Applicant to ameliorate the harmful effects of catecholamines while maintaining an adequate perfusion pressure.

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The MAP by hour during the crucial Stage 2 of the study (Hours 0—3) and selected hours in Stage 3 are shown in Table 36. Within Stage 2, the MAP rose per hour from Hour 0 to Hour 3 in the LJPC-501 arm (66→77→77→77 mmHg). In the placebo arm, the MAP rose per hour from Hour 0 to Hour 3 (65→68→69→70) mmHg. Beyond Hour 3, the MAP stabilized at 74 mmHg in both treatment arms. These numbers were consistent with the efficacy of LJPC-502 over placebo in Stage 2, the catecholamine titration effect in Stage 3, and the resolution of shock in survivors.

The Forrest Plot representing subgroup analyses for baseline demographics is shown in Figure 6. The efficacy of LJPC-501 over placebo was evident for all analyzed subgroups: age (< 65 years vs $\geq$ 65 years), gender, race (non-white, white), baseline Body Mass Index (< 30 vs $\geq$ 30 kg/m²), and geographical location (USA/Canada vs Rest-of-World).

The Forrest Plot representing subgroup analyses for baseline disease characteristics is shown in Figure 7. The efficacy of LJPC-501 over placebo was evident for all subgroups of the following *yes/no* disease categories: history of acute respiratory distress syndrome (ARDS), x-ray showing ARDS, history of sepsis, history of taking ACE-inhibitors, and history of taking angiotensin receptor blockers. The efficacy of LJPC-501 over placebo was also evident for all subgroups of the following baseline strata: albumin (< 2.5 vs $\geq$ 2.5 g/dL), MAP (< 65 vs $\geq$ 65 mmHg), APACHE II score ($\leq$ 30 vs > 30), NED (< 0.5 vs $\geq$ 0.5 ug/kg/min), endogenous angiotensin I level (< 253 vs $\geq$ 253 pg/mL), endogenous angiotensin II level (< 83.75 vs $\geq$ 83.75 pg/mL), angiotensin I/II ratio (< 1.63 vs $\geq$ 1.63) and LJPC-501 dose at 30 min (<20 vs > 20 ng/kg/min).

Enrollment at the highest enrolling sites is summarized in Table 37. Most of the highest enrolling sites were located in the USA with Cleveland Clinic and Duke University as the top sites enrolling a combined 51 subjects. Of the 128 activated sites, 73 sites enrolled at least 1 subject. The 8 sites listed in the table enrolled 122 of the 344 ITT subjects (11% of enrolling sites or 6% of activated sites responsible for enrolling 35% of the ITT population). The Forrest plot shown in Figure 8 depicts the primary efficacy endpoint for each global region / country cluster: USA, Canada, Australia / New Zealand, and Belgium / Germany / Finland / France / UK. The efficacy results were similar across the regions / countries. The US had the highest enrollment and therefore most closely approximated the overall results.

Table 32: Primary Efficacy Endpoint: MAP

Primary Endpoint	Placebo (N=158)	LJPC-501 (N=163)	Statistics
<i>3-hr MAP Response</i>	<i>n(%)</i>	<i>n(%)</i>	<i>OR (95%CI), p</i>
Responder	37 (23%)	114 (70%)	8 (5-13), p<0.00001
Non-responder	121 (77%)	49 (30%)	

Source: Table 14.2.1.1.1, LJ501-CRH CSR

Table 33: Primary Efficacy Endpoint for the ITT, mITT, and PP Populations

Primary Endpoint	Placebo (N)	LJPC-501 (N)	Statistics
<i>3-hr MAP Response</i>	<i>n(%)</i>	<i>n(%)</i>	<i>OR (95%CI), p</i>
ITT	N= 172	N= 172	
	41 (24%)	116 (67%)	7 (4-11), p<0.00001
mITT	N= 158	N= 163	
	37 (23%)	114 (70%)	8 (5-13), p<0.00001
PP	N= 149	N= 150	
	35 (24%)	104 (69%)	8 (5-13), p< 0.00001

Source: Tables 14.2.1.1.3; 14.2.1.1.1; and 14.2.1.1.2, LJ501-CRH CSR

Table 34: Reasons for Non-Response to Angiotensin II

Reason for non-response	ITT		mITT		PP	
	Placebo N=131 n(%)	LJPC-501 N=56 n(%)	Placebo N=121 n(%)	LJPC-501 N=49 n(%)	Placebo N=114 n(%)	LJPC-501 N=46 n(%)
NED increase	13 (10%)	7 (13%)	12 (10%)	7 (14%)	12 (11%)	7 (15%)
MAP <75 mmHg or Change < 10 mmHg	81 (62%)	39 (70%)	74 (61%)	34 (69%)	70 (61%)	33 (72%)
NED increase and MAP <75 mmHg or Change < 10 mmHg	37 (28%)	10 (18%)	35 (29%)	8 (16%)	32 (28%)	6 (13%)

Source: Tables 14.2.1.1.3; 14.2.1.1.1; and 14.2.1.1.2, LJ501-CRH CSR

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Table 35: MAP by Study Period

MAP mmHg By Study Period	Placebo (N=158)	LJPC-501 (N=163)
Baseline Subj with Hour 48		
<i>N</i>	157	163
<i>Mean MAP (SD)</i>	65 (6)	66 (5)
Hour 0—3		
<i>N</i>	158	163
<i>Mean MAP (SD)</i>	68 (8)	79 (7)
Hour > 3—48		
<i>N</i>	157	163
<i>Mean MAP (SD)</i>	70 (7)	72 (6)

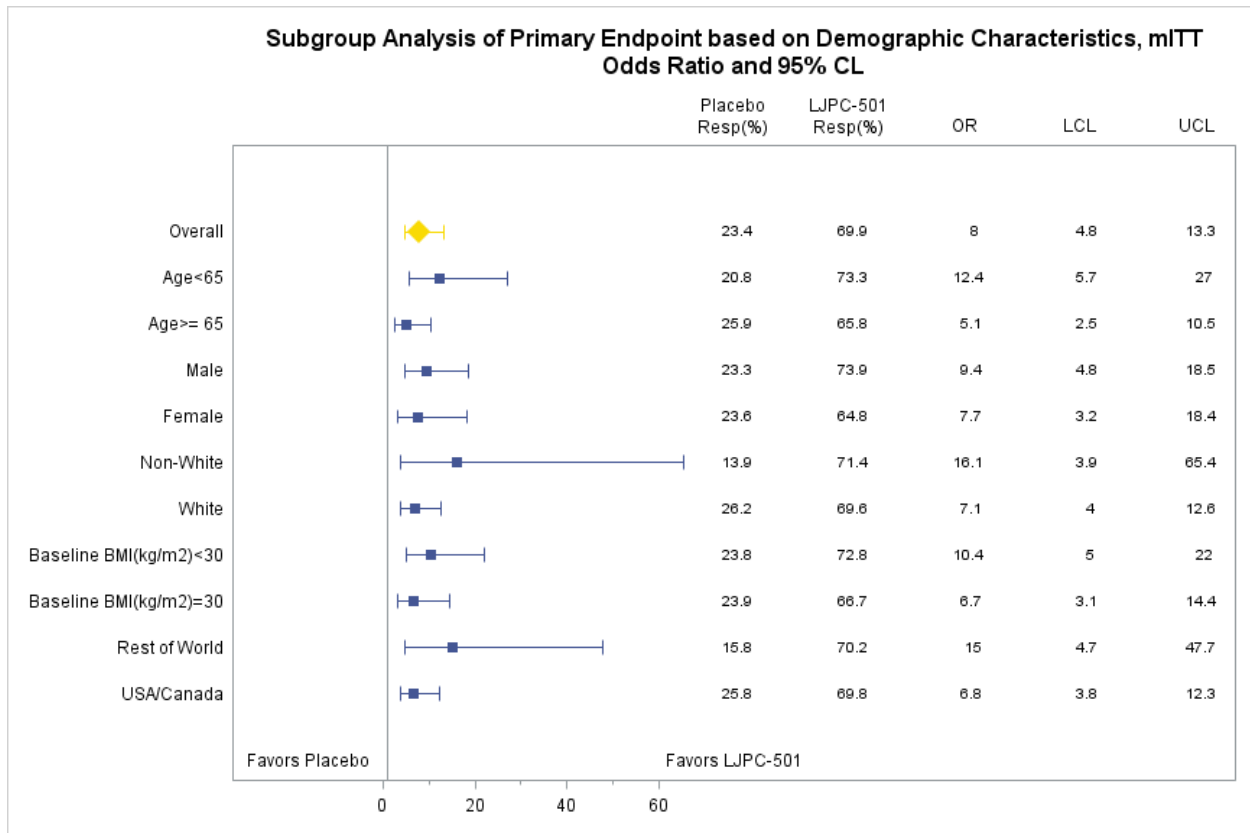
Source: Table 14.2.1.4.1, LJ501-CRH CSR

Table 36: MAP by Hour

MAP mmHg By Hour	Placebo (N=158)	LJPC-501 (N=163)
Hour 0		
N	158	163
Mean (SD)	65 (6)	66 (5)
Hour 1		
N	158	163
Mean (SD)	68 (8)	77 (6)
Hour 2		
N	158	163
Mean (SD)	69 (9)	77 (7)
Hour 3		
N	158	163
Mean (SD)	70 (9)	77 (7)
Hour 6		
N	153	157
Mean (SD)	70 (9)	72 (8)
Hour 12		
N	145	153
Mean (SD)	70 (9)	72 (9)
Hour 24		
N	136	148
Mean (SD)	71 (9)	73 (10)
Hour 36		
N	125	136
Mean (SD)	74 (18)	74 (11)
Hour 48		
N	112	123
Mean (SD)	74 (11)	74 (13)

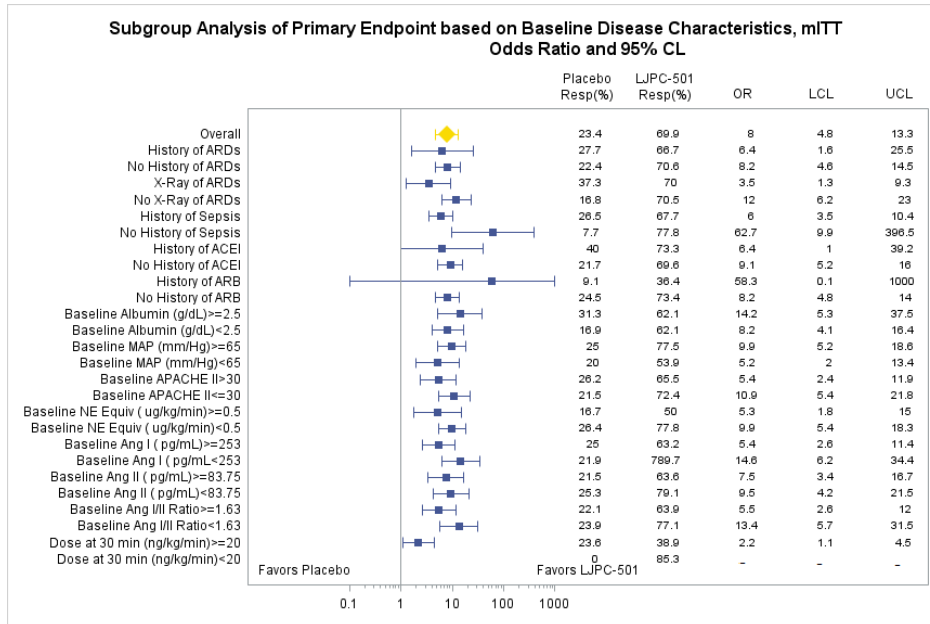
Source: Table 14.2.1.5.1, LJ501-CRH CSR

Figure 6: Forrest Plot-Primary Efficacy Endpoint based on Demographic Characteristics



Source: Office of Biostatistics, FDA

Figure 7: Forrest Plot-Primary Efficacy Endpoint based on Baseline Disease Characteristics



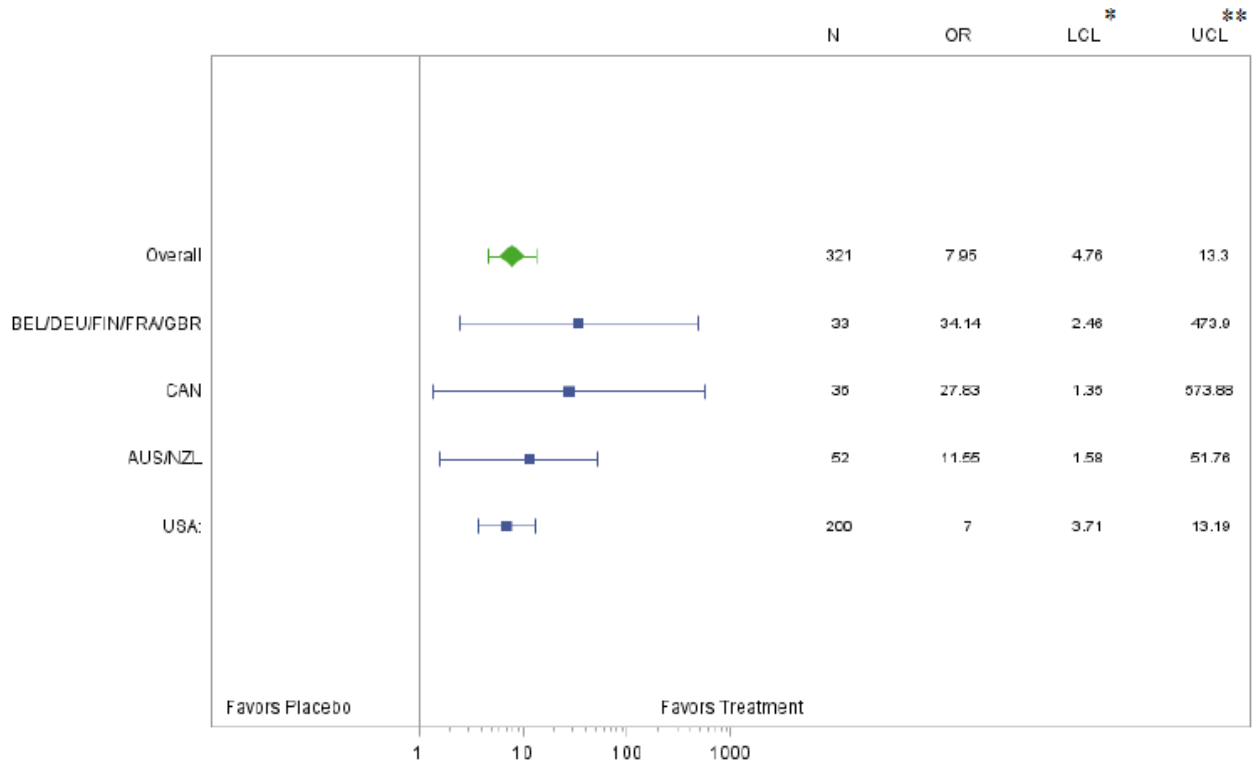
Source: Office of Biostatistics, FDA

Table 37: Highest Enrolling Sites

Site	Number of Subjects Enrolled
US Sites	
Cleveland Clinic	30
Duke University	21
Inova Fairfax Hospital	12
Baylor University	12
Emory University	11
University of Maryland Medical Center	10
Outside US Sites	
Kingston General Hospital (Canada)	16
Royal Adelaide Hospital (Australia)	10

Source: NDA: module 5354-other study report\bimo

Figure 8: Forrest Plot-Efficacy by Number of Subjects Enrolled Across Regions / Sites



Source: Dr. Ququan (Cherry) Liu, Biostatistics, FDA (*=lower bound 95% confidence interval; **= upper bound of 95% confidence interval); OR = Odds Ratio; N = sample size per country / region

Data Quality and Integrity – Reviewers’ Assessment

Following a meeting with OSI, we concluded that an audit was not necessary. There was no evidence of potential fraud. With the exception of one site (i.e., Cleveland Clinic), the results from individual sites were within the 95% CI of the overall result for sites of variable sample size. The Cleveland Clinic was slightly outside the 95% CI but not enough to precipitate a concern. There were no observable anomalies (e.g., results driven by region, individual site or site cluster, or specific subgroups).

There was no evidence of financial impropriety. Out of 814 investigators/subinvestigators that were required to submit form 3454, 27 failed to do so for acceptable reasons (i.e., departed from site, removed from study, passed away, did not participate in the study, maternity leave, not in country).

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoint was the change in cardiovascular and total SOFA score at Hour 48.

The cardiovascular SOFA scores at baseline, Hour 3 and Hour 48 are shown in Table 38. The changes from baseline in the cardiovascular SOFA score at Hour 3 and Hour 48 are shown in Table 39. All subjects in the study had a screening cardiovascular SOFA score of 4. This was expected because of their clinical diagnosis of catecholamine resistant septic shock. There was minimal to no change in the cardiovascular SOFA score at Hour 3 for each treatment arm. Eleven (11) of 163 subjects in the LJPC-501 arm (7%) had a shift in the cardiovascular SOFA score from 4 to 3. Two (2) of 158 subjects in the placebo arm (1%) had a shift in the cardiovascular SOFA score from 4 to 3. At Hour 48, there was an improvement in the distribution of mean cardiovascular SOFA scores in both treatment arms. This improved the mean cardiovascular SOFA in both arms: from 4 to 2.72 in the placebo arm and from 4 to 2.25 in the LJPC-501 arm representing a -1.28 reduction of the mean cardiovascular SOFA in the placebo arm and a -1.75 reduction of the mean cardiovascular SOFA in the LJPC-501 arm ($p=0.0129$). The median change from baseline in the cardiovascular SOFA score was 0 in the placebo arm and -1 in the LJPC-501 arm.

The total SOFA scores at baseline, Hour 3 and Hour 48 are shown in Table 40. The changes from baseline in the total SOFA score at Hour 3 and Hour 48 are shown in Table 41. The screening mean total SOFA score was 12.7 (median 13) in the placebo arm and 11.8 (median 12) in the LJPC-501 arm. At Hour 3, there was no change to a slight worsening of the total SOFA scores in both treatment arms as demonstrated by slight increases in the mean total SOFA scores in both treatment arms, no change in the median total SOFA score in the placebo arm, and a worsening of the median total SOFA score in the LJPC-501 arm (i.e., 12 to 13). This slight worsening trend in both treatment arms continued at Hour 48. At that timepoint, the mean total SOFA scores worsened by +1 compared to baseline in each treatment arm. There was no change in the median total SOFA score compared to baseline in each treatment arm.

The data showed that LJPC-501 did not improve the mean total SOFA score and did not attenuate the worsening of the mean total SOFA score over placebo following 48 hours of treatment. However, LJPC-501 improved the mean cardiovascular SOFA score over placebo at Hour 48 from baseline. The decreases in the NED were much more pronounced in the LJPC-501 arm relative to the smaller reduction in the NED in the placebo arm (see Table 30) as a consequence of catecholamine sparing in the LJPC-501 arm. Consequently, the improvement in cardiovascular SOFA over placebo was expected based on increasing the MAP to levels above 70 mmHg and reducing the dependency of maintaining the MAP on catecholamines (see Analysis of Condition).

Angiotensin II exerts its effect directly on the vascular wall smooth muscle cells as one of its mechanisms. It also acts on the RAAS by increasing fluid retention and on the CNS by increasing ADH production (reference: Mechanism of Action in this review). Thus, angiotensin II is a vasoconstrictor. If angiotensin II were included as a vasopressor in the list of vasopressors that determined the cardiovascular SOFA score, there would have been no change in this score due to the substitution of one vasopressor for another. The improvement in the cardiovascular SOFA score of LPC-501 over placebo at Hour 48 might have therefore been an artifact of the criteria defining the cardiovascular SOFA score. This, in addition to having no effect on total SOFA, raised a question about the clinical meaningfulness of this secondary endpoint and consequent utility as a claim.

Table 38: Secondary Efficacy Endpoint: Cardiovascular SOFA (Screening, Hour 3, and Hour 48)

Cardiovascular SOFA	Placebo (N=158)	LPC-501 (N=163)
Screening	N=158	N=163
Mean (SD)	4.00 (0.00)	4.00 (0.00)
Median (Range)	4 (no range)	4 (no range)
Hour 3	N=158	N=163
Mean (SD)	3.99 (0.11)	3.87 (0.55)
Median (Range)	4 (3—4)	4 (0—4)
Score Distribution		
0	0	2 (1%)
1	0	1 (0.6%)
2	0	0
3	2 (1%)	11 (7%)
4	155 (98%)	149 (91%)
4 (last observation carried forward)	1 (0.6%)	0
Hour 48	N=158	N=163
Mean (SD)	2.72 (1.65)	2.25 (1.77)
Median (Range)	4 (0—4)	3 (0—4)
Score Distribution		
0	36 (23%)	54 (33%)
1	9 (6%)	12 (7%)
2	0	2 (1%)
3	31 (20%)	30 (18%)
4	51 (32%)	44 (27%)
4 (last observation carried forward)	2 (1%)	0
4 (worst case, death)	29 (18%)	21 (13%)

Source: Table 14.2.2.1.1, LJ501-CRH01 CSR

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Table 39: Secondary Efficacy Endpoint: Cardiovascular SOFA Change from Baseline

Cardiovascular SOFA	Placebo (N=158)	LJPC-501 (N=163)
Change from Screening to Hour 3	N=158	N=163
Mean (SD)	-0.01 (0.11)	-0.13 (0.55)
Median (Range)	0 (-1—0)	0 (-4—0)
p-value (van Elteren Wilcoxon)	0.002	
Change from Screening to Hour 48		
Mean (SD)	-1.28 (1.65)	-1.75 (1.77)
Median (Range)	0 (-4—0)	-1 (-4—0)
p-value (van Elteren Wilcoxon)	0.013	

Source: Table 14.2.2.1.1, LJ501-CRH01 CSR

Table 40: Secondary Efficacy Endpoint: Total SOFA (Screening, Hour 3, and Hour 48)

Total SOFA	Placebo (N=158)	LJPC-501 (N=163)
Screening	N=158	N=158
Mean (SD)	12.72 (3.31)	11.77 (2.84)
Median (Range)	13 (5—21)	12 (5—18)
Hour 3	N= 158	N=163
Mean (SD)	13.18 (3.31)	12.53 (3.01)
Median (Range)	13 (no range reported)	13 (no range reported)
Hour 48	N=158	N=163
Mean (SD)	13.76 (6.70)	12.69 (6.03)
Median (Range)	13.5 (1—24)	11.0 (2—24)

Source: Table 14.2.2.2.1, LJ501-CRH01 CSR

Table 41: Secondary Efficacy Endpoint: Total SOFA Change from Baseline

Total SOFA	Placebo (N=158)	LJPC-501 (N=163)
Change from Screening to Hour 3	N=158	N=158
Mean (SD)	0.47 (1.82)	0.81 (1.93)
Median (Range)	0 (-3—7)	1 (-6—7)
p-value (van Elteren Wilcoxon)	0.136	
p-value (general linear model)	0.254	
Change from Screening to Hour 48	N=158	N=158
Mean (SD)	1.04 (5.34)	1.05 (5.50)
Median (Range)	0 (-9—16)	0 (-10—15)
p-value (van Elteren Wilcoxon)	0.9755	
p-value (general linear model)	0.4901	

Source: Table 14.2.2.2.1, LJ501-CRH01 CSR

Dose/Dose Response

The clinical development strategy did not include a standard dose-response analysis. The dose selection for initiating treatment was based on an antecedent pilot study where the dose in that study appeared to be efficacious. Doses subsequent to the initial dose in the Phase 3 study were based on a titration-to-effect strategy towards achieving the target MAP. Groups of subjects were identified as receiving “maximum doses” after titration began from the initial 20 ng/kg/min. The Applicant analyzed the responder rate for subgroups of subjects who were titrated to specific doses within the protocol allowed range. This analysis was verified by review of the data listings and production table, and is shown in Table 42. One subject received a “maximum dose” of 10 ng/kg/min following titration. This subject achieved the target MAP (i.e., 100% responder rate at this maximum dose). The majority of subjects met the primary efficacy endpoint at the dose of 20 ng/kg/min where 92 of 102 subjects achieved the target MAP. Eight (8) of 10 subjects achieved the target MAP at the dose of 30 ng/kg/min. The highest dose was 150 ng/kg/min where only 1 of 5 subjects at this dose achieved the target MAP. In total, 114 of 163 mITT subjects (70%) in the LJPC-501 arm met the target MAP at the various doses within the pre-specified dose range. The starting dose of 20 ng/kg/min appeared to be an efficacious dose.

Table 42: Response Rate to Subgroups of Maximum Doses of LJPC-501

Maximum Dose Subgroups of LJPC-501 (ng/kg/min)	Number of Subjects in Maximum Dose Subgroup	Number of Responders at Hour 3
	<i>Total N = 163</i>	<i>n =114 (70%)</i>
10	1	1 (100%)
20	102	92 (90%)
30	10	8 (80%)
40	4	2 (50%)
50	6	3 (50%)
60	2	1 (50%)
70	5	0
80	7	5 (71%)
90	4	1 (25%)
100	1	0
110	1	0
120	4	0
130	1	0
139.1	1	0
140	2	0
150	5	1 (20%)
180	1	0
200	6	0

Source: Table 14.3.1.5, Listing 16.2.5.1, Listing 16.2.6.1.1, LJ501-CRH01

Durability of Response

As illustrated in Table 35 and Table 36, there was a significant difference between the LJPC-501 arm and the placebo arm in achieving the primary efficacy endpoint for the 3 hours where catecholamines and vasopressin remained constant. Beyond 3 hours, the trial objective was to examine a catecholamine sparing effect in maintaining the MAP. Therefore, there was no difference between placebo and LJPC-501 in the MAP because of the dose-changing impact of background catecholamine treatment. The durability of response was therefore not formally tested.

Persistence of Effect

There was no test of persistence for the primary efficacy endpoint. There was no expectation of efficacy in maintaining MAP after discontinuation of LJPC-501. Persistence of normalized MAP would have been more likely attributed to treating the cause of the high-output shock.

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However, there appeared to be persistence in a mortality trend benefiting the LJPC-501 arm (see next section: Additional Analyses Conducted on the Individual Trial).

Additional Analyses Conducted on the Individual Trial

A pre-specified exploratory endpoint was mortality at 7 days and 28 days.

The cumulative mortality rate in each treatment arm from Day 1 to Day 7 in the mITT population is shown in Table 43. The Kaplan-Meier plot of mortality to Day 7 is shown in Figure 9. At Day 7, the mortality rate in the placebo arm was 35% and the mortality rate in the LJPC-501 arm was 29%. The hazard ratio (95% CI) was 0.78 (0.53—1.16) with a p-value of 0.22. The empirical trend towards a mortality benefit was evident on Day 1 and was consistent for subgroups based on demographic characteristics shown in the Forrest Plot (Figure 10) and baseline disease characteristics shown in the Forrest Plot (Figure 11). However from Figure 11, point estimates showed that a dose of LJPC-501 ≥ 20 ng/kg/min at 30 minutes favored placebo over this dose with respect to 7-day mortality. A history of taking angiotensin receptor blockers also favored placebo over LJPC-501 with respect to 7-day mortality. Treatment and demographic /baseline characteristics were investigated in a multivariate proportional hazards model of mortality to Day 7. The results are shown in Table 44. Treatment with LJPC-501 did not have a significant association with 7-Day mortality. The variables that did have a significant association with 7-Day mortality included a baseline MAP < 65 mmHg, baseline APACHE II score > 30 , enrollment in the US/Canada, chest x-ray showing ARDS, and a baseline NED ≥ 0.5 ug/kg/min the latter being very significant ($p < 0.0001$).

The cumulative mortality rate in each treatment arm to Day 28 in the mITT population is shown in Table 45. The Kaplan-Meier plot of mortality to Day 28 is shown in Figure 12. At Day 28, the mortality rate in the placebo arm was 54% and the mortality rate in the LJPC-501 arm was 46%. The hazard ratio (95% CI) was 0.78 (0.57—1.07) with a p-value of 0.12. The empirical trend towards a mortality benefit was evident on Day 1 and was consistent for subgroups based on demographic characteristics shown in the Forrest Plot (Figure 13) and baseline disease characteristics shown in the Forrest Plot (Figure 14). However from Figure 14, point estimates showed that a dose of LJPC-501 ≥ 20 ng/kg/min at 30 minutes slightly favored placebo over this dose with respect to 28-day mortality. A history of taking angiotensin receptor blockers also favored placebo over LJPC-501 with respect to 28-day mortality. Treatment and demographic /baseline characteristics were investigated in a multivariate proportional hazards model of mortality to Day 28. The results are shown in Table 46. As with the 7-day mortality, treatment with LJPC-501 did not have a significant association with 28-Day mortality. Similar to the 7-day mortality results, the variables that did have a significant association with 28-Day mortality included age ≥ 65 years, a baseline MAP < 65 mmHg, baseline APACHE II score > 30 , enrollment in the US/Canada, chest x-ray showing ARDS, and a baseline NED ≥ 0.5 ug/kg/min.

The variables that had an adverse effect on mortality for both Day 7 and Day 28 (i.e., age, MAP < 65 mmHg, APACHE II > 30, NED levels $\geq$ 0.5ug/kg/min-even $\geq$ 2 ug/kg/min in some publications) were known to increase the risk of mortality based on published studies. The analyses in this trial were consistent with these known findings.

The higher risk of death associated with enrollment in the US/Canada compared to Europe / Australia / New Zealand might be associated with the medical management of these subjects and the baseline clinical status. The baseline NEDs were similar between all regions but the use of vasopressin was overwhelmingly higher in the US/Canada region (see Table 20). The need for rescue therapy with vasopressin was generally associated with mortality rates greater than 50% (Bassi, 2013). This finding by itself might account for the finding of a higher mortality risk by virtue enrollment in the US/Canada region. APACHE II scores greater than 30 occurred at a higher frequency in the US/Canada region compared to the other regions. The MELD scores were also slightly higher in the US/Canada region (see Table 22). These differences might have contributed to the increased risk of mortality due to enrollment in the US/Canada region.

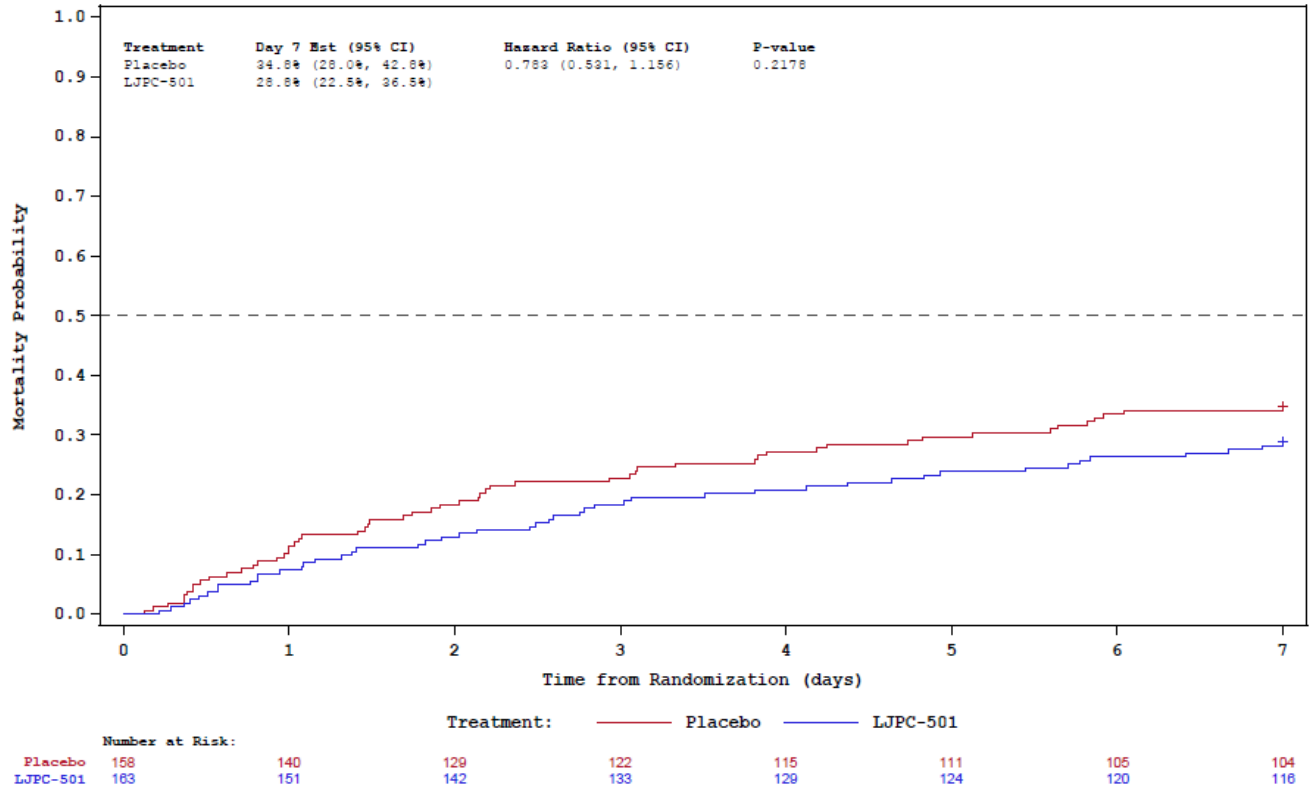
Table 43: Cumulative Mortality to Day 7 (mITT population)

Mortality in mITT population (Day #)	Placebo (N=158) Percent Accumulative Death	LJPC-501 (N= 163) Percent Accumulative Death
Day 1	11%	7%
Day 2	18%	13%
Day 3	23%	18%
Day 4	27%	21%
Day 5	30%	24%
Day 6	34%	26%
Day 7	35%	29%

Source: Table 14.2.3.1.1, LJ501-CRH01

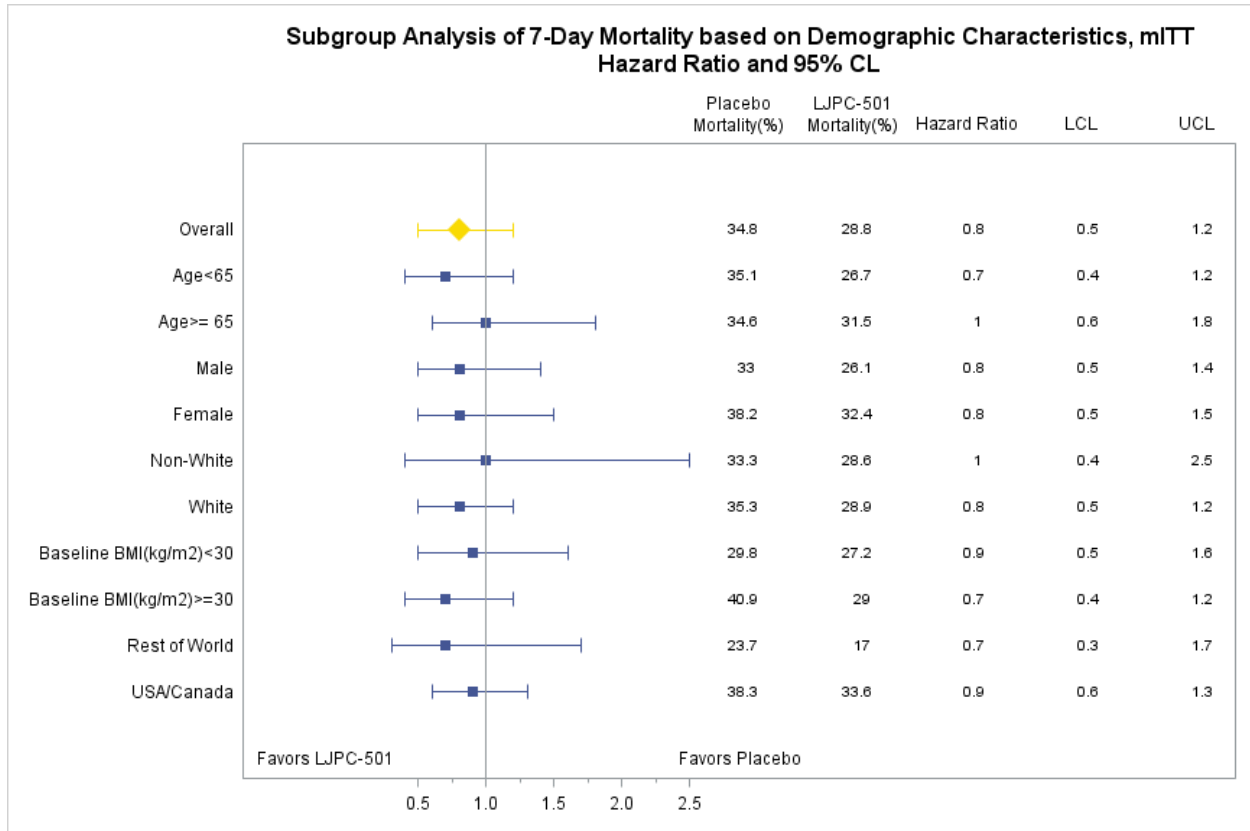
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Figure 9: Kaplan-Meier Plot of Mortality to Day 7 (mITT population)



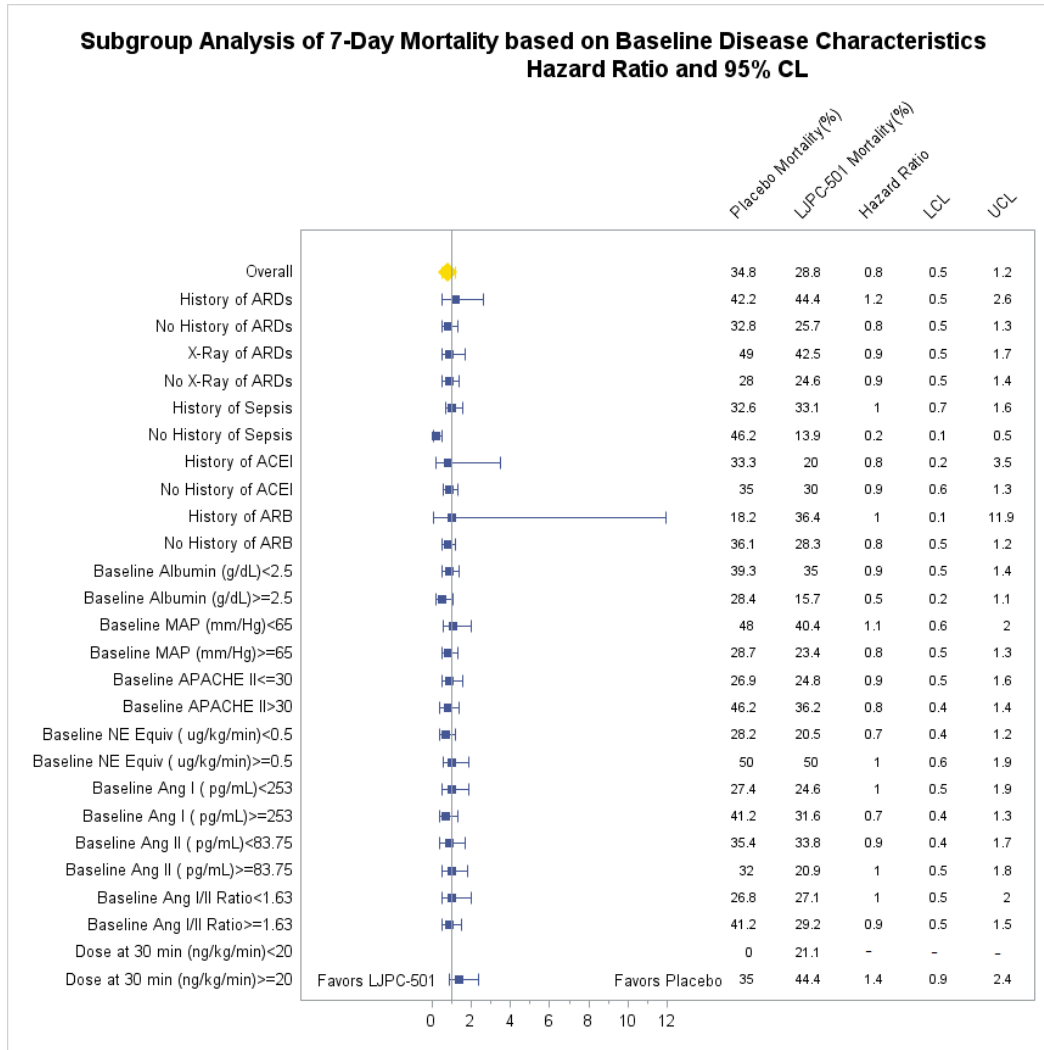
Source: Figure 14.2.6.4.5, LJ501-CRH01 verified by Office of Biostatistics, FDA

Figure 10: Forrest Plot-7-Day Mortality based on Demographic Characteristics



Source: Office of Biostatistics, FDA

Figure 11: Forrest Plot-7-Day Mortality based on Baseline Disease Characteristics



Source: Office of Biostatistics, FDA. Note: the term “history of” was defined as present within the 7 days prior to and including the day of randomization.

Table 44: Mortality to Day 7: Multivariate Analysis (mITT population)

Covariate	Hazard Ratio (95% C I)	P-Value
Treatment with LJPC-501	0.88 (0.58—1.34)	0.56
Age $\geq$ 65 years	1.36 (0.90—2.07)	0.15
Male sex	0.75 (0.50—1.14)	0.18
Baseline MAP < 65 mmHg	1.75 (1.15—2.66)	0.01
Baseline APACHE Score > 30	1.74 (1.14—2.65)	0.01
US/Canada	1.99 (1.13—3.50)	0.02
Chest X-Ray with ARDS	1.73 (1.13—2.66)	0.01
Baseline Ned > 0.5 ug/kg/min	2.45 (1.61—3.73)	<0.00001

Source: Table 14.2.9.4.1, LJ501-CRH01

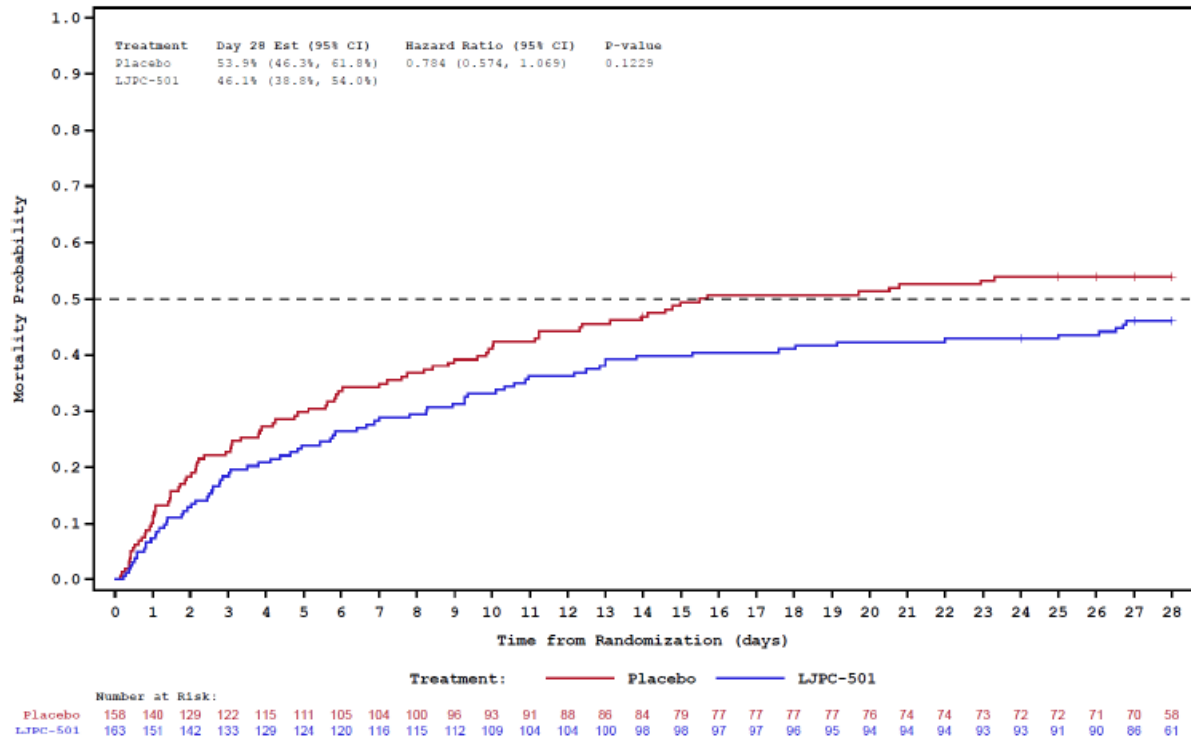
Table 45: Cumulative Mortality to Day 28 (mITT population)

Mortality in mITT population (Day #)	Placebo (N=158) Percent Accumulative Death	LJPC-501 (N= 163) Percent Accumulative Death
Day 7	35%	29%
Day 14	47%	40%
Day 21	53%	42%
Day 28	54%	46%

Source: Table 14.2.3.2.1, LJ501-CRH01

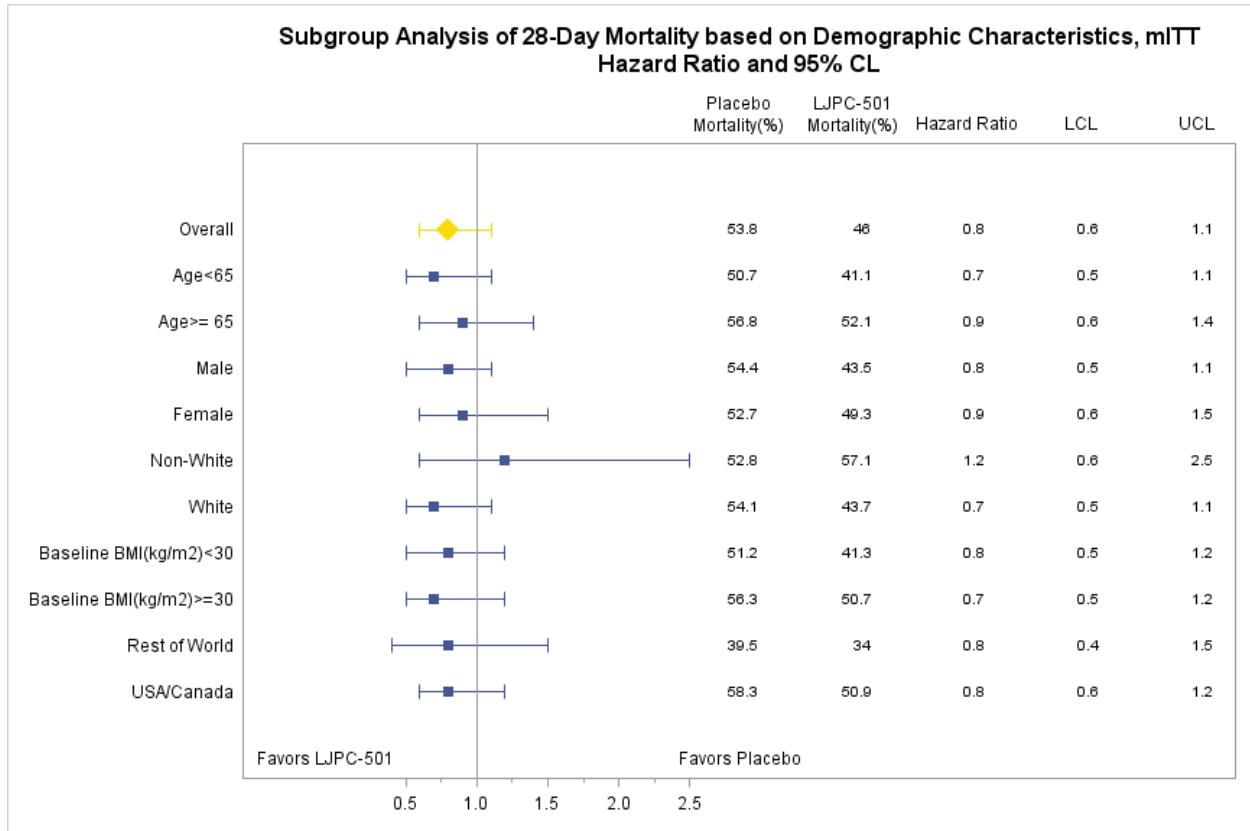
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Figure 12: Kaplan-Meier Plot of Mortality to Day 28 (mITT population)



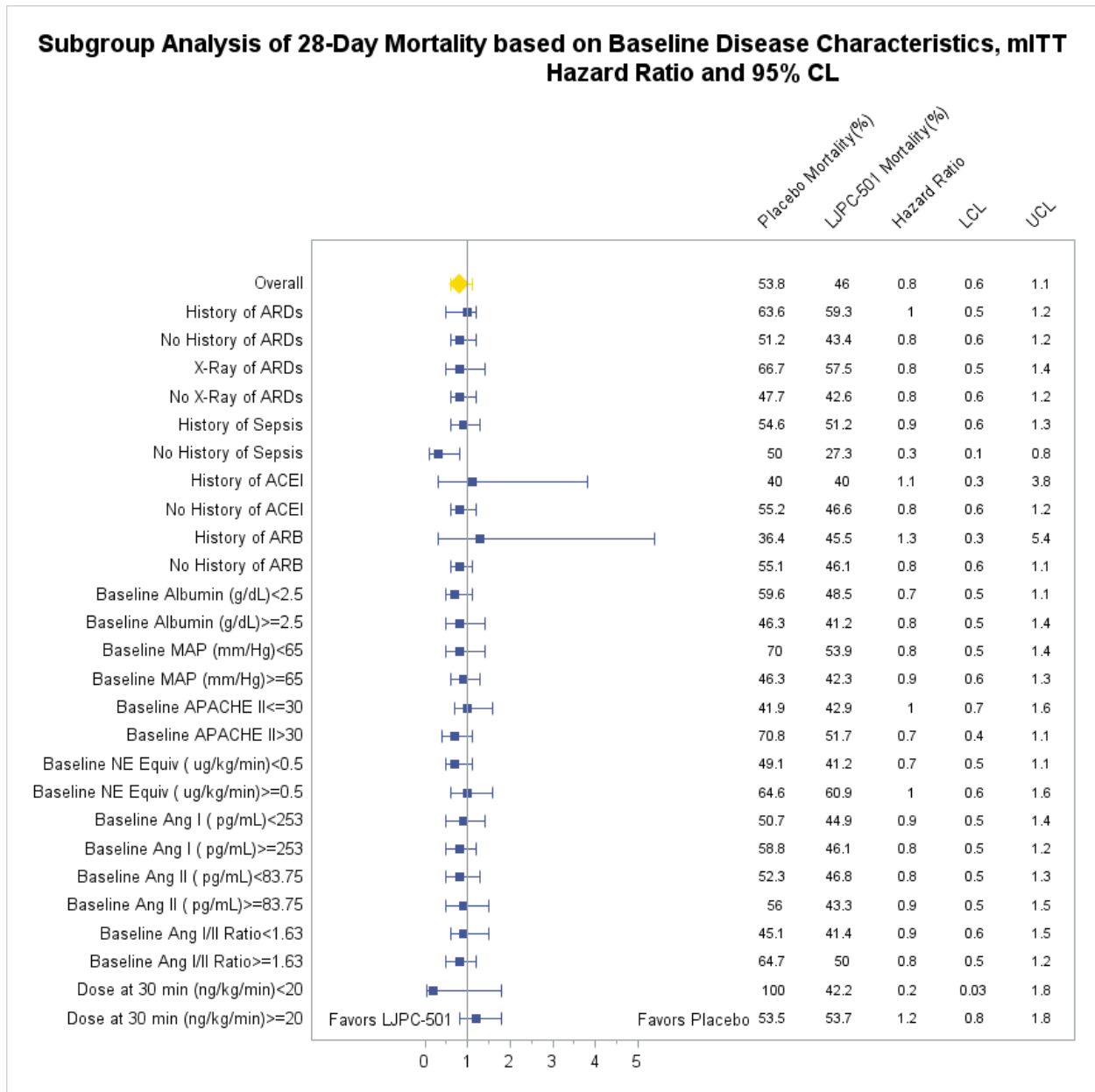
Source: Figure 14.2.6.4.6, LJ501-CRH01 verified by Office of Biostatistics, FDA

Figure 13: Forrest Plot-28-Day Mortality based on Demographic Characteristics



Source: Office of Biostatistics, FDA

Figure 14: Forrest Plot-28-Day Mortality based on Baseline Disease Characteristics



Source: Office of Biostatistics, FDA

Table 46: Mortality to Day 28: Multivariate Analysis (mITT population)

Covariate	Hazard Ratio (95% C I)	P-Value
Treatment with LJPC-501	0.89 (0.64—1.24)	0.49
Age $\geq$ 65 years	1.44 (1.04—2.01)	0.03
Male sex	0.90 (0.65—1.26)	0.55
Baseline MAP < 65 mmHg	1.61 (1.15—2.26)	0.06
Baseline APACHE Score > 30	1.67 (1.19—2.33)	0.003
US/Canada	1.80 (1.18—2.76)	0.007
Chest X-Ray with ARDS	1.58 (1.10—2.25)	0.01
Baseline Ned > 0.5 ug/kg/min	1.77 (1.25—2.51)	0.001

Source: Table 14.2.9.6.1

The effect of exogenous angiotensin II on the levels of endogenous angiotensin I and angiotensin II was examined. There were no differences in serum endogenous angiotensin II at baseline or Hour 3 or changes from baseline to Hour 3 between the 2 treatment arms. Treatment with LJPC-501 had a larger effect compared to placebo on decreasing angiotensin I, with a mean decrease in angiotensin I of 32% from baseline in the LJPC-501 treatment arm at Hour 3. The potential mechanism for this observation was the negative feedback by angiotensin II on renin release from the juxtaglomerular cells. The data suggested that this mechanism had no effect on the primary efficacy endpoint.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Not applicable because there was only one trial.

7.1.2. Secondary and Other Endpoints

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Not applicable because there was only one trial.

7.1.3. **Subpopulations**

Not applicable because there was only one trial.

7.1.4. **Dose and Dose-Response**

Not applicable because there was only one trial.

7.1.5. **Onset, Duration, and Durability of Efficacy Effects**

Not applicable because there was only one trial.

7.2. **Additional Efficacy Considerations**

7.2.1. **Considerations on Benefit in the Postmarket Setting**

We expect the benefit/risk profile in the post-market setting to be like what was shown in the pivotal trial. Patients with distributive shock will be admitted to hospitals with an intensive care unit that will contain the requisite diagnostic and monitoring techniques used to assess the blood pressure effects of LJPC 501.

7.2.2. **Other Relevant Benefits**

Not applicable.

7.3. **Integrated Assessment of Effectiveness**

LJPC-501 was shown to be efficacious in raising the MAP to target levels: ≥ 75 mmHg or a 10 mmHg increase in baseline MAP. For subjects whose baseline MAP was < 65 mmHg (38% of the mITT population), thereby placing these patients at high risk of death, raising the MAP to target levels attenuated that risk. The efficacy of LJPC-501 was demonstrated for all demographic and disease characteristic subgroups.

The data from this trial did not conclusively demonstrate a clinical benefit other than raising the blood pressure. There was no change in the total SOFA score. The improvement in the cardiovascular SOFA score was insufficient to change the total SOFA score and was probably due to the substitution of a vasoconstrictor (i.e. catecholamine) listed on the cardiovascular

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SOFA equation with a vasoconstrictor (i.e., angiotensin II) not listed on the cardiovascular SOFA equation. The clinical meaningfulness of this substitution is questionable because there is no data to suggest that angiotensin II is a safer vasoconstrictor than catecholamines. The argument that angiotensin II utilizes other blood pressure raising mechanisms (i.e., RAAS and ADH stimulation) does not offset the direct vasoconstrictive property of angiotensin II.

There was a statistically insignificant but small mortality benefit trend for LJPC-501 over placebo that was evident at Day 7 and at Day 28. This observation was consistent for all demographic and disease characteristic subgroups.

The benefit observed in this trial could be extrapolated to patients with distributive shock who are not refractory to catecholamine therapy. This is based on the direct vasoconstrictive properties of angiotensin II similar to catecholamines. If treating patients with distributive shock not refractory to catecholamines, I suggest the starting dose of 20 ng/kg/min followed by rapid titration every 5 minutes until the target MAP of 75 mmHg or 10 mmHg above baseline is achieved.

8 Review of Safety

Safety Review Approach

The pivotal phase 3 trial, LJ501-CRH01, serves as the primary source of safety data for this application. CDER Jumpstart service was requested for data fitness and safety exploratory analyses. Safety analyses used the safety set in LJ501-CRH01— all patients who took at least one dose of study drug (N = 321). The safety review focused on characterizing the risk of the known adverse effects of vasopressors including arrhythmia and ischemia/vasoconstriction as well as identifying potential safety signals by searching AE data using all MedDRA hierarchical terms and MedDRA SMQs. AEs/SAEs were reported up to Day 28 in LJ501-CRH01. Additional exploratory analyses including incidence of on-treatment AEs (last treatment + 1 day), evaluation of important and relevant laboratory parameters were performed for the safety topics of interest.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population came from two clinical studies (see [Table 47](#)):

Phase 1/2 study (LJPC-501-CS-5001, N =6) in patients with hepatorenal syndrome (HRS)

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Phase 3 study (LJ501-CRH01, N = 321) in patients with CRH

Due to the size difference and heterogeneity of the two studies, the primary safety analyses summarized in the following sections were based on data from the phase 3 study alone.

Table 47 Safety Population, Size and Denominators

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review N=327 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=163)	Active Control (n= 0)	Placebo (n=158)
Normal Volunteers	0	NA	0
Controlled trials conducted for this indication ²	163	NA	158
All other than controlled trials conducted for this indication ³	0	0	0
Controlled trials conducted for other indications ⁴	6	0	0

Duration of exposure was summarized in [Figure 15](#) and [Table 48](#). Overall, the two arms had a similar duration of exposure (the medium duration was 48 hours for both arms) but the LJPC-501 arm had a higher percent of subjects with a longer exposure. There were 13 subjects in the LJPC-501 arm with study drug exposure $\geq$ 72 hours compared to 0 subject in the placebo arm.

Figure 15 Duration of Exposure by Treatment Arm in LJ501-CRH01

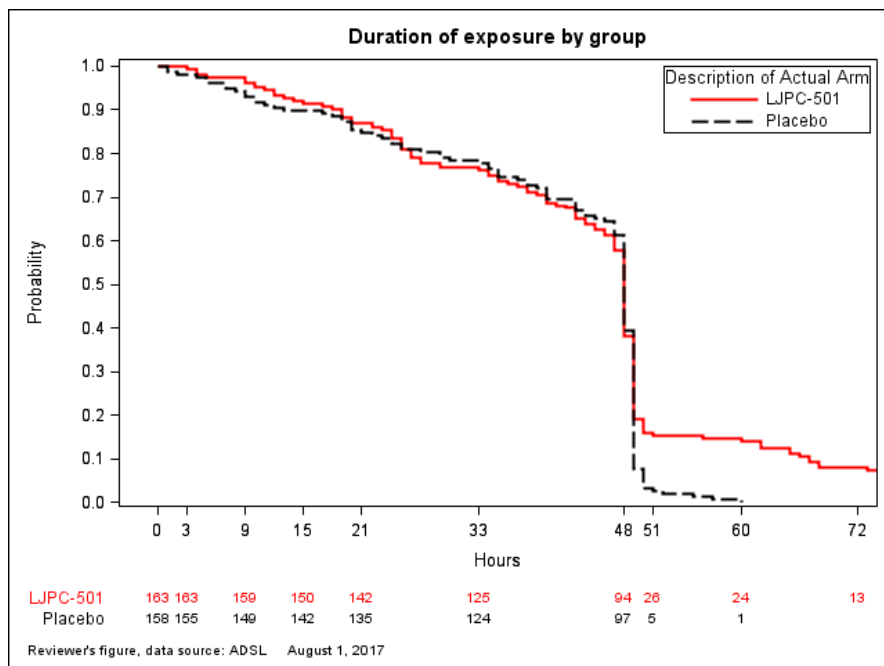


Table 48 Duration of Exposure by Arm and Selected Categories in LJ501-CRH01

	Number of patients exposed to Study Drug			
	>0 to <45 hours	45 to <51 hours	51 to <72 hours	≥72 hours
LJPC-501	N= 61 (37.4%)	N= 77 (47.2%)	N= 12 (7.4%)	N= 13 (8.0%)
Placebo	N = 54 (34.1%)	N =99 (62.7%)	N = 5 (3.2%)	N = 0

Source: Table 64 in the CSR

Reviewer's Comment: Study drug was intended to be down-titrated from Hour 3 to Hour 48 and discontinued at Hour 48. However, the protocol allows an optional re-initiation of study drug at the investigator's discretion if discontinuation at Hour 48 resulted in a CV SOFA score of 4. The higher percentage of patients with treatment after 48 hours in the LJPC-501 arm compared to the placebo arm should have minimal impacts on primary safety analyses discussed in the following sections.

8.2.2. Relevant characteristics of the safety population:

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The safety population (subjects who received at least one treatment) is the MITT population. See [Table 15](#) in [section 6.1.2](#) for characteristics of the safety population.

8.2.3. Adequacy of the safety database:

The size of safety database is acceptable and the characteristics of patients in the phase 3 trial are generally adequate to represent the indicated US patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Jumpstart service provided a data fitness evaluation. The overall data and submission quality is good. AE coding was evaluated using the Jumpstart output in which matching score was calculated comparing verbatim term to coded preferred term (PT). There were 305/935 terms (33%) with a matching score < 80 between the verbatim term and PT (a score of 100 indicates a direct match) and I evaluated these terms to look for any incorrect and/or irregular coding (see [Appendix 13.3](#)). The overall coding is reasonable.

8.3.2. Categorization of Adverse Events

The applicant categorized AEs/SAEs by systemic organ class (SOC) and preferred term (PT) using MedDRA version 18.0. The applicant predefined the known vasopressor toxicities: arrhythmias and vasoconstriction as the adverse events of special interest (AESIs) in LJ501-CRH01. The definition of AESIs was described in the protocol and statistical analysis plan.

The applicant defined arrhythmia using the MedDRA SMQ Arrhythmias narrow search and QT prolongation. For ischemia and vasoconstriction, the applicant grouped relevant PTs across different SOCs (see [Appendix 13.4](#)). AEs were captured from the first dose of study drug through the End-of Study Visit (EOS, Day 7). AESIs and SAEs between Day7/EOS and Day 28 were collected by a follow-up phone call on Day 28.

Reviewer's comment: The applicant's method to categorize AESIs is reasonable. However, instead of aggregating all the relevant terms based on two safety topics of interest, the applicant regrouped PTs and reported these events based on cardiac events and ischemic events from other SOCs. This approach is ok but I found that it is more straightforward to evaluate safety signals by reporting all the relevant terms under the topics of interest, which is the approach I used to evaluate AESIs (see [section 8.4](#)). AESIs were followed up until Day 28. Events that occurred long after the discontinuation of the study drug were included in the applicant's

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analyses. I also performed analyses to evaluate on-treatment AESIs (last treatment + 1 day) (see [section 8.4](#)).

8.3.3. Routine Clinical Tests

See [Table 11](#) for safety assessments by study period. Briefly, AE/SAE was evaluated at every time point: screening, Day 1 (0 to 3 hours), Day 1 (3 to 24 hours), Day 2, Days 3 to 6, and Day 7 (End of study). A phone call or a chart-review was conducted on Day 28 (follow-up visit) to capture reportable safety events occurred between end of study and Day 28. Laboratory chemistries and hematology were collected at screening, Day 1 at 3 hours and Day 2 at 48 hours. ECG assessments was performed at screening and on Day 2 at 48 hours.

Reviewer's comment: Overall, the safety assessments in LJ501-CRH01 were acceptable considering the duration of treatment and short half-life of LJPC-501. However, some patients might have study drug exposure greater than 2 days, the laboratory measurements were only collected up to Day 2. Potential long term effect of LJPC-501 on laboratory data (e.g. serum creatinine change) was not known in LJ501-CRH01.

8.4. Safety Results

Deaths

The mortality results on Day 7 and Day 28 were discussed in the [section 6.1.2](#). Overall, there is a mortality trend in favor of the LJPC-501 arm. Through the end of follow-up period, there were a total of 76 (47%) and 85 (53.8%) deaths in the LJPC-501 and placebo arm, respectively (these results were consistent with the efficacy findings¹). Multi-organ failure was the most common fatal SAE in both arms (14.1% vs. 13.3% in the LJPC-501 vs. placebo arm, respectively). In general, the frequency and type of SAEs resulting in death are similar between arms ([Table 49](#)).

¹ The 28 mortality results in efficacy reported 75 deaths in the LJPC-501 arm and 85 deaths in the placebo arm. One additional death in the LJPC-501 arm occurred outside the pre-specified window for the efficacy analysis.

Table 49 Most Frequent Deaths Due to SAEs in LJ501-CRH01

SAEs with fatal outcome reported in >1% of subjects*	LJPC-501 (N=163)	Placebo (N=158)
Any Death due to SAE	76 (46.6%)	85 (53.8%)
Multiple organ failure	23 (14.1%)	21 (13.3%)
Septic shock	15 (9.2%)	9 (5.7%)
Respiratory failure	6 (3.7%)	6 (3.8%)
Cardiac arrest	3 (1.8%)	6 (3.8%)
Sepsis	3 (1.8%)	2 (1.3%)
Cardio-respiratory arrest	2 (1.2%)	4 (2.5%)
Cardiogenic shock	2 (1.2%)	4 (2.5%)
Pneumonia	2 (1.2%)	0 (0.0%)

*fatal SAEs with a frequency of $\geq 1\%$ in the LJPC-501 arm. Source: Table 72 in the CSR

See [section 6.1.2](#) for the discussions on the mortality results on Day 7 and Day 28. Overall, there is a mortality trend in favor of the LJPC-501 arm.

Reviewer's comment: Mortality results are reassuring from safety perspective.

8.4.2. Serious Adverse Events

The incidence of SAEs was similar in the two treatment arms (61% for LJPC-501 vs. 67% for placebo) ([Table 50](#)). Most SAEs were related to the underlying disease (i.e. septic shock/ sepsis) and expected in this patient population. There was a slightly higher incidence of septic shock SAE in the LJPC-501 vs placebo arm (11.0% vs. 6.3%). SAEs for adverse event of special interest (AESI) are discussed in [section 8.4.4](#); no other safety signals were observed from SAEs.

Table 50 Most Frequent SAEs in LJ501-CRH01

SAEs reported in >2% of Subjects*	LJPC-501 (N=163)	Placebo (N=158)
Any SAE	99 (60.7%)	106 (67.1%)
Multi-organ failure	25 (15.3%)	23 (14.6%)
Septic shock	18 (11.0%)	10 (6.3%)
Respiratory failure	8 (4.9%)	11 (7.0%)
Cardiac arrest	7 (4.3%)	9 (5.7%)
Atrial fibrillation	5 (3.1%)	5 (3.2%)
Acute respiratory failure	5 (3.2%)	3 (1.8%)
Cardio-respiratory failure	5 (3.2%)	3 (1.8%)
Hypotension	5 (3.1%)	3 (1.9%)
Peripheral ischemia	5 (3.1%)	3 (1.9%)
Ventricular tachycardia	5 (3.1%)	3 (1.9%)

* SAEs with a frequency of $\geq 2\%$ in the LJPC-501 arm. Source: Table 73 in the CSR

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to permanent discontinuation of study drug were reported in 14.1% in the LJPC-501 arm and 21.5% in the placebo arm. There were only 5 AEs reported for more than 1 subject in either treatment arm (Table 51). The most frequent AE resulting in treatment discontinuation was septic shock in the LJPC-501 arm (4.9%) and multiorgan failure (3.8%) in the placebo arm.

Table 51 Most Frequent AEs Leading to Treatment Discontinuation

AEs leading to treatment discontinuation in 2 or more subjects	LJPC-501 (N=163)	Placebo (N=158)
Any AE leading to treatment discontinuation	23 (14.1%)	34 (21.5%)
Multiple organ failure	6 (3.7%)	6 (3.8%)
Septic shock	8 (4.9%)	4 (2.5%)
Cardiogenic shock	2 (1.2%)	4 (2.5%)
Cardiac arrest	0 (0.0%)	5 (3.2%)
Peripheral ischemia	1 (0.6%)	1 (0.6%)

Source: Table 75 in the CSR

8.4.4. Significant Adverse Events

The applicant predefined two AESIs based on the known vasopressor-related toxicities: arrhythmia and ischemia/vasoconstriction. The search for these events using MedDRA SMQ and grouped PTs are summarized in the below sections.

8.4.4.1 Arrhythmia-related AEs and SAEs

The incidence of arrhythmia-related AEs and SAEs was similar in the two arms ([Table 52](#)). Most of these events were classified as recovered/resolved by the end of the study. There were 6 fatal cases in the LJPC-501 arm and 10 fatal cases in the placebo arm ([Table 53](#)). All the fatal events were due to cardiac arrest or cardio-respiratory arrest except one fatal event of ventricular tachycardia in the LJPC-501 arm.

Table 52 Arrhythmia-related AEs and SAEs during the study period (up to Day 28) in LJ501-CRH01

SMQ/Preferred term	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Cardiac arrhythmias (SMQ, broad term)	51 (31.3%)	60 (38.0%)	22 (13.5%)	23 (14.6%)
Atrial fibrillation	22 (13.5%)	21 (13.3%)	5 (3.1%)	5 (3.2%)
Bradycardia	7 (4.3%)	11 (7.0%)	1 (0.6%)	2 (1.3%)
Cardiac arrest	7 (4.3%)	9 (5.7%)	7 (4.3%)	9 (5.7%)
Ventricular tachycardia	5 (3.1%)	8 (5.1%)	5 (3.1%)	3 (1.9%)
Tachycardia	8 (4.9%)	4 (2.5%)	2 (1.2%)	0 (0.0%)
Cardio-respiratory arrest	3 (1.8%)	5 (3.2%)	3 (1.8%)	5 (3.2%)
Supraventricular tachycardia	3 (1.8%)	4 (2.5%)	1 (0.6%)	4 (2.5%)
Atrial flutter	2 (1.2%)	5 (3.2%)	0 (0.0%)	0 (0.0%)
Electrocardiogram QT prolonged	1 (0.6%)	4 (2.5%)	0 (0.0%)	0 (0.0%)
Sinus tachycardia	3 (1.8%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Ventricular extrasystoles	1 (0.6%)	3 (1.9%)	0 (0.0%)	0 (0.0%)
Arrhythmia	3 (1.8%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Ventricular fibrillation	2 (1.2%)	0 (0.0%)	2 (1.2%)	0 (0.0%)
Bundle branch block right	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulseless electrical activity	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Atrioventricular block	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Sinus arrest	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atrial tachycardia	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Electrocardiogram QRS complex prolonged	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Nodal arrhythmia	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)

*The results are similar using the narrow terms for Cardiac arrhythmia (SMQ)
 Reviewer's table data source: ADSL & ADAE

Table 53 Outcome of arrhythmia-related events in LJ501-CRH01

Outcome of AE	LJPC-501 N = 163	Placebo N=158
Cardiac arrhythmias (SMQ, broad term)	51 (31.3%)	60 (38.0%)
Recovered/Resolved	43 (26.4%)	48 (30.4%)
Fatal	6 (3.7%)	10 (6.3%)
Recovered/Resolved with Sequelae	2 (1.2%)	6 (3.8%)
Recovering/Resolving	3 (1.8%)	2 (1.3%)
Not Recovered/Not Resolved	3 (1.8%)	1 (0.6%)
Unknown	1 (0.6%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

Because the treatment duration was short (medium duration of 48 hours) and AESIs were reported up to day 28, it might introduce some noises to include events that occurred long after the end of treatment. Therefore, the search for on-treatment AEs, defined as AEs occurred within 1 day after the end of treatment (last treatment + 1 day) was performed (Table 54). The on-treatment results did not reveal any safety signal of concern.

Table 54 Arrhythmia-related AEs and SAEs (on-treatment events*) in LJ501-CRH01

SMQ/Preferred term	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Cardiac arrhythmias (SMQ, broad term)	37 (22.7%)	50 (31.6%)	10 (6.1%)	17 (10.8%)
Cardiac arrhythmias (SMQ, narrowed term)	32 (19.6%)	34 (21.5%)	9 (5.5%)	7 (4.4%)

*event occurred within last treatment + 1 day

Reviewer's table data source: ADSL & ADAE

Subgroup analyses for arrhythmia-related AEs were performed based on age, sex, baseline MAP (<65 vs. ≥ 65 mmHg), baseline APACHE II (≤ 30 vs. >30), and baseline NED dose (<0.2 vs. ≥ 0.2 µg/kg/min). Overall, the arrhythmia results were consistent across subgroups (see Table 55).

Table 55 Subgroup analyses for arrhythmia-related AEs in LJ501-CRH01

	LJPC-501 N = 163	Placebo N=158
Age		
<65	31/90 (34%)	26/77 (34%)
≥65	20/73 (27%)	34/81 (42%)
Sex		
F	21/71 (30%)	18/55 (33%)
M	30/92 (33%)	42/103 (41%)
Baseline MAP		
<65	13/52 (25%)	23/50 (46%)
≥65	38/111 (34%)	37/108 (34%)
Baseline APACHE II		
≤30	28/105 (27%)	34/93 (37%)
>30	23/58 (40%)	26/65 (40%)
Baseline NED dose		
<0.5	34/117 (29%)	39/110 (35%)
≥0.5	17/46 (40%)	21/48 (44%)

Reviewer's table data source: ADSL & ADAE

8.4.4.2 Ischemia/vasoconstriction

The incidence of ischemia/vasoconstriction-related AEs and SAEs was similar in the two arms ([Table 56](#)). Most of these events were serious in nature. The outcome of these events was slightly worse in the LJPC-501 arm compared to the placebo arm ([Table 57](#)): less than half of these events in the LJPC-501 were fully recovered/resolved by the end of the study. There were 4 vs. 1 fatal cases in the LJPC-501 vs. placebo arm.

Table 56 Ischemia/vasoconstriction-related AEs and SAEs during the study period (up to Day 28) in LJ501-CRH01

Grouped AEs	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Ischemia/vasoconstriction AEs	17 (10.4%)	16 (10.1%)	14 (8.6%)	11 (7.0%)
Peripheral ischemia	7 (4.3%)	4 (2.5%)	5 (3.1%)	3 (1.9%)
Ischemic hepatitis	2 (1.2%)	4 (2.5%)	0 (0.0%)	1 (0.6%)
Acute myocardial infarction	2 (1.2%)	3 (1.9%)	2 (1.2%)	2 (1.3%)
Intestinal ischemia	1 (0.6%)	3 (1.9%)	1 (0.6%)	3 (1.9%)
Skin necrosis	1 (0.6%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Poor peripheral circulation	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Brain hypoxia	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Hypoxic-ischemic encephalopathy	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Ischemic stroke	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Cerebral infarction	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Vasospasm	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Cerebral ischemia	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Myocardial infarction	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Peripheral coldness	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

Table 57 Outcome of ischemia/vasoconstriction AEs in LJ501-CRH01

Outcome of AE	LJPC-501 N = 163	Placebo N=158
Ischemia/vasoconstriction AEs	17 (10.4%)	16 (10.1%)
Recovered/Resolved	8 (4.9%)	13 (8.2%)
Recovered/Resolved with Sequelae	3 (1.8%)	2 (1.3%)
Fatal	4 (2.5%)	1 (0.6%)
Recovering/Resolving	3 (1.8%)	0 (0.0%)
Not Recovered/Not Resolved	1 (0.6%)	1 (0.6%)
Unknown	1 (0.6%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

There were 4 patients who had an ischemia event in the central nervous system (CNS) in the LJPC-501 arm vs. 1 in the placebo arm ([Table 58](#)). Three out of the 4 events in the LJPC-501 arm resulted in a fatal outcome.

Table 58 Ischemia/vasoconstriction-related AEs in the central nervous system

Grouped AEs	AE	
	LJPC-501 N = 163	Placebo N=158
Ischemia/vasoconstriction AEs in the CNS	4 (2.5%)	1 (0.6%)
Brain hypoxia	1 (0.6%)	0 (0.0%)
Hypoxic-ischemic encephalopathy	1 (0.6%)	0 (0.0%)
Ischemic stroke	1 (0.6%)	0 (0.0%)
Cerebral infarction	1 (0.6%)	0 (0.0%)
Cerebral ischemia	0 (0.0%)	1 (0.6%)

*Highlighted PTs resulted in a fatal outcome Reviewer's table data source: ADSL & ADAE

Reviewer's comment: Ischemic events occurred in the CNS could result in serious or fatal outcomes. Although the small number of these events limit the interpretation of the data, the findings are nonetheless concerning. Some of these events might also be related to the risk of thrombosis (see section [8.4.5.2](#)).

This incidence of on-treatment ischemia/vasoconstriction-related events was similar between the arms and did not reveal additional safety concern ([Table 59](#)).

Table 59 ischemia/vasoconstriction AEs and SAEs (on-treatment events*) in LJ501-CRH01

Grouped AEs	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Ischemia/vasoconstriction AEs	13 (8.0%)	14 (8.9%)	8 (4.9%)	8 (5.1%)

*event occurred within last treatment + 1 day
 Reviewer's table data source: ADSL & ADAE

Subgroup analyses for ischemia/vasoconstriction-related AEs were performed based on age, sex, baseline MAP (<65 vs. ≥ 65 mmHg), baseline APACHE II (≤ 30 vs. >30), and baseline NED dose (<0.2 vs. ≥ 0.2 µg/kg/min)([Table 60](#)). In general, the incidence of ischemia/vasoconstriction was higher among patients who had worse medical conditions at baseline (i.e. baseline APACHE II >30, baseline NED dose ≥0.5) in both groups with the exception that a lower incidence in patients with baseline MAP <65 mmHg in the placebo arm. This observation is probably due to higher motility rate in this subgroup (70%). Overall, the results were consistent across the selected subgroups.

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Table 60 Subgroup analyses for ischemia/vasoconstriction AEs during the study period (up to Day 28) in LJ501-CRH01

Group	LJPC-501 N = 163	Placebo N=158
Age		
<65	9/90 (10%)	7/77 (9%)
≥65	8/73 (11%)	9/81 (11%)
Sex		
F	8/71 (11%)	6/55 (11%)
M	9/92 (10%)	10/103 (10%)
Baseline MAP		
<65	7/52 (13%)	4/50 (8%)
≥65	10/111 (9%)	12/108 (11%)
Baseline APACHE II		
≤30	9/105 (9%)	9/93 (9%)
>30	8/58 (14%)	7/65 (11%)
Baseline NED dose		
<0.5	9/117 (8%)	8/110 (7%)
≥0.5	8/46 (17%)	8/48 (17%)

Reviewer's table data source: ADSL & ADAE

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In addition to the safety topics of interest (see [section 8.4.4](#)), I also performed routine safety assessments for hypersensitivity reactions, liver toxicity and renal toxicity. Potential safety signals were also evaluated by searching AE data using all MedDRA hierarchical terms and SMQs. [Table 61](#) shows the results of these assessments. The incidence of AEs related to hypersensitivity, liver and renal toxicities was similar in the two treatment arms.

Table 61 Additional safety assessments of AEs during the study period (up to Day 28) in LJ501-CRH01

Safety assessment topics	LJPC-501 N = 163	Placebo N=158
Hypersensitivity (SMQ, broad) ^a - Stevens-Johnson syndrome	39 (23.9%) 1	36 (22.8%) 0
Drug related hepatic disorders- comprehensive search (SMQ) ^a	23 (14.1%)	21 (13.3%)
Acute renal failure (SMQ, broad) ^a	14 (8.6%)	18 (11.4%)
Notable imbalanced AEs^b		
Lactic acidosis (SMQ)	12 (7.4%)	1 (0.6%)
Embolic and thrombotic events (SMQ)	21 (12.9%)	5 (5.1%)
Psychiatric disorders (SOC)	21 (12.9%)	11 (7.0%)
Hemorrhage (SMQ, narrowed)	21 (12.9%)	12 (7.6%)
Fungal infection AEs	10 (6.1%)	2 (1.3%)

^a See [Appendix 13.5](#) for the completed list of the PTs in each SMQ ([Table 76](#) for hypersensitivity, [Table 77](#) for liver toxicity & [Table 78](#) for renal toxicity)

^b This table only lists imbalanced AEs where the magnitude of imbalance merit further discussion.

Reviewer's table data source: ADSL & ADAE

Reviewer's comment: LJPC-501 is metabolized rapidly in the plasma with a half-life of less than one minute. The metabolism of LJPC-501 (angiotensin II) is not dependent on hepatic or renal clearance. Thus, the potential for renal and liver toxicities might be minimal. However, LJPC-501 as a vasopressor could have excessive vasoconstrictive effects on specific organs such as the liver or kidneys, and thus affect the function of those organs. The AE data do not indicate toxicities in both liver and kidney. However, it should be noted that the initiation of renal replacement therapy was not included in the AE dataset thus could potentially mask some signals for renal toxicity (see section [8.4.6.2](#)). In general, the AE findings for liver and renal toxicities were consistent with laboratory findings on liver parameters (see section [8.4.6.3](#)) and renal-related efficacy endpoints (i.e. urine output and individual SOFA score in renal system, see [Appendix 13.6](#)). However, there was a trend indicating a slightly worse renal profile in the LJPC-501 arm compared to the placebo arm based on the creatinine results (see section [8.4.6.2](#)).

The incidence of hypersensitivity-related AEs was similar in both arms. There was one case of

Stevens-Johnson syndrome in the LJPC-501 arm. The case was not serious and the event was later resolved and recovered. Of note, this patient was one of the 6 subjects who had received a maximum dose of 200 mg prior to hour 3 (all other five subjects died mainly due to their underlying medical conditions during the study). It is uncertain whether the development of Stevens-Johnson syndrome was associated with the administration of a high dose of LJPC-501. Current labeling recommends that the maximum dose should not exceed (b) (4) which could mitigate the potential risk of dose-related toxicity.

Notable imbalanced AEs that are deserved for further discussions are summarized in the below sections.

8.4.5.1 Acidosis-related events

The incidence of acidosis-related events was higher in the LJPC-501 vs. placebo arm (7.4% vs. 0.6%) (Table 62). None of these AEs resulted in a fatal outcome. However, these AEs occurred in critical ill patients as 7 patients in the LJPC-501 arm and 1 patient in the placebo died during the study mainly due to worsening of the underlying disease.

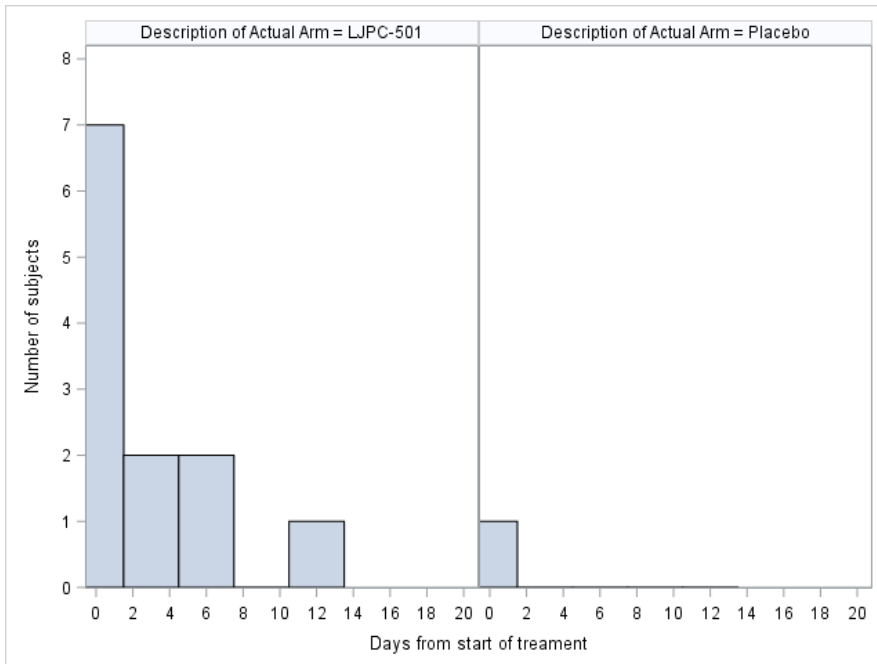
Table 62 Acidosis-related AEs/SAEs in LJ501-CRH01

SMQ/Preferred term	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Lactic acidosis (SMQ)	12 (7.4%)	1 (0.6%)	2 (1.23%)	0 (0.0%)
Metabolic acidosis	4 (2.5%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Lactic acidosis	4 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood lactic acid increased	3 (1.8%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Hyperlactacidaemia	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acidosis	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

To further explore the potential association between these events and the study drug, the timing of the event relative to the start of treatment was shown in Figure 16. Most of these events occurred during the study treatment, which suggests a temporal relationship between the study drug and the event.

Figure 16 Timing of the acidosis-related AEs relative to the start of treatment in LJ501-CRH01



Reviewer's figure data source:

ADSL & ADAE

However, the laboratory data do not suggest major differences in changes of lactic acid levels from baseline between the arms and indicate that acidosis was common in this patient population at baseline (See Section [8.4.6.1](#) for the discussions about the laboratory findings).

Reviewer's comment: Based on the evidence in the phase 3 study, it is not clear whether or not LJPC-501 is associated with the risk of acidosis. However, acidosis is common in this patient population and it is likely that the reported AEs are associated with the progression of the underlying disease, rather than the study drug.

8.4.5.2 Embolic and thrombotic-related events

There was a higher incidence of embolic and thrombotic-related events in the LJPC-501 vs. placebo arm (13% vs. 5%). The signal was primary driven by thrombosis-related AEs, particularly deep vein thrombosis (DVT). There were 7 DVT, 2 jugular vein thrombosis and 2 peripheral artery thrombosis in the LJPC-501 arm vs. 0 of these events in the placebo arm ([Table 63](#)).

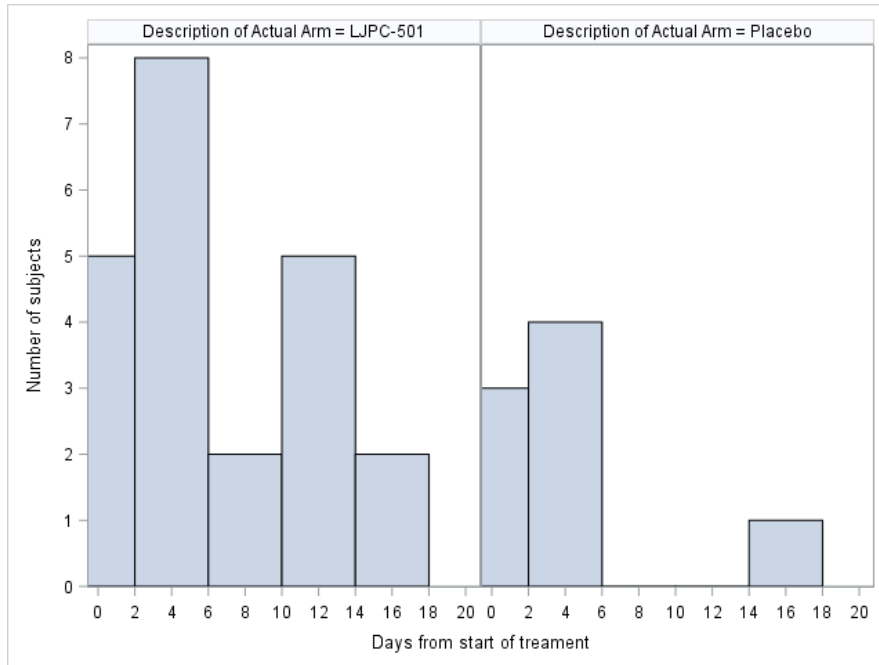
Table 63 Embolic and Thrombotic -related AEs/SAEs in LJ501-CRH01

SMQ/Preferred term	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Embolic and Thrombotic events (SMQ)	21 (12.9%)*	8 (5.1%)	9 (5.5%)	4 (2.5%)
Deep vein thrombosis	7 (4.3%)	0 (0.0%)	3 (1.8%)	0 (0.0%)
Acute myocardial infarction	2 (1.2%)	3 (1.9%)	2 (1.2%)	2 (1.3%)
Jugular vein thrombosis	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Arterial occlusive disease	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Disseminated intravascular coagulation	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Peripheral artery thrombosis	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hemiplegia	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatic vascular thrombosis	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Ischemic stroke	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Cerebral infarction	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Hemiparesis	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Embolism	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stress cardiomyopathy	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombophlebitis superficial	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombosis	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebral ischemia	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Cerebrovascular accident	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Device occlusion	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)

*There were 25 events occurred in 21 patients
 Reviewer's table data source: ADSL & ADAE

Several exploratory analyses were performed to understand the nature of this safety signal. I evaluated the timing of the event and found that these events did not seem to cluster around the start of treatment but rather spread throughout the study (Figure 17). I also examined whether there was imbalanced baseline risk between the arms and found that the percentage of subjects who reported any medical history associated with embolic and thrombotic events was similar (52% vs. 49%) in the two arms. However, among patients with reported embolic and thrombotic AEs, there was a higher percent of subjects who had a history of relevant events in the LJPC-501 arm [n=14/21 (67%)vs. n=4/8 (50%)in the LJPC-501 vs. placebo]. The standard care for patients with sepsis includes treatment for prophylaxis of DVT. Prior to the start of the treatment, 50% vs. 54% of patients in the LJPC-501 vs. placebo arm received at least one dose of heparin-related treatment. During the study treatment, 52% of subjects in the LJPC-501 arm reported at least one concomitant anticoagulation therapy (heparin and related drugs) compared to 32% in the placebo arm. These data did not indicate that subjects in the LJPC-501 arm received less adequate therapy for prophylaxis of DVT compared to the placebo arm.

Figure 17 Timing of the embolic and thrombotic-related AEs relative to the start of treatment in LJ501-CRH01



Reviewer's figure data source: ADSL & ADAE

To explore if these embolic and thrombotic-related AEs were dose-related in the LJPC-501 arm, I evaluated (1) mean dose titration level and (2) maximum dose titration level by patients with or without a reported embolic and thrombotic-related AE (Figure 18 & Figure 19). These findings did not suggest that these AEs were particularly related to high dose of LJPC-501.

Reviewer's comment: Considering that animal and human studies have shown that angiotensin II has prothrombotic effects through various mechanisms, the totality of evidence suggest that the risk of thrombosis could be drug-related. In addition, the proposed indicated patient population is at high risk for thrombosis. Hence, I recommend that this safety concern should be adequately addressed in the labeling.

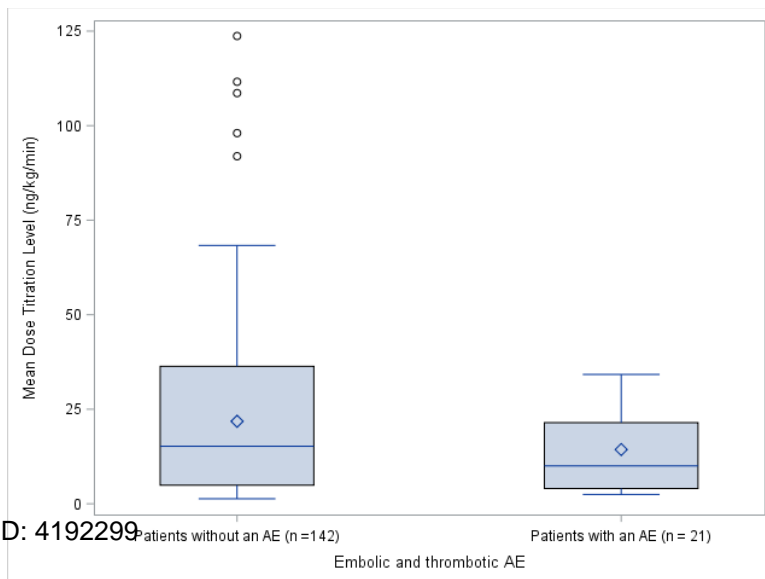
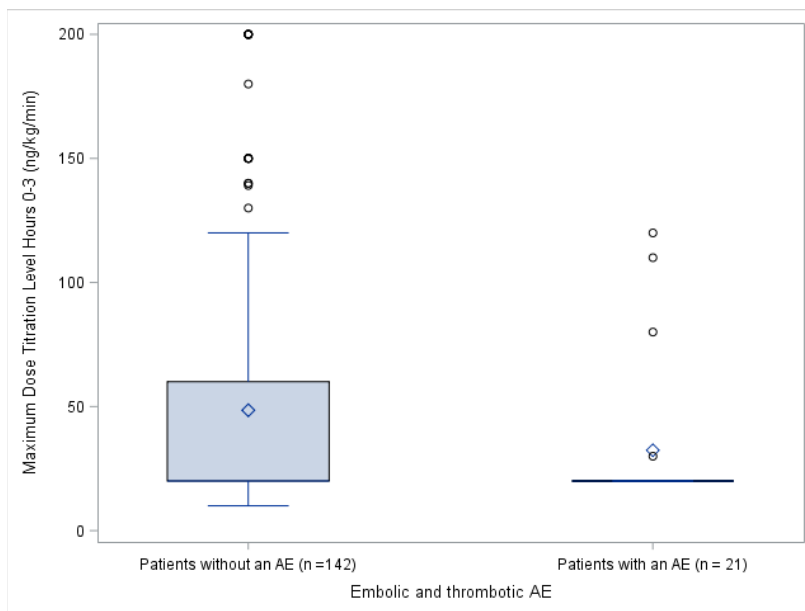


Figure 18 Mean dose titration level by patients with or without embolic and thrombotic AEs in the LJPC-501 arm

(LA reviews)

Reviewer's figure data source: ADSL, ADEX & ADAE

Figure 19 Maximum dose titration level by patients with or without embolic and thrombotic AEs in the LJPC-501 arm*



* 17 out of 21 patients who had an embolic and thrombotic AE had maximum titration level of 20 mg/kg/min

Reviewer's figure data source: ADSL, ADEX & ADAE

8.4.5.3 Psychiatric disorders-related events

The incidence of AEs related to psychiatric disorders was higher in the LJPC-501 arm compared to the placebo arm (12.9% vs. 7.0%). The signal was primarily driven by a higher incidence of delirium in the LJPC-501 arm vs. placebo arm (n = 9 vs. 1). It should be noted that the duration

of many of these AEs was long and persistent beyond the end of study treatment, suggesting

MedDRA/Preferred term	AE	SAE

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that these events were likely not drug-related. Reviewing timing of the event and patient characteristics did not reveal any signal of concern.

Table 64 Psychiatric disorder-related AEs/SAEs in LJ501-CRH01

SOC/Preferred term	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Psychiatric disorders (SOC)	21 (12.9%)	11 (7.0%)	1 (0.6%)	0 (0.0%)
Agitation	6 (3.9%)	8 (5.1%)	0 (0.0%)	0 (0.0%)
Delirium	9 (5.5%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Anxiety	4 (2.5%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Mental status changes	2 (1.2%)	2 (1.3%)	1 (0.6%)	0 (0.0%)
Insomnia	0 (0.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Restlessness	2 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

Reviewer's comment: This imbalanced finding is likely related to the background risk as delirium-like AEs are common in this patient population as well as in the ICU setting.

8.4.5.4 Hemorrhage

The incidence of hemorrhage AEs was higher in the LJPC-501 arm compared to the placebo arm (12.9% vs. 7.6%). The location of hemorrhage varied and the observed signal was not driven by bleeding at any particular site. Most of the events were not serious; the incidence of hemorrhage SAEs was low in both arms (Table 65).

Table 65 Hemorrhage AEs/SAEs in LJ501-CRH01

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 Fred Senatore MD, PhD, FACC; Tzu-Yun McDowell PhD
 505(b)(2) NDA 209360
 Angiotensin II

	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
	21(12.9%)	12 (7.6%)	3 (1.8%)	6 (3.8%)
Gastrointestinal Hemorrhage	2 (1.2%)	4 (2.5%)	0 (0.0%)	1 (0.6%)
Disseminated intravascular coagulation	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Melaena	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Catheter site Hemorrhage	0 (0.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Haematemesis	2 (1.2%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Gastric Hemorrhage	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Post procedural Hemorrhage	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Subarachnoid Hemorrhage	0 (0.0%)	2 (1.3%)	0 (0.0%)	1 (0.6%)
Eye Hemorrhage	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematochezia	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematoma	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Epistaxis	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ecchymosis	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Occult blood positive	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Periorbital haematoma	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pharyngeal Hemorrhage	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Conjunctival Hemorrhage	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Procedural Hemorrhage	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retroperitoneal haematoma	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Scleral Hemorrhage	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shock haemorrhagic	1 (0.6%)	0 (0.0%)	1 (0.6%)	0 (0.0%)
Upper gastrointestinal Hemorrhage	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Haematuria	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebral Hemorrhage	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Hemorrhage intracranial	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Hemorrhage subcutaneous	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Pulmonary contusion	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.6%)
Abdominal wall Hemorrhage	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

Reviewer's comment: No pre-clinical evidence indicating the potential risk of bleeding for angiotensin II. In fact, the pro-thrombotic effect of angiotensin II seems contradictory to the observed findings. However, it should be noted that angiotensin II has tendency to promote adhesion and aggregation of platelets. Thus, it is possible that the free platelet count may appear depressed due to this indirect phenomenon. The incidence of thrombocytopenia was 9.8% (n =16/163) in the LJPC-501 arm compared to 7% (n = 11/158) in the placebo arm. It is not

clear whether or not many minor bleeding events in the LJPC-501 arm such as hematoma could be secondary to thrombocytopenia. Small differences between the arms were observed for platelet counts and hemoglobin (see [section 8.4.6.4](#)). Overall, the findings of AE and laboratory data are not strong enough to suggest a definitive association between LJPC-501 and the risk of thrombocytopenia/hemorrhage (secondary to thrombocytopenia).

8.4.5.5 Fungal Infectious disorders

The incidence of fungal infection AEs was higher in the LJPC-501 arm compared to the placebo arm (6.1% vs. 1.3%). The location of infectious sites varied and the observed signal was not driven by infection at any site. None of the events were serious.

Table 66 Fungal Infection AEs in LJ501-CRH01

Grouped PTs	LJPC-501 N = 163	Placebo N=158
Fungal Infection AEs	10 (6.1%)	2(1.3%)
Fungaemia	2 (1.2%)	1(0.6%)
Oral candidiasis	2 (1.2%)	0 (0.0%)
Candida endophthalmitis	0 (0.0%)	1(0.6%)
Candida infection	1(0.6%)	0 (0.0%)
Fungal skin infection	1(0.6%)	0 (0.0%)
Lower respiratory tract infection fungal	1(0.6%)	0 (0.0%)
Pneumonia fungal	1(0.6%)	0 (0.0%)
Respiratory moniliasis	1(0.6%)	0 (0.0%)
Urinary tract infection fungal	1(0.6%)	0 (0.0%)

Reviewer's comment: Considering the various infectious sites and high background risk for infection in this patient population, it is unlikely that this safety signal is due to LJPC-501. In addition, subjects with these AEs were not clustered in a single site, thereby suggesting that site-related contamination was not a concern.

8.4.6. Laboratory Findings

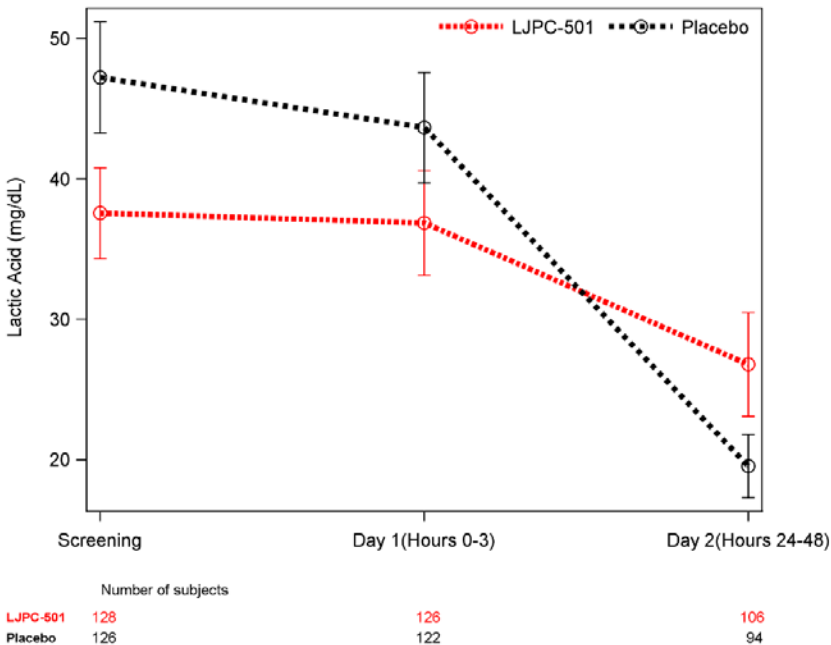
In general, analyses of the laboratory data did not raise any major safety concerns. Laboratory parameters of interest are discussed below:

8.4.6.1 Laboratory parameters associated with acidosis

8.4.6.1.1 Lactic Acid

Lactic concentration was measured at screening, Day 1 (hour 0-3) and Day 2 (hour 24-48) (Figure 20). For both arms, there were minimal changes of the concentration from screening to Day 1 and the concentration decreased on Day 2. There was a significant difference between the arms on Day 2, primary due to a greater decrease in the placebo arm compared to the LJPC-501 arm ($p = 0.02$). It should be noted that the baseline level for both arms were very high compared to the normal range (4-19.8 mg/dL), indicating that acidosis was common in this patient population. In addition, there was 25% missing data on Day 2 in the placebo arm and 15% missing data in the LJPC-501 arm; the differences between the arms on Day 2 could be likely due to missing values from very sick patients. Overall, the time course data does not suggest a considerable difference between the arms in lactic acid.

Figure 20 Mean lactic acid across time in LJ501-CRH01



Reviewer's figure data source: ADLB

The proportion of subjects who had a substantial increase in lactic acid from baseline was also similar in the two arms. There were slightly more subjects in the LJPC-501 arm with a greater than 100% increase from baseline compared to the placebo arm (10% vs. 6%).

Table 67 Changes in lactic acid during study period^a

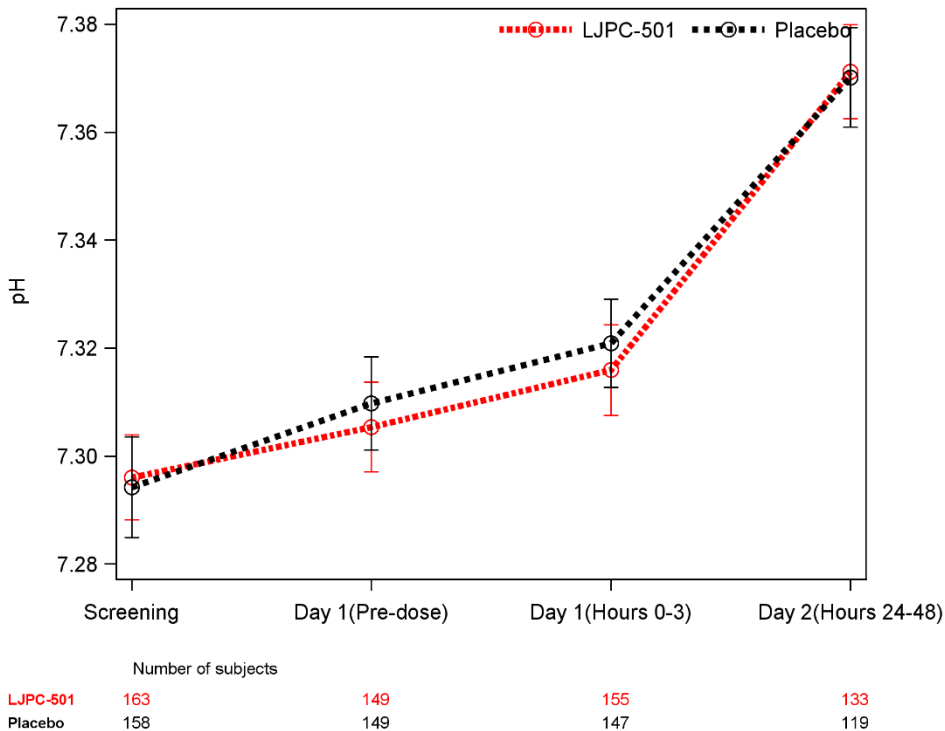
Lactic Acid increase	LJPC-501 N = 138 ^b	Placebo N=132 ^b
> 20% increase from baseline	41 (15.2%)	38 (14.1%)
> 50% increase from baseline	25 (9.3%)	25 (9.3%)
> 80% increase from baseline	15 (5.6%)	13 (4.8%)
>100% increase from baseline	14 (10.1%)	8 (6.1%)

^a Lactic acid was measured at screening, Day 1 and Day 2 or any unscheduled visit
^b Number of patients with a non-missing value at baseline and post-baseline values.
 Reviewer's table data source: ADLB

8.4.6.1.2 pH

The time course of pH level and the frequency of post-baseline abnormal level were similar in the two arms (Figure 21 and Table 68).

Figure 21 Mean pH level across time in LJ501-CRH01



Reviewer's figure data source: ADLB

Table 68 Number of subjects with abnormal pH level in LJ501-CRH01

Abnormal pH	LJPC-501 N = 163	Placebo N=158
>7.45	31 (19.0%)	26 (16.5%)
<7.35	119 (73.0%)	117 (74.1%)
<7.25	64 (39.3%)	53 (33.5%)
<7.15	24 (14.7%)	20 (12.7%)

Reviewer's table data source: ADLB

8.4.6.1.3 Bicarbonate

Bicarbonate level also appeared to be very similar between the arms (Figure 22).

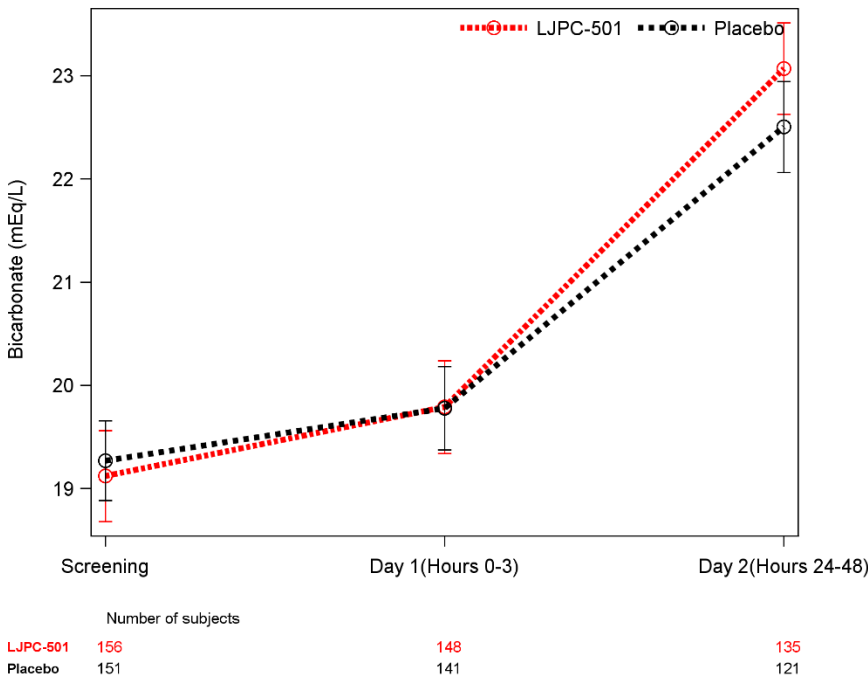


Figure 22 Mean bicarbonate across time in LJ501-CRH01

Reviewer's figure data source: ADLB

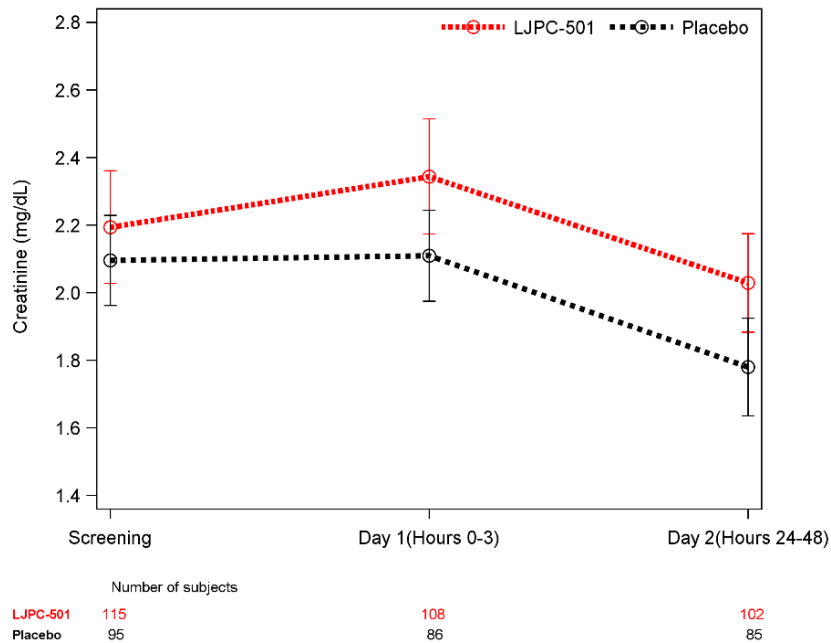
Reviewer's comment: Findings from the laboratory parameters related to acidosis do not suggest a systematic effect of LJPC-501. In addition, acidosis (high lactic acid and low pH level) was common at baseline in this patient population.

8.4.6.2 Renal Parameters

The applicant collected serum creatinine at screening, Day 1, and Day 2. In the protocol, the investigators were instructed to pay particular attention on signs of vasopressor toxicity including renal hypoperfusion but there were no pre-defined laboratory criteria for assessment of renal toxicity. During the review, we requested an IR, dated Oct 17, 2017 regarding information about renal replacement therapy in LJ501-CRH01. There were 48 (29.4%) subjects in the LJPC-501 arm and 63 (39.9%) subjects in the placebo arm received renal replacement therapy at baseline (prior to the start of treatment). To evaluate the change of serum creatinine, we excluded those subjects who were on dialysis at baseline. Creatinine changes across time was similar in both arms; there were minimal changes from screening to Day 1 and creatinine decreased on Day 2 (Figure 23). The outlier analysis shows that the LJPC-501 arm had more subjects with creatinine increased greater than 50% from baseline compared to the placebo arm (12.2% vs. 9.5%, Table 69). There were similar numbers of subjects with creatinine increased greater than 100% in both arms. In addition, renal replacement therapy was initiated during the study in ~30% of subjects in the LJPC-501 compared to ~24% of subjects in the placebo arm.

Figure 23 Mean serum creatinine in patients without dialysis at baseline across time in LJ501-CRH01

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 505(b)(2) NDA 209360
 Angiotensin II



Reviewer's figure data source: ADLB

Table 69 Abnormal serum creatinine levels among subjects without renal replacement therapy at baseline in LJ501-CRH01

Serum creatinine increase	LJPC-501 N = 115 ^a	Placebo N=95 ^a
Mean creatinine at baseline ^b		
>50% increase from baseline	14 (12.2%)	9 (9.5%)
>100% increase from baseline	4 (3.5%)	3 (3.2%)
Initiation of dialysis during the study	34 (29.6%)	23 (24.2%)

^a Number of subjects without renal replacement therapy at baseline

^b Baseline creatinine was measured at the screening visit prior to study treatment initiation

Reviewer's table data source: ADLB

Reviewer's comment: The laboratory results indicated a slightly worse renal profile in the LJPC-501 arm compared to the placebo arm. It should be noted that some concomitant therapy and procedures may confound the observed results. However, the potential harmful effect of LJPC-501 on renal function cannot be ruled out based on the mechanism of action. Another consideration is that the longer-term effect of LJPC-501 on renal function is not known because creatinine was only measured up to Day 2. Whether the effect is treatment duration dependent is unknown. Despite of these uncertainties, the safety concern for potential renal toxicity is somewhat alleviated considering the modest size of the observed effect on creatinine as well as

the mortality findings trending in favor of LJPC-501.

8.4.6.3 Liver Parameters

The incidence of abnormal liver enzymes was similar in the two treatment arms (Table 70).

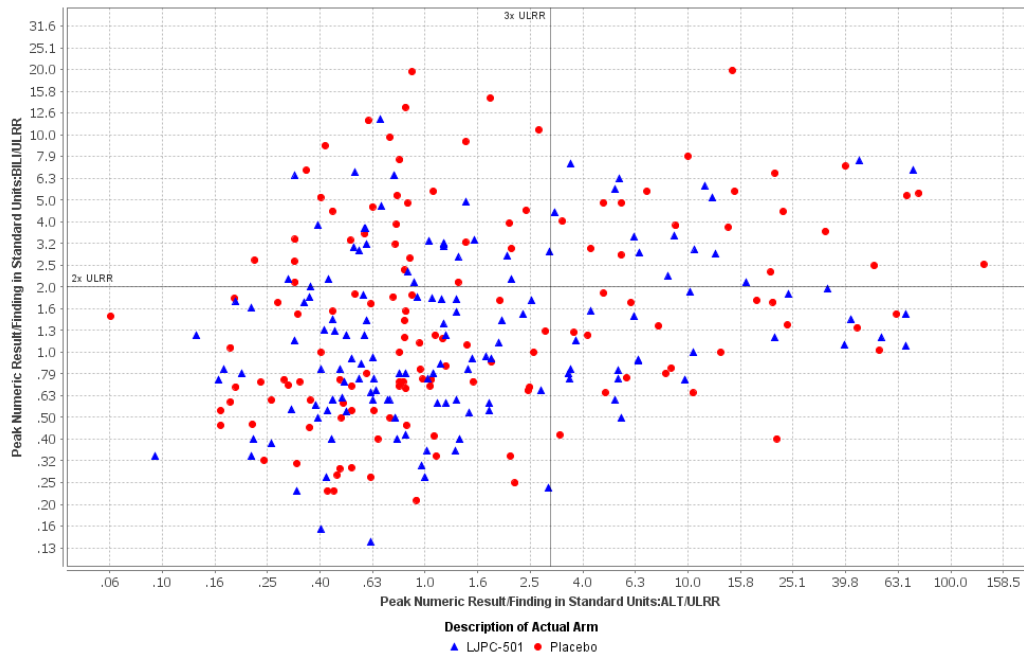
Table 70 Number of events and subjects with notable abnormal liver enzymes in LJ501-CRH01

Liver Lab Test	Ljpc-501 N = 163			Placebo N = 158		
	Event Count	Subject Count	% of Subjects	Event Count	Subject Count	% of Subjects
ALT ≥ ULN						
2x ULN	79	52	31.90	82	55	34.81
3x ULN	64	44	26.99	67	45	28.48
5x ULN	51	36	22.09	54	36	22.78
10x ULN	26	20	12.27	38	26	16.46
20x ULN	17	12	7.36	25	20	12.66
AST ≥ ULN						
2x ULN	133	89	54.60	123	83	52.53
3x ULN	101	73	44.79	100	69	43.67
5x ULN	74	56	34.36	76	54	34.18
10x ULN	48	36	22.09	62	48	30.38
20x ULN	33	25	15.34	38	30	18.99
TB ≥ ULN						
1.5x ULN	111	71	43.56	115	72	45.57
2x ULN	81	53	32.52	97	60	37.97
3x ULN	47	32	19.63	73	49	31.01

Source: JumpStart Liver labs analyses

Figure 24 shows the peak serum ALT on the x-axis and the peak TBL on the y-axis as multiples of the ULN. The number of subjects with peak ALT versus peak TBL in the upper right hand quadrant of the plot (potential His low case based on chemistry findings) was similar (n = 15 and 20 in the LJPC501 vs. placebo arm, respectively).

Figure 24 His Law Plot of peak ALT vs. peak TBL (with ALP ≤ 2xULN) in LJ501-CRH01



Source: JReview's liver standard analysis

8.4.6.4 Hematology

8.4.6.4.1 Hemoglobin

The time course plot shows decreases in hemoglobin in two treatment arms (Figure 25). It is noted that the LJPC-501 arm entered the study with somewhat higher mean hemoglobin levels. In general, the LJPC-501 arm had a larger decrease from baseline in hemoglobin compared with the placebo arm. More subjects had hemoglobin drops ≥ 2 g/dL or ≥ 4 g/d in the LJPC-501 arm compared with the placebo arm, particularly on Day 2. Similarly, a larger decrease in red blood cell count and hematocrit was also observed in the LJPC-501 arm compared with the placebo arm (Table 71).

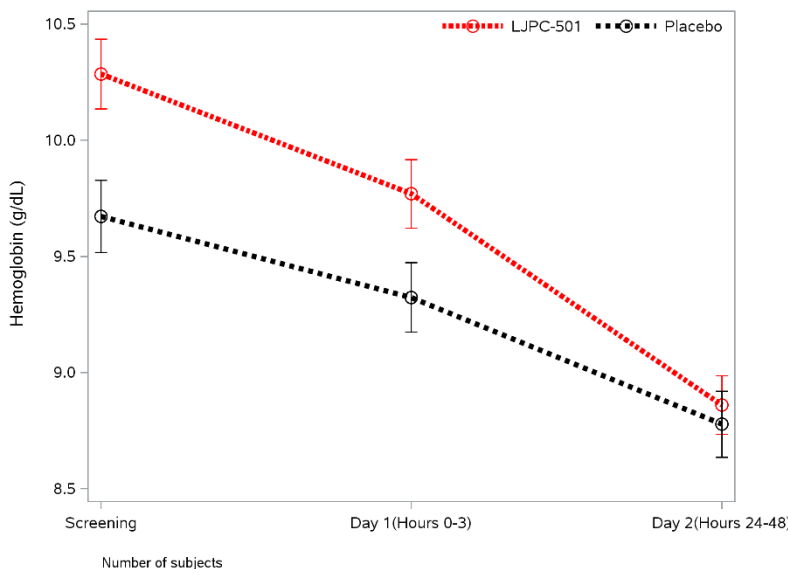


Figure 25 Mean hemoglobin across time in LJ501-CRH01

Reviewer's figure data source: ADLB

Table 71 Changes in hemoglobin in LJ501-CRH01

Hemoglobin	LJPC-501 N = 160^a	Placebo N=157^a
Mean hemoglobin at baseline, g/l.d.(SD)	10.3 (1.9)	9.7 (2.0)
Hemoglobin drop on Day 1 (Hour 0-3)		
≥2 g/l.d.	18 (11.5%) ^b	8 (5.4%) ^b
≥4 g/l.d.	2 (1.3%) ^b	0 (0.0%) ^b
>25% decrease from baseline	5 (3.2%) ^b	2 (1.4%) ^b
Hemoglobin drop (Any post-baseline value)		
≥2 g/l.d.	49 (30.6%)	35 (22.3%)
≥4 g/l.d.	9 (5.6%)	6 (3.8%)
>25% decrease from baseline	21(13.1%)	17 (10.8%)

a Subjects who had baseline value and at least one post-baseline measurement

b Percentage was calculated based on number of subjects who had Hour 3 measurement. There were 156 subjects in the LJPC-501 arm and 148 subjects in the placebo arm had hemoglobin value at Hour 3.

Reviewer's table data source: ADLB

Reviewer's Comment: Both arms had similar averaged hemoglobin levels on Day 2 but the LJPC-501 arm had a higher value at baseline. The larger differences between the two arms (greater decreases in the LJPC-501 arm) were observed on Day 2. It should be noted that on Day 2, there were 20% missing data in the placebo arm and 13% in the LJPC-501 arm. Missing data in this population is likely not random (e.g. missing data from deceased subjects) and could potentially confound the observations. Overall, the observed differences in hemoglobin changes between the arms were small, which is consistent with the AE finding: the incidence of anemia AEs (i.e. anemia, hemoglobin decreases) was similar in the two treatment arms (8.6% vs. 7.0%) in the LJPC-501 and placebo arms, respectively).

8.4.6.4.2 Platelet

The time course plot also shows decreases in platelets in the two treatment arms (Figure 26). The magnitude of decrease was similar in the two arms. More subjects had platelet drops >50% or > 75% from baseline on Day 2 in the LJPC-501 arm compared to the placebo arm. There were no differences found on Day 1. The percentage of subjects who had platelet count < 50,000 per microliter was similar in the two arms (Table 72).

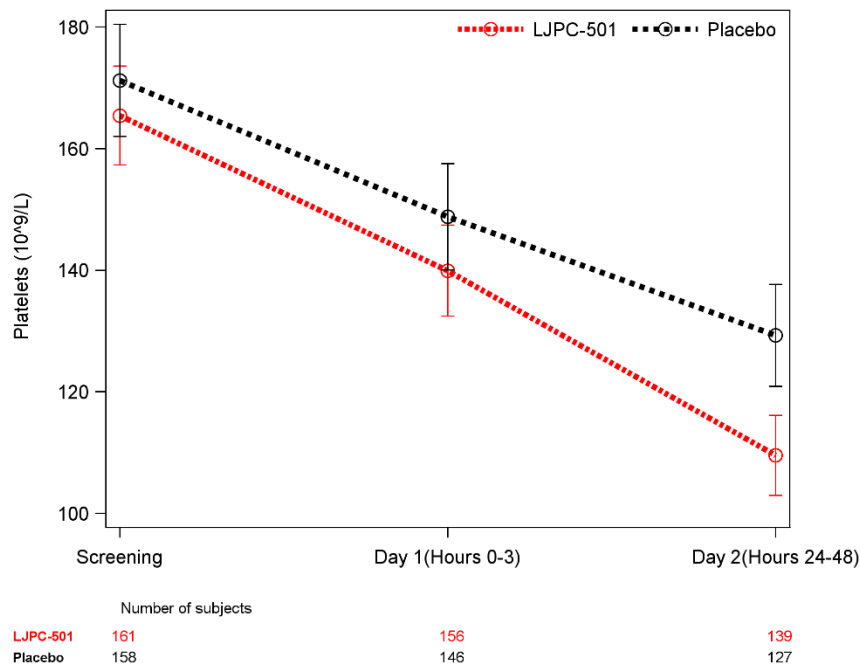


Figure 26 Mean platelet across time in LJ501-CRH01

Reviewer's figure data source: ADLB

Table 72 Abnormal platelet count in LJ501-CRH01

Platelet	LJPC-501 N = 160^a	Placebo N=157^a
Mean platelet counts at baseline, 10⁹/L (SD)	165.2 (103)	171.3 (116)
Abnormal values on Day 1 (Hour0-3)		
>50% decrease from baseline	8(5.1%) ^b	11 (7.5%) ^b
>75% decrease from baseline	0 (0.0%) ^b	2 (1.3%) ^b
Platelet on Day 1 < 50 10 ⁹ /L	22 (14.1%) ^b	22 (15.1%) ^b
Abnormal values (any post-baseline value)		
>50% decrease from baseline	42 (26.3%)	30 (19.1%)
>75% decrease from baseline	10 (6.2%)	4 (2.5%)
Platelet at any post-baseline value < 50 10 ⁹ /L	38 (23.8%)	39 (24.8%)

^aSubjects who had a baseline value and at least one post-baseline value

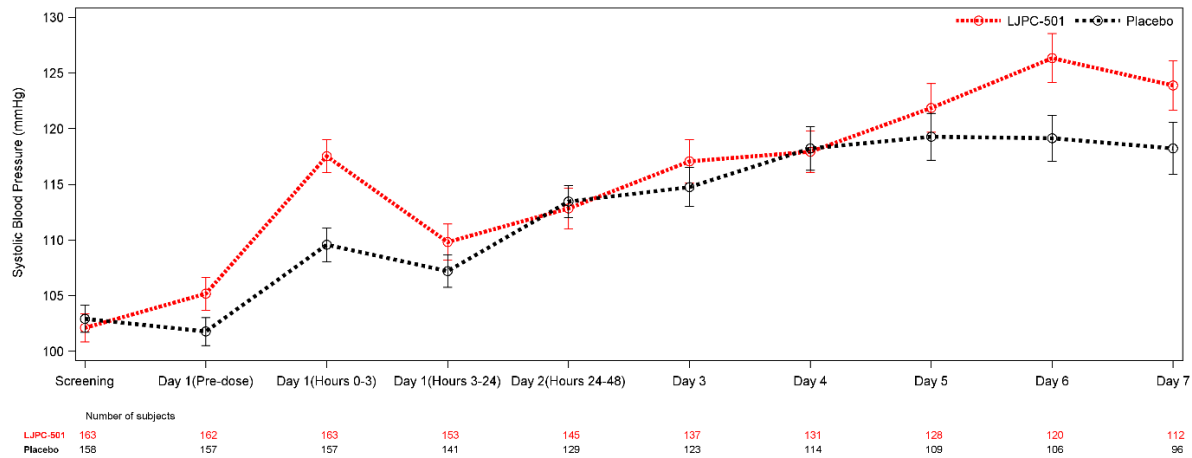
^bPercentage was calculated based on number of subjects who had Hour 3 measurement. There were 156 subjects in the LJPC-501 arm and 146 subjects in the placebo arm had hemoglobin value at Hour 3.

Reviewer Comment: The laboratory data indicates modest differences in platelet count between the arms. Particularly, there appeared to be no differences on Day 1.

8.4.7. Vital Signs

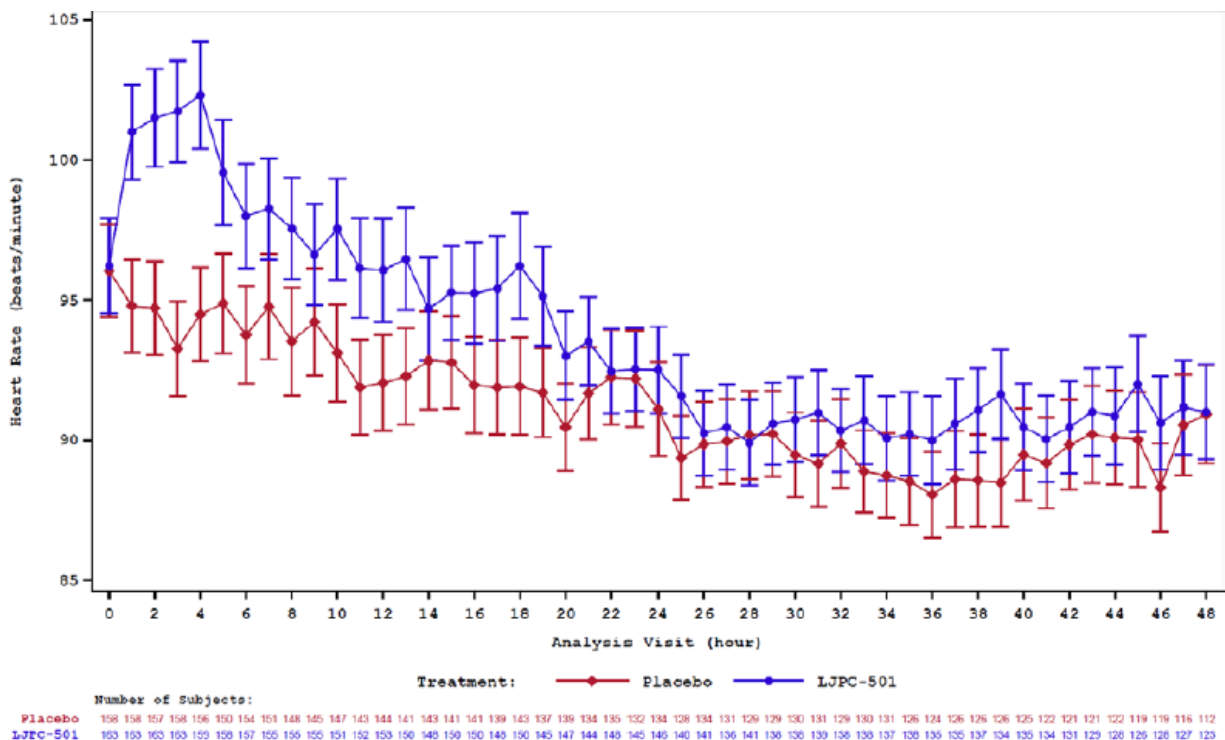
Consistent with the efficacy results, cuff measurements of SBP and DBP on Day 0 (hours 0-3) were notable higher in the LJPC-501 arm compared to the placebo arm (Figure 27).

Figure 27 Time course of SBP in LJ501-CRH01



Reviewer's figure data source: ADVS

Heart rate (HR) was an exploratory efficacy endpoint in LJ501-CRH01. Mean HR increased from Hour 0 to Hour 3 in the LJPC-501 arm (an increase of 4.4 beats per minutes) compared to a small decrease in the placebo arm (-1.1 beats per minutes, $p < 0.0001$). HR was similar during hour 3- hour 48 in both treatment arms.



Source: Figure 20 in the CSR

Reviewer's comment: Increased HR was only observed in animals receiving the highest dose of LJPC-501 (1800 ng/kg). The magnitude of HR increase in the LJPC-501 arm during the first 3 hour of treatment in the phase 3 study was small and did not raise any major safety concern.

8.4.8. Electrocardiograms (ECGs)

ECG data were collected at baseline and Hour 48 in LJ501-CRH01. There was no evidence of QTc prolongation in the two treatment arms. The mean (SD) change in QTcF² was +0.6 (61.1) msec in the LJPC-501 arm and -2.1 (62.2) in the placebo arm ($p = 0.7$). The only significant difference between the arms was for the change in PR interval. Mean (SD) change in PR interval was 5.9 (24.9) msec in the LJPC-501 arm and -3.6 (32.3) msec in the placebo arm ($p = 0.04$). The outlier analyses showed that very few patients in the study in either arm had prolonged PR interval (Table 73).

Table 73 PR interval based on categorical outliers in LJ501-CRH01

Any post-baseline PR	LJPC-501 N = 163	Placebo N=158
PR >200 msec + 25% increase from baseline	2/80 ^a (1.3%)	0/77 ^a (0.0%)
PR >220 msec	4/94 ^b (2.1%)	3/93 ^b (1.6%)
PR >240 msec	2/94 (1.1%)	2/93 (1.1%)

^a Number of subjects had PR measurements at baseline & hour 48

^b Number of subjects had PR measurement at hour 48

Reviewer's table, data source: ADEG

Reviewer's comment: A mean change from baseline in PR interval of <10 ms is not too concerning; however, the SD is quite large thus some individual subjects might have substantial increases in PR. Of note, one clinical study in the literature documented a higher incidence of first degree AV block in patients received angiotensin II compared to norepinephrine (n=6/30 vs. 0/30) despite of a similar frequency for rhythm disturbances³ in the two groups. Thus, I performed some exploratory analyses to assess the outliers and the results were similar between the arms. It should be noticed that there was about 38% of patients in each arm who did not have PR measurements at both baseline and hour 48. There was only one reported case of atrioventricular block AE in the LJPC-501 arm vs. 0 in the placebo arm. Overall, the ECG data did not indicate a major safety concern.

² QT interval corrected by heart rate using Fridericia's formula

³ Singh S, and Malhotra RP. Comparative study of angiotensin and nor-adrenaline in hypotensive states (shock). J Assoc Physicians India. 1966;14(11):639-45.

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Fred Senatore MD, PhD, FACC; Tzu-Yun McDowell PhD
505(b)(2) NDA 209360
Angiotensin II

8.4.9. QT

There was no evidence of QT prolongation from the ECG data collected in the phase 3 study ([section 8.4.8](#)). The incidence of AEs grouped under the Torsade de pointes/QT prolongations SMQ was similar in the two treatment arms (9.8% vs. 15.2% in the LJPC-501 arm and placebo arm, respectively).

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

Two pre-defined safety topics of interests: arrhythmia and ischemia/vasoconstriction were evaluated primarily based on the AE data (see [section 8.4.4](#)). Relevant to arrhythmia, ECG data were collected in the phase 3 trial (see [section 8.4.8](#)). There is no additional study conducted to assess these safety issues. Overall, the frequency of the events was similar for both AESIs in the two arms.

8.6. Safety Analyses by Demographic Subgroups

See [section 8.4.4](#) for information on drug-demographic interactions for two AESIs. There were no age or gender differences observed for the incidence of AESIs.

8.7. Specific Safety Studies/Clinical Trials

Not applicable

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Duration of treatment for LJPC-501 was short (medium duration = 48 hours), thus the risk of potential human carcinogenicity or tumor development is probably minimum. The search of AE using malignancies (SMQ) did not reveal any safety concern (1.2 vs. 3.2 in the LJPC-501 vs. placebo arm).

8.8.2. Human Reproduction and Pregnancy

Pregnancy women were excluded from LJ501-CRH01. No adequate and well-controlled studies

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have been conducted with LJPC-501 in pregnant women. The potential effect of LJPC-501 on fetal development or reproduction capacity is not known.

8.8.3. Pediatrics and Assessment of Effects on Growth

LJPC-501 is not currently proposed for use in pediatric patients. The applicant proposed to conduct two studies to evaluate effect of LJPC-501 on MAP in agreed Initial Pediatric Study Plan (iPSP): one in pediatric patients >2-17 years of age (b) (4) and the other in patients 0-2 years of age.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

LJPC-501 is developed for short term use with titrations to the target blood pressure in the ICU setting. The safety concerns regarding overdose and drug abuse potential should be minimal. Withdrawal of LJPC-501 may lead to hypotension in some patients. There were 21 reported hypotension-related AEs (in 17 subjects) in the LJPC-501 arm vs. 10 events (in 10 subjects) during the study. In the LJPC-501 arm, 12 of these events (in 10 subjects) occurred either during the down titration phase (hour 3-48) or within 3 days after the end of treatment.

The applicant also provided analyses on MAP changes in a subgroup of subjects (N = 13) who received an optional re-initiation of LJPC-501 after hour 48 (Table 74). The data indicates that MAP decreased below the target of 65 mmHg during the down-titration phase (a mean decrease of 8.6 mmHg) and increased again after reintroduction of LJPC-501. These findings suggest that subjects remain sensitive to LJPC-501 treatment throughout and after 48 hours. Thus, hypotension may occur in some patients after withdrawal of LJPC-501.

Table 74 Study drug administration and mean arterial blood pressure at late dose down-titration and later up-titration in LJ501-CRH01

Patient ID/Age/ Sex/Treatment	Prior to Down-Titration		Down-Titration Hours 45 to 51		Up-Titration	
	Dose ng/kg/min	MAP (mmHg)	Lowest Dose ng/kg/min	1 st MAP at Lowest Dose (mmHg)	Highest Dose ng/kg/min	MAP at End of Titration (mmHg)
042-005/84/M/Pbo	40	83	20	63	40	74
001-004/87/F/501	10	61	0	55	10	93
004-001/54/F/501	40	71	20	67	40	71
017-003/80/F/501	40	73	10	60	30	82
022-001/56/F/501	40	67	30	68	40	67
022-005/87/M/501	40	74	0	67	40	73
022-008/62/M/501	40	69	0	69	10	71
026-003/79/F/501	20	63	0	57	20	74
042-006/80/M/501	40	73	30	64	40	68
060-004/43/M/501	30	68	2.5	62	5	77
067-007/30/M/501	30	85	0	61	10	73
090-001/75/F/501	10	68	0	66	10	66
100-007/78/F/501	15	77	2.5	63	10	80
124-001/70/M/501	40	75	20	64	30	65
LJPC-501 (n = 13)	30.38	71.85	8.08	63.23	22.69	74.31
Mean (SD)	(12.326)	(7.057)	(10.663)	(4.246)	(14.233)	(7.543)
Median	40	71	2.5	63	20	73
Range	10 - 40	61 - 85	0 - 30	55 - 69	5 - 40	65 - 93

Source: ISS table 51 on page 91

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

LJPC-501 is not currently marketed in the United States or any other countries.

8.9.2. Expectations on Safety in the Postmarket Setting

The risk of thrombosis was higher in the LJPC-501 arm compare to the placebo arm in the phase 3 study. This risk could be higher in the postmarket setting if patients do not receive adequate

prophylactic anticoagulation. This potential risk should be managed through labeling and monitored in the postmarket setting.

LJPC-501 could have pharmacodynamic effects on some hematology parameters (see [section 8.6.4.4](#), glucose level (see [section 8.10](#)) and renal function (see [section 8.4.6.2](#)). Although the safety results from the phase 3 study was not strong enough to conclude the association, the potential risk for thrombocytopenia, hyperglycemia and renal impairment cannot be ruled out and should be monitored in the post-marketing setting.

8.10. Additional Safety Issues From Other Disciplines

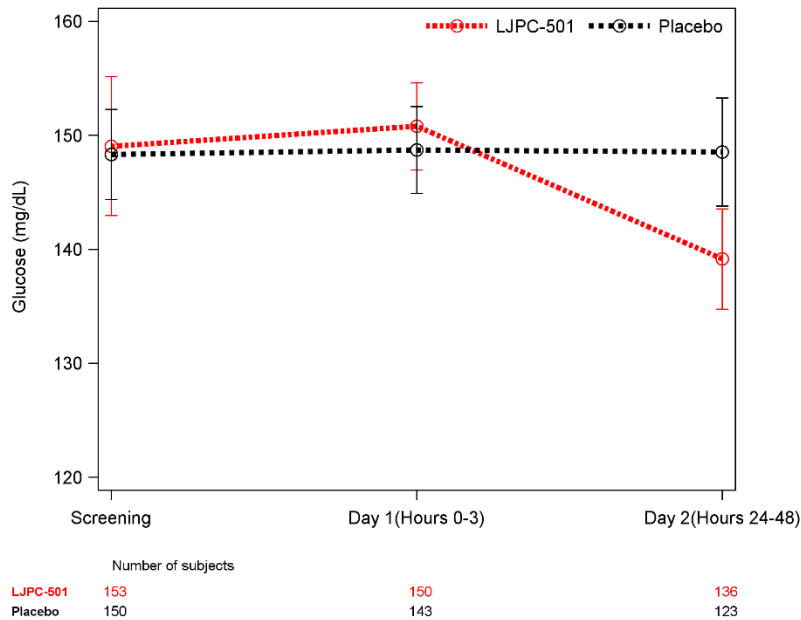
In addition to the risk of thrombosis, pre-clinical studies also suggest that angiotensin II is involved in the regulation of metabolic and endocrine functions, especially blood glucose homeostasis. It causes hyperglycemia and insulin resistance. The incidence of hyperglycemia/new onset diabetes mellitus (SMQ, broad) in LJ501-CRH01 was 14.7% vs. 7.6 % in the LJPC-501 vs. placebo arm ([Table 75](#)). However, the signal was driven primary by the acidosis-related AEs (see [Section 8.4.5.1](#)). The incidence of hyperglycemia AE was 4.3% in the LJPC-501 arm and 2.5% in the placebo arm. The laboratory data for glucose level do no suggest a marked difference between the two arms ([Figure 28](#)). It is noted that there was a greater decrease on Day 2 in the LJPC-501 arm compared to the placebo arm, though not statistically significant between the arms.

Table 75 Incidence of hyperglycemia-related AEs/SAEs in LJ501-CRH01

SMQ/Preferred term	AE		SAE	
	LJPC-501 N = 163	Placebo N=158	LJPC-501 N = 163	Placebo N=158
Hyperglycemia/new onset diabetes mellitus (SMQ, broad)	24 (14.7%)	12 (7.6%)	3 (1.8%)	0 (0.0%)
Hyperglycaemia	7 (4.3%)	4 (2.5%)	0 (0.0%)	0 (0.0%)
Hypoglycaemia	4 (2.5%)	6 (3.8%)	0 (0.0%)	0 (0.0%)
Metabolic acidosis	4 (2.5%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Lactic acidosis	4 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blood lactic acid increased	3 (1.8%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Depressed level of consciousness	1 (0.6%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Hyperlactacidaemia	1 (0.6%)	0 (0.00%)	0 (0.0%)	0 (0.0%)
Acidosis	1 (0.6%)	0 (0.00%)	0 (0.0%)	0 (0.0%)
Blood triglycerides increased	1 (0.6%)	0 (0.00%)	0 (0.0%)	0 (0.0%)
Weight increased	1 (0.6%)	0 (0.00%)	0 (0.0%)	0 (0.0%)
Polyuria	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)

Reviewer's table data source: ADSL & ADAE

Figure 28 Time course of glucose level in LJ501-CRH01



Reviewer's comment: The difference on the incidence of hyperglycemia was small between the two arms. It is plausible that LJPC-501 has pharmacodynamic effects on glucose level but the effect seems modest with the short-term use of LJPC-501. I cannot conclude that LJPC-501 is associated with the risk of hyperglycemia based on the AE and laboratory findings in LJ501-CRH01. However, even if the risk is real, it should be manageable considering that careful monitoring and adjustment of blood glucose is required and standard in the ICU.

8.11. Integrated Assessment of Safety

Overview of Safety Database

The clinical safety of LJPC-501 in patients with CRH was evaluated primarily using the safety data from the phase 3 trial, LJ501-CRH01. The safety dataset contains a total of 321 subjects who were received at least one dose of the study drug (n = 163 and 158 in the LJPC-501 and placebo arm, respectively). Subjects were to receive study drug for 48 hours with an option to continue after 48 hours based on patients' clinical conditions. Overall, the two treatment arms had a similar duration of drug exposure (median drug exposure was 48 hours in both arms).

Additional supportive safety data were provided by a literature review of 7 studies, in which prospective safety data was collected (2 RCTs in patients with hypotensive shock, 5 studies in healthy volunteers). There was a total of 107 patients received angiotensin II from these studies (n = 35 from RCTs and 72 from studies with healthy volunteer). The utility of these data is limited due to lack of information on the reported AEs (see [Appendix 13.7](#) for the reported AEs). Overall, no consistent safety signals were identified besides the intended effect of angiotensin II of increasing blood pressure.

Overview of Safety Results and Safety Topics of Interest

In study LJ501-CRH01, the incidence of AEs, SAEs, fatal SAEs and discontinuation due to AEs was similar in the two treatment arms (Table 49, Table 50 and Table 51). Based on the mechanism of action, safety topics of interest included the known toxicities associated with vasopressors: arrhythmia and ischemia/vasoconstriction. Moreover, the risk of thrombosis was identified as a plausible safety signal. The main findings of these safety topics of interest are discussed below.

(1) Arrhythmia

The incidence of arrhythmia-related AEs was similar in the LJPC-501 arm compared to the placebo arm (31.3% vs. 34.3%) (Table 52). The incidence of arrhythmia SAEs was also similar in the two treatment arms. These results were consistent across subgroups (Table 55). ECG data collected in LJ501-CRH01 did not indicate a prolonged QT interval in either arm. LJPC-501 increase the PR interval compared to the placebo to some extent (difference= ~10 msec, $p=0.04$) but the percentage of subjects with prolonged PR interval (e.g. > 200 msec) was similar in the two arms. There was only one reported atrioventricular block AE in the LJPC-501 arm vs. 0 in the placebo arm. Overall, there was no major safety concern from arrhythmia-related AEs and the ECG data.

(2) Ischemia/vasoconstriction

The incidence of ischemia/vasoconstriction-related AEs was similar in the LJPC-501 arm compared to the placebo arm (10.4% vs. 10.1%) (Table 56). The incidence of ischemia/vasoconstriction-related SAEs was also similar in the two treatment arms. These results were consistent across subgroups (Table 60). There were 4 ischemia events in the CNS in the LJPC-501 arm and 3 had a fatal outcome compared to 1 non-fatal ischemia CNS event in the placebo arm. (b) (4)

(3) Risk of thrombosis

There was a higher incidence of venous and arterial thromboembolic events in the LJPC-501 arm compared to the placebo arm (12.9% vs. 5.1%). The major imbalance arose from a higher frequency of thrombotic events in the LJPC-501 arm; there were 7 DVTs, 2 jugular vein thrombosis & 2 peripheral artery thrombosis AEs in the LJPC-501 arm vs. none in the placebo arm (Table 63). Subjects in both arms also had similar background risk and DVT prophylaxis treatment (heparin and related drugs) at baseline. This risk is particularly plausible considering the prothrombotic effect of angiotensin II found in animal and human studies. Moreover, the population for which LJPC-501 is proposed to treat is at high risk for DVT. Hence, the safety concern about the risk of thrombosis should be adequately addressed in the labeling and carefully monitored in the post-market setting.

(4) Other safety topics of interest

Safety concern about initiation and withdrawal of LJPC-501

LJPC-501 is developed for short term use with an initial dose of 20 ng/kg/min following by frequent titrations to target hemodynamic effects in the ICU setting. Thus, the dosing and drug exposure is expected to vary across patients. Transient hypertension (a MAP increase to ≥ 100 mmHg during the initial 15 mins) was observed in some patients (n =37, 23%) in LJ501-CRH01 (range; 101.3 to 142 mmHg). All these patients' MAP returned < 85 mmHg after dose down titration (median time to MAP < 85 was 25 mins). The risk of transient hypertension is expected in some patients (i.e. "hyper-responders") but this risk could be mitigated and manageable by dose down titration.

Hypotension may occur in some patients during down-titration and/or following withdrawal of LJPC-501 (see [section 8.8.4](#)). This potential risk should be manageable by avoiding an abrupt discontinuation and performing a gradual down-titration according to blood pressure response.

Other potential risks for LJPC-501

There are few potential risks that could be associated with LJPC-501 but the safety results in the phase 3 study did not indicate a strong imbalance between the arms. Nevertheless, these risks cannot be ruled out due to plausible mechanistic bases.

- a. Thrombocytopenia: Angiotensin II has tendency to promote adhesion and aggregation of platelets. Thus, it is plausible that the free platelet count may appear depressed due to this indirect phenomenon. The incidence of thrombocytopenia was 9.8% vs. 7.0% in the LJPC-501 arm vs. the placebo arm. There was a higher percentage of subjects who had $> 50\%$ decrease in platelet count from baseline in the LJPC-501 arm compared to the placebo arm (26.3% vs.19.1%). However, similar numbers of subjects had platelet count $< 50,000$ per microliter in the two arms.
- b. Hyperglycemia: Pre-clinical studies indicate that angiotensin II causes hyperglycemia and insulin resistance. The incidence of hyperglycemia was 4.3% vs. 2.5% in the LJPC-501 arm vs. the placebo arm. The laboratory data for glucose level do no suggest a marked difference between the two arms. This potential risk is manageable considering that careful monitoring and adjustment of blood glucose is required and standard in the ICU.
- c. Renal toxicity: LJPC-501 could have excessive vasoconstrictive effects on the kidney, thus impacting renal function. The incidence of renal toxicity related AEs was lower in the LJPC-501 arm vs. the placebo arm (8.6% vs. 11.4%). However, it should be noted that the initiation of renal replacement therapy was not included in the AE dataset thus could potentially mask some signals for renal toxicity. Dialysis was initiated during the study in $\sim 30\%$ of subjects in the LJPC-501 compared to $\sim 24\%$ of subjects in the placebo arm. The outlier analysis on serum creatinine shows that the LJPC-501 arm had slightly

more subjects with creatinine increased greater than 50% from baseline compared to the placebo arm (12.2% vs. 9.5%). It should be noted that these small differences could be due to chance or attributed by other confounding factors. The safety concern about the consequences of potential renal toxicity is alleviated considering the observed mortality trend benefiting the LJPC-501 arm.

Overall, LJPC-501 has an acceptable safety profile in patients with CRH. We believe the key toxicities of LJPC-501 can be managed through proper labeling. There are no safety issues that would preclude the approval of LJPC-501.

9 Advisory Committee Meeting and Other External Consultations

Not applicable

10 Labeling Recommendations

10.1. Prescribing Information

11 We have provided our labeling recommendations and received the Sponsor's responses dated November 30, 2017 (please refer to the proposed draft labeling under NDA 209360 seq 0021). Risk Evaluation and Mitigation Strategies (REMS)

There are no safety issues that warrant consideration of a REMS.

Postmarketing Requirements and Commitments

Not applicable

13 Appendices

13.1. References

Clinical Review
Fred Senatore MD, PhD, FACC; Tzu-Yun McDowell PhD
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13.2. Financial Disclosure

[See section 6.1.2.]

Covered Clinical Study (Name and/or Number): Study LJ501 CRH01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

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		Applicant)
Total number of investigators identified: <u>814</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>787</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. AE coding

This AE coding table was provided by Jumpstart service. I only included terms with a matching score <80 between the verbatim term and PT (a score of 100 indicates a direct match).

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Elevated transaminases ALAT	Alanine aminotransferase increased	Could not match	0
Rectal Skin Abrasion	Anal injury	Could not match	0
Recurrent Cardiac Dysrhythmia	Arrhythmia	Could not match	0
Elevated transaminases , ASAT	Aspartate aminotransferase increased	Could not match	0
Afibrillation with RVR	Atrial fibrillation	Could not match	0
E.Coli anal colonization	Bacterial disease carrier	Could not match	0
edema bullae	Blister	Could not match	0
SKIN VESICLES ON THE WRIST	Blister	Could not match	0
Diffuse cerebral edema	Brain oedema	Could not match	0
Probable cerebral edema	Brain oedema	Could not match	0
Septic Myocardial Dysfunction	Cardiac disorder	Could not match	0
Rehospitalization due to CHF excacerbation	Cardiac failure congestive	Could not match	0
Transient circulatory imparment	Cardiovascular disorder	Could not match	0
LEFT FRONTOTEMPORAL INTRACEREBRAL HEMORRHAGE	Cerebral haemorrhage	Could not match	0
bilateral occipital cva's	Cerebrovascular accident	Could not match	0
Worsening Septic Shock secondary to fulminant C. diff colitis	Clostridium difficile sepsis	Could not match	0
ocular chemosis	Conjunctival oedema	Could not match	0
Left anterior heel deep tissue injury (pressure ulcer)	Decubitus ulcer	Could not match	0
Upper extremity DVT	Deep vein thrombosis	Could not match	0
Bilateral lower extremity bulbous lesions	Dermatitis bullous	Could not match	0
ureteral stent displacement	Device dislocation	Could not match	0

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Vancomycin allergy	Drug hypersensitivity	Could not match	0
Zosyn allergy	Drug hypersensitivity	Could not match	0
difficulty swallowing	Dysphagia	Could not match	0
Difficulty swallowing	Dysphagia	Could not match	0
vascular thromboembolic disorders	Embolism	Could not match	0
Dysconjugate gaze	Eye movement disorder	Could not match	0
Regurgitation of Nasogastric feed	Feeding tube complication	Could not match	0
Black coffee ground output from nasogastric tube	Gastric haemorrhage	Could not match	0
Decreased GI motility	Gastrointestinal hypomotility	Could not match	0
Decreased Gut Motility	Gastrointestinal hypomotility	Could not match	0
Delayed GI motility	Gastrointestinal hypomotility	Could not match	0
Poor bowel peristaltic function due to intensive care treatment	Gastrointestinal hypomotility	Could not match	0
Submucosal Shedding of the Bowel	Gastrointestinal mucosal exfoliation	Could not match	0
blood clots in the colostomy bag	Gastrointestinal stoma complication	Could not match	0
Worsening anasarca (generalized edema)	Generalised oedema	Could not match	0
Worsening of edema - Anasarca	Generalised oedema	Could not match	0
Worsening of anasarca	Generalised oedema	Could not match	0
critically low hemoglobin	Haemoglobin decreased	Could not match	0
Drop in hemoglobin	Haemoglobin decreased	Could not match	0
Left sided weakness	Hemiparesis	Could not match	0
NOT MOVING LEFT SIDE	Hemiplegia	Could not match	0
Adenocarcinoma of Liver	Hepatic cancer	Could not match	0
Worsening of lactacidaemia	Hyperlactacidaemia	Could not match	0
high blood pressure	Hypertension	Could not match	0

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Worsening INR elevation	International normalised ratio increased	Could not match	0
Worsened diffuse bilateral airspace opacities	Interstitial lung disease	Could not match	0
"Liver shock"	Ischaemic hepatitis	Could not match	0
Shcok Liver	Ischaemic hepatitis	Could not match	0
shock liver	Ischaemic hepatitis	Could not match	0
Worsening Shock Liver	Ischaemic hepatitis	Could not match	0
MULTIPLE SKIN TEARS UPPER BACK	Laceration	Could not match	0
Derranged LFT's	Liver function test abnormal	Could not match	0
Increasing (worsening) LFTs	Liver function test abnormal	Could not match	0
Worsening Elevated LFTs	Liver function test abnormal	Could not match	0
Worsening LFTs (increased)	Liver function test abnormal	Could not match	0
PREOGRESSIVE ALVEOLAR OPACITES	Lung disorder	Could not match	0
High MAP d/t accidental change to high dose study drug IV bag	Mean arterial pressure increased	Could not match	0
Improperly Placed VV-ECMO Cannula	Medical device complication	Could not match	0
Lower Extremity Flexion Disorder	Neuromyopathy	Could not match	0
Peroneal nerve dysfunc	Neuropathy peripheral	Could not match	0
body edema	Oedema	Could not match	0
WORSENING EDEMA	Oedema	Could not match	0
+2 pitting edema bilateral lower extremities	Oedema peripheral	Could not match	0
Left upper extremity edema	Oedema peripheral	Could not match	0
Pitting left extremity edema	Oedema peripheral	Could not match	0
Left lung collapse	Pneumothorax	Could not match	0
Right lung collapse	Pneumothorax	Could not match	0
Intermittent vasovagal episodes	Presyncope	Could not match	0

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Bleeding at Surgical Site (Scrotum)	Procedural haemorrhage	Could not match	0
Significant fevers	Pyrexia	Could not match	0
Worsening Fevers	Pyrexia	Could not match	0
Worsening Kidney Function	Renal impairment	Could not match	0
Worsening of bilateral lower extremity mottling	Skin discolouration	Could not match	0
LEAKING AROUND GASTRIC TUBE	Stoma site extravasation	Could not match	0
Non-occlusive clot in left common femoral vein	Thrombosis	Could not match	0
occasional pre-ventricular contractions	Ventricular extrasystoles	Could not match	0
Cardiac arrhythmia V Fib	Ventricular fibrillation	Could not match	0
Left Facial Droop	VIIIth nerve paralysis	Could not match	0
Eccentric jet to anterior leaflet of mitral valve, regurgitation	Aortic valve incompetence	Partial word match to PT	9
Cellulitis/skin tear: Left neck due to central line	Catheter site cellulitis	Partial word match to PT	10
Small pressure ulcer on auricle of ear both sides	Decubitus ulcer	Partial word match to PT	10
granuloma at the exit of the endotracheal tube	Medical device site granuloma	Partial word match to PT	10
Bloody Output From Naso Gastric Tube due to Gastric Bleeding	Gastric haemorrhage	Partial word match to PT	11
Nonocclusive thrombus in the right brachial vein	Peripheral artery thrombosis	Partial word match to PT	11
symmetrical drug-related intertriginous and flexural exanthem	Drug eruption	Partial word match to PT	13
INTERMITTENT BLEEDING AROUND VASCATH SITE	Catheter site haemorrhage	Partial word match to PT	14
Increased QT interval on ECG	Electrocardiogram QT prolonged	Partial word match to PT	14
Weak Bilateral Dorsalis Pedis Pulse	Pedal pulse abnormal	Partial word match to PT	14
new onset digital ischaemia left hand	Peripheral ischaemia	Partial word match to PT	14
New onset digital ischaemia right	Peripheral ischaemia	Partial word match to PT	14

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
hand			
Refractory shock secondary to overwhelming sepsis	Septic shock	Partial word match to PT	14
Reperforation of gastric suture line	Suture related complication	Partial word match to PT	14
Severe Acute Aortic Insufficiency	Aortic valve incompetence	Partial word match to PT	17
Global hypoxic-ischemic brain injury.	Cerebral ischaemia	Partial word match to PT	17
Coccyx and buttock pressure ulcer	Decubitus ulcer	Partial word match to PT	17
Wide QRS rhythm	Electrocardiogram QRS complex prolonged	Partial word match to PT	17
Unsurvivable end stage liver failure	Hepatic failure	Partial word match to PT	17
Increased elevated INR	International normalised ratio increased	Partial word match to PT	17
Asynchronous breathing on ventilator	Mechanical ventilation complication	Partial word match to PT	17
Worsening Digital and Limb Ischemia	Peripheral ischaemia	Partial word match to PT	17
Worsening right lower lobe effusion	Pleural effusion	Partial word match to PT	17
Possible localized contained perforation in upper abdomen in area of small bowel	Small intestinal perforation	Partial word match to PT	17
MRSA Positive Nasal Swab	Staphylococcus test positive	Partial word match to PT	17
Positive Blood Culture Stenotrophomonas Maltophilia (infection)	Stenotrophomonas infection	Partial word match to PT	17
Positive Sputum Culture Stenotrophomonas Maltophilia (Infection)	Stenotrophomonas infection	Partial word match to PT	17
Elevated Lactate	Blood lactic acid increased	Partial word match to PT	20
Low Magnesium Level	Blood magnesium	Partial word match to PT	20

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
	decreased		
Low inorganic phosphorus	Blood phosphorus decreased	Partial word match to PT	20
Right Heel Pressure Ulcer	Decubitus ulcer	Partial word match to PT	20
stage 2 pressure ulcer	Decubitus ulcer	Partial word match to PT	20
Stage I pressure ulcer	Decubitus ulcer	Partial word match to PT	20
Worsening Coccyx Pressure Ulcer	Decubitus ulcer	Partial word match to PT	20
Reduced conciousness	Depressed level of consciousness	Partial word match to PT	20
Increased QT interval	Electrocardiogram QT prolonged	Partial word match to PT	20
left chest subcutaneous hemorrhage	Haemorrhage subcutaneous	Partial word match to PT	20
Worsening liver function	Hepatic function abnormal	Partial word match to PT	20
Bilateral airspace disease	Interstitial lung disease	Partial word match to PT	20
Asynchronous with ventilator	Mechanical ventilation complication	Partial word match to PT	20
Dysynchronous with ventilator	Mechanical ventilation complication	Partial word match to PT	20
Endotracheal tube pain	Medical device pain	Partial word match to PT	20
Progressive Multi-organ dysfunction due to severe septic shock	Multi-organ failure	Partial word match to PT	20
High NG aspirates	Nasogastric output high	Partial word match to PT	20
LOW BLOOD OXYGEN	Oxygen saturation decreased	Partial word match to PT	20
Bilateral Lower Limb Ischaemia	Peripheral ischaemia	Partial word match to PT	20
digital ischaemia both hands	Peripheral ischaemia	Partial word match to PT	20
trace bilateral lung effusions	Pleural effusion	Partial word match to PT	20
Bilateral lower extremity pulselessness	Pulse absent	Partial word match to PT	20
Type I Resp Failure	Respiratory failure	Partial word match to PT	20
Fungal UTI	Urinary tract infection fungal	Partial word match to PT	20
Frequent premature Ventricular	Ventricular	Partial word match to PT	20

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Contractions	extrasystoles		
3 cm vegetation of aortic valve with perforation	Cardiac valve vegetation	Partial word match to PT	22
Decreased bowel function due to intensive care treatment	Functional gastrointestinal disorder	Partial word match to PT	22
Fast Atrial fibulation	Atrial fibrillation	Partial word match to PT	25
Low phosphate	Blood phosphorus decreased	Partial word match to PT	25
low potassium	Blood potassium decreased	Partial word match to PT	25
ventricular fibrillation arrest	Cardiac arrest	Partial word match to PT	25
INTERMITTENT BLEEDING FROM THE FEMORAL CATHETER SITE	Catheter site haemorrhage	Partial word match to PT	25
dialysis catheter occlusion	Device occlusion	Partial word match to PT	25
Non specific ST and T wave abnormality with myocardial changes	Electrocardiogram ST-T segment abnormal	Partial word match to PT	25
bleeding left eye	Eye haemorrhage	Partial word match to PT	25
Increased GGT	Gamma-glutamyltransferase increased	Partial word match to PT	25
Delayed gastrointestinal (GI) motility	Gastrointestinal hypomotility	Partial word match to PT	25
Worsening Liver Failure	Hepatic failure	Partial word match to PT	25
Small bowel ischaemia	Intestinal ischaemia	Partial word match to PT	25
suspected mesenteric ischemia	Intestinal ischaemia	Partial word match to PT	25
recurrent perforated bowel	Intestinal perforation	Partial word match to PT	25
acute liver impairment	Liver disorder	Partial word match to PT	25
left lung opacification	Lung disorder	Partial word match to PT	25
Impaired functional mobility	Mobility decreased	Partial word match to PT	25
upper extrimity weakness	Muscular weakness	Partial word match to PT	25
Mild peripheral edema	Oedema peripheral	Partial word match to PT	25
pain in penis	Penile pain	Partial word match to PT	25
Bilateral Digital Ischemia	Peripheral ischaemia	Partial word match to PT	25
Left Arm Swelling	Peripheral swelling	Partial word match to PT	25
Right Arm Swelling	Peripheral swelling	Partial word match to PT	25

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Upper Extremity swelling	Peripheral swelling	Partial word match to PT	25
Excess pleural fluid	Pleural effusion	Partial word match to PT	25
Impaired peripheral perfusion	Poor peripheral circulation	Partial word match to PT	25
DIFFUSE PULMONARY EDEMA	Pulmonary oedema	Partial word match to PT	25
Increased pulmonary edema	Pulmonary oedema	Partial word match to PT	25
WORSENING PULMONARY EDEMA	Pulmonary oedema	Partial word match to PT	25
worsening pulmonary edema	Pulmonary oedema	Partial word match to PT	25
Worsening Respiratory sepsis	Pulmonary sepsis	Partial word match to PT	25
Full Body Rash	Rash generalised	Partial word match to PT	25
Worsening Renal Function	Renal impairment	Partial word match to PT	25
worsening renal function	Renal impairment	Partial word match to PT	25
Acute hemorrhagic shock	Shock haemorrhagic	Partial word match to PT	25
Small Subarachnoid Hemorrhage	Subarachnoid haemorrhage	Partial word match to PT	25
Tracheostomy Stoma dehiscence	Wound dehiscence	Partial word match to PT	25
Non-traumatic compartment of the abdomen	Abdominal compartment syndrome	Partial word match to PT	29
Worsening of severe hypoxic ischemic brain injury	Brain hypoxia	Partial word match to PT	29
acute compensated systolic congestive heart failure	Cardiac failure congestive	Partial word match to PT	29
bilateral lower extremity deep venous thrombosis	Deep vein thrombosis	Partial word match to PT	29
worsening of Multiple Organ Dysfunction Syndrome	Multi-organ failure	Partial word match to PT	29
worsening of fulminant hepatic failure	Acute hepatic failure	Partial word match to PT	33
ELEVATED AMMONIA	Ammonia increased	Partial word match to PT	33
worsening of anemia	Anaemia	Partial word match to PT	33
Rise in bloodgas lactate	Blood lactic acid increased	Partial word match to PT	33
Worsening lactic acid, increased	Blood lactic acid increased	Partial word match to PT	33
Bradycardic arrest	Cardiac arrest	Partial word match to PT	33
PEA arrest	Cardiac arrest	Partial word match to PT	33

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
PEA arrest	Cardiac arrest	Partial word match to PT	33
impaired myocardial function test	Cardiac function test abnormal	Partial word match to PT	33
PULSELESS ELECTRICAL ACTIVITY CARDIOPULMONARY ARREST	Cardio-respiratory arrest	Partial word match to PT	33
Left hand cyanotic	Cyanosis	Partial word match to PT	33
Candida Glabrata fungemia	Fungaemia	Partial word match to PT	33
Worsening of hyperbilirubnia	Hyperbilirubinaemia	Partial word match to PT	33
Colon ischemia	Intestinal ischaemia	Partial word match to PT	33
Right internal jugular vein DVT	Jugular vein thrombosis	Partial word match to PT	33
On lower lip a small blister	Lip blister	Partial word match to PT	33
Fungal Lung Infection	Lower respiratory tract infection fungal	Partial word match to PT	33
Left hand dusky nail bed	Nail bed disorder	Partial word match to PT	33
Limb Ischaemia	Peripheral ischaemia	Partial word match to PT	33
limb ischemia	Peripheral ischaemia	Partial word match to PT	33
left hand distal necrosis of skin	Skin necrosis	Partial word match to PT	33
BAL CULTURE POSITIVE Staph aureus	Staphylococcus test positive	Partial word match to PT	33
BLOOD CULTURE POSITIVE Staph aureus	Staphylococcus test positive	Partial word match to PT	33
Elevated transaminases	Transaminases increased	Partial word match to PT	33
elevated transaminases	Transaminases increased	Partial word match to PT	33
Worsening Transaminitis	Transaminases increased	Partial word match to PT	33
ELEVATED TROPONIN	Troponin increased	Partial word match to PT	33
Worsening Troponitis	Troponin increased	Partial word match to PT	33
OCCCLUSIVE DEEP VENOUS THROMBOSIS ON LEFT BRACHIAL VIEN	Deep vein thrombosis	Partial word match to PT	38
Rise in Alanine Aminotransferase	Alanine aminotransferase increased	Partial word match to PT	40
LEFT RADIAL ARTERY OCCLUSION	Arterial occlusive	Partial word match to PT	40

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
	disease		
Low cardiac output state	Cardiac output decreased	Partial word match to PT	40
Non-resolution of distriubutive shock	Distributive shock	Partial word match to PT	40
LESS RESPONSIVE to stimuli	Hyporesponsive to stimuli	Partial word match to PT	40
Right internal jugular thrombus	Jugular vein thrombosis	Partial word match to PT	40
right radial artery thrombus	Peripheral artery thrombosis	Partial word match to PT	40
Metastatic small cenll carcinoma	Small cell carcinoma	Partial word match to PT	40
worsening anemia	Anaemia	Partial word match to PT	50
WORSENING ANEMIA	Anaemia	Partial word match to PT	50
Worsening anemia	Anaemia	Partial word match to PT	50
Worsening Anemia	Anaemia	Partial word match to PT	50
WOSENING ANEMIA	Anaemia	Partial word match to PT	50
Radial Artery Occlusion	Arterial occlusive disease	Partial word match to PT	50
Increasing Total Bilirubin	Blood bilirubin increased	Partial word match to PT	50
Worsening creatinine, increased	Blood creatinine increased	Partial word match to PT	50
Increased Lactate	Blood lactic acid increased	Partial word match to PT	50
Worsening Cardio respiratory failure	Cardiopulmonary failure	Partial word match to PT	50
C-difficile infection	Clostridium difficile infection	Partial word match to PT	50
Worsening Hyperkalemia	Hyperkalaemia	Partial word match to PT	50
Acute hypernatremia	Hypernatraemia	Partial word match to PT	50
INTERMITTENT HYPERTENSIVE	Hypertension	Partial word match to PT	50
Intermittent hypertensive	Hypertension	Partial word match to PT	50
Ionized hypocalcemia	Hypocalcaemia	Partial word match to PT	50
worsening hypocalcemia	Hypocalcaemia	Partial word match to PT	50
INTERMITTENT HYPOGLYCEMIA	Hypoglycaemia	Partial word match to PT	50
Intermittent Hypoglycemia	Hypoglycaemia	Partial word match to PT	50

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Worsening Hypokalemia	Hypokalaemia	Partial word match to PT	50
INTERMITTENT HYPOPHOSPHATEMIA	Hypophosphataemia	Partial word match to PT	50
intermittent hypophosphotemia	Hypophosphataemia	Partial word match to PT	50
Intermittent Hypoxemia	Hypoxia	Partial word match to PT	50
Severe Hypoxic Encephalopathy	Hypoxic-ischaemic encephalopathy	Partial word match to PT	50
altered mental status	Mental status changes	Partial word match to PT	50
Altered Mental status	Mental status changes	Partial word match to PT	50
ALTERED MENTAL STATUS	Mental status changes	Partial word match to PT	50
worsening multiorgan failure	Multi-organ failure	Partial word match to PT	50
WORSENING MULTIORGAN FAILURE	Multi-organ failure	Partial word match to PT	50
Poor oxygen saturation	Oxygen saturation decreased	Partial word match to PT	50
MATASTATIC PANCREATIC CANCER	Pancreatic carcinoma metastatic	Partial word match to PT	50
worsening of septic shock	Septic shock	Partial word match to PT	50
Skin breakdown with blisters on torso, arms, face weeping wounds.	Skin disorder	Alternate spelling of LLT Skin disorder (NOS)	50
Low urine output	Urine output decreased	Partial word match to PT	50
LOW URINE OUTPUT	Urine output decreased	Partial word match to PT	50
increase in activated partial thromboplastin time	Activated partial thromboplastin time prolonged	Partial word match to PT	57
Diagnosis of Stage IV Adenocarcinoma of the Lung	Lung adenocarcinoma stage IV	Partial word match to PT	57
Nonspecific T wave abnormality	Electrocardiogram T wave abnormal	Partial word match to PT	60
Multi-organ system failure secondary to pre-existing sepsis	Multi-organ failure	Alternate spelling of LLT Multi-organ failure	60
Worsening Multi system organ failure	Multi-organ failure	Partial word match to PT	60
Worsening Multi-System Organ Failure	Multi-organ failure	Partial word match to PT	60
Worsening of Multi organ failure	Multi-organ failure	Partial word match to PT	60

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
worsening of multiple organ failure	Multi-organ failure	Partial word match to PT	60
POSITIVE OCCULT BLOOD IN STOOL	Oculta blood positive	Partial word match to PT	60
Infected right leg post operative at graft harvest site	Postoperative wound infection	Alternate spelling of LLT Infection of amputation stump	61
Candida albicans culture positive from bronchial discharge	Respiratory moniliasis	Alternate spelling of LLT Candidiasis of bronchi	62
INTERMITTENT FLUID LEAK AROUND THE CHEST TUBE SITE	Medical device complication	Alternate spelling of LLT Intrauterine device disorder	63
intra abdominal abscess requiring surgical intervention	Abdominal abscess	Alternate spelling of LLT Intra-abdominal abscess	67
Fast atrial fibrillation	Atrial fibrillation	Partial word match to PT	67
increased bilirubin	Blood bilirubin increased	Partial word match to PT	67
Increased triglycerides	Blood triglycerides increased	Partial word match to PT	67
WIDE QRS WITH RIGHT BUNDLE BRANCH BLOCK	Bundle branch block right	Partial word match to PT	67
extremity pain	Pain in extremity	Partial word match to PT	67
Worsening necrotizing pancreatitis	Pancreatitis necrotizing	Partial word match to PT	67
secondary bacterial peritonitis	Peritonitis bacterial	Partial word match to PT	67
OROPHARYNGEAL BLEEDING DUE TO AGGRESSIVE SUCTIONING	Pharyngeal haemorrhage	Alternate spelling of LLT Oropharyngeal hemorrhage	67
left pleural effusion	Pleural effusion	Partial word match to PT	67
Staphylococcus haemolyticus culture positive from abdominal cavity	Staphylococcus test positive	Alternate spelling of LLT Staphylococcus saprophyticus test positive	67
intermittent urine retention	Urinary retention	Partial word match to PT	67
Yeast grown in pleural fluid and blood cultures	Fungal test positive	Alternate spelling of LLT Yeast in stool identified	68
acute kidney injury on chronic kidney injury stage 4	Acute kidney injury	Alternate spelling of LLT Acute on chronic renal	69

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
		failure	
skin lesions to left hand and bilateral feet	Skin lesion	Alternate spelling of LLT Skin lesion NOS	69
Accidental change to high dose study drug IV bag	Incorrect dose administered	Alternate spelling of LLT Accidental dose decrease	70
Microcytic Anaemia secondary to Heparin Infusion	Microcytic anaemia	Alternate spelling of LLT Microcytic anaemia	70
Staphylococcus saprophyticus culture positive in removed CV-catheter	Staphylococcus test positive	Alternate spelling of LLT Staphylococcus saprophyticus test positive	71
macular rash bilateral upper extremities	Rash macular	Alternate spelling of LLT Macular rash	72
Stevens Johnson Syndrome/Toxic Epidermal Necrolysis	Stevens-Johnson syndrome	Alternate spelling of LLT Stevens Johnson syndrome	72
Pulmonary contusion from trauma from procedure	Pulmonary contusion	Alternate spelling of LLT Pulmonary contusion	73
superficial venous thrombi to bilateral upper extremities	Thrombophlebitis superficial	Alternate spelling of LLT Superficial venous thrombosis of arm	74
Ventricular tachycardia short runs self reversing	Ventricular tachycardia	Alternate spelling of LLT Ventricular tachycardia	74
Pressure ulcer on right plantar foot	Decubitus ulcer	Alternate spelling of LLT Pressure sore	75
Prolonged QT	Electrocardiogram QT prolonged	Alternate spelling of LLT Prolonged ventricular repolarization	75
Cutaneous yeast infection of the groin	Fungal skin infection	Alternate spelling of LLT Cutaneous fungal disease	75
Worsening Multi organ failure	Multi-organ failure	Partial word match to PT	75
WORSENING MULTI ORGAN FAILURE	Multi-organ failure	Partial word match to PT	75
Worsening Multi Organ Failure	Multi-organ failure	Partial word match to PT	75
Worsening multi organ failure	Multi-organ failure	Partial word match to PT	75
WORSENING MULTISYSEM ORGAN FAILURE	Multi-organ failure	Partial word match to PT	75
Worsening Multisystem Organ	Multi-organ failure	Partial word match to PT	75

Reported Term (AETERM)	MedDRA PT (AEDECOD)	Match Details	Score
Failure			
WORSENING MULTISYSTEM ORGAN FAILURE	Multi-organ failure	Partial word match to PT	75
WORSENING Multisystem organ failure	Multi-organ failure	Partial word match to PT	75
Worsening multisystem organs failure	Multi-organ failure	Partial word match to PT	75
Worsening Plasma cell leukemia	Plasma cell leukaemia	Partial word match to PT	75
Aspiration / Regurgitation event into Lungs	Aspiration	Alternate spelling of LLT Aspiration of gastrointestinal contents into airways	76
Cardiogenic Shock with withdrawal of care	Cardiogenic shock	Alternate spelling of LLT Cardiogenic shock	76
overmedication of treatment "ARGANOVA"	Overdose	Alternate spelling of LLT Overmedication	76
prolonged QT on ECG	Electrocardiogram QT prolonged	Alternate spelling of LLT Prolonged ventricular repolarization	77
Ascites of right upper quadrant	Ascites	Alternate spelling of LLT Ascites chylous	78
C-difficile gastrointestinal infection	Clostridium difficile colitis	Alternate spelling of LLT C.difficile colitis	78
Pressure ulcer in left inner nare	Decubitus ulcer	Alternate spelling of LLT Pressure sore	78
necrotic skin of toes bilaterally	Skin necrosis	Alternate spelling of LLT Necrosis skin	78
necrotic ulceration of fingers	Skin necrosis	Alternate spelling of LLT Necrosis skin	79

13.4. Definition of Adverse events of interest

The applicant defined the events of special interest for this study in the protocol and in the statistical analysis plan. The protocol (page 37) defines the events of interest this way:

- Myocardial infarction/ischemia, not simply elevated troponin levels
- Relevant dysrhythmias including atrial fibrillation
- Re-entrant atrio-ventricular nodal tachycardia, or ventricular tachycardia

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Angiotensin II

- Cerebral ischemia
- Hypoperfusion such as digital ischemia, mesenteric ischemia or shock liver
- Renal hypoperfusion
- Local vasoconstriction or necrosis at or near infusion site

In the statistical analysis plan these events are translated into the following definitions of group terms in MedDRA

- *Arrhythmia: MedDRA SMQ Arrhythmias narrow search and QTc prolongation*
- *Ischemia and vasoconstriction: SOC Vascular disorders with High Level Group Term (HLGT) of Arteriosclerosis, stenosis, vascular insufficiency and necrosis and SOC-General disorders and administration site reactions with HLGT of Administration site conditions*

In the event listing below all events observed that correspond to the above definitions are included and are organized according to the two main groups: Ischemia/vasoconstriction and Arrhythmia and sub grouped according to system organ class.

Events that have a ~~line through~~ are events that have been suggested do not match the definitions and are not part of the commitment specified in the protocol and the SAP and therefore should not be included

Ischemia/vasoconstriction

Nervous system disorders

Brain hypoxia
Cerebral infarction
Cerebral ischaemia
Hypoxic-ischaemicencephalopathy

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Ischemic stroke



Cardiac disorders

Acute myocardial infarction
Myocardial infarction

Vascular disorders

Peripheral ischemia
Peripheral coldness
Poor peripheral circulation
Vasospasm



Gastrointestinal disorders

Intestinal ischaemia

Hepatobiliary disorders

Ischaemic hepatitis

Skin and subcutaneous tissue disorders

Skin necrosis



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Arrhythmia

Cardiac disorders

Arrhythmia Atrial
fibrillation Atrial
flutter
Atrial tachycardia
Atrioventricular block
Bundle branch block right
Nodal arrhythmia Pulseless
electrical activity Sinus
arrest
Sinus tachycardia Supraventricular
extrasystoles Supraventricular
tachycardia Tachycardia
Ventricular extrasystoles
Ventricular fibrillation
Ventricular tachycardia

Investigations

Electrocardiogram QT prolonged

13.5. Completed list of PTs for Routine Safety Assessment

Table 76 Incidence of hypersensitivity-related AEs

SMQ/Preferred term	AE	
	LJPC-501 N = 163	Placebo N=158
Hypersensitivity (SMQ, broad)	39 (23.9%)	36 (22.8%)
Respiratory failure	9 (5.5%)	12 (7.6%)
Acute respiratory failure	5 (3.1%)	5 (3.2%)
Generalised oedema	3 (1.8%)	5 (3.2%)
Shock	4 (2.5%)	3 (1.9%)
Distributive shock	1 (0.6%)	4 (2.5%)
Blister	3 (1.8%)	1 (0.6%)
Respiratory distress	1 (0.6%)	2 (1.3%)
Conjunctival oedema	2 (1.2%)	0 (0.0%)
Wheezing	1 (0.6%)	1 (0.6%)
Skin necrosis	1 (0.6%)	1 (0.6%)
Interstitial lung disease	0 (0.0%)	2 (1.3%)
Pruritus	2 (1.2%)	0 (0.0%)
Rash	1 (0.6%)	1 (0.6%)
Rash generalised	1 (0.6%)	1 (0.6%)
Rash maculo-papular	1 (0.6%)	0 (0.0%)
Respiratory arrest	1 (0.6%)	0 (0.0%)
Dermatitis bullous	1 (0.6%)	0 (0.0%)
Conjunctivitis	1 (0.6%)	0 (0.0%)
Mouth ulceration	1 (0.6%)	0 (0.0%)
Eye swelling	1 (0.6%)	0 (0.0%)
Skin erosion	1 (0.6%)	0 (0.0%)
Laryngeal oedema	1 (0.6%)	0 (0.0%)
Stevens-Johnson syndrome	1 (0.6%)	0 (0.0%)
Stridor	1 (0.6%)	0 (0.0%)
Drug eruption	1 (0.6%)	0 (0.0%)
Circulatory collapse	0 (0.0%)	1 (0.6%)
Drug hypersensitivity	0 (0.0%)	1 (0.6%)
Hypersensitivity	0 (0.0%)	1 (0.6%)
Scleral oedema	1 (0.6%)	0 (0.0%)
Localised oedema	0 (0.0%)	1 (0.6%)
Rash macular	0 (0.0%)	1 (0.6%)
Scrotal oedema	0 (0.0%)	1 (0.6%)

Table 77 Incidence of drug-induced liver toxicities-related AEs

SMQ/Preferred term	AE	
	LJPC-501 N = 163	Placebo N=158
Drug related hepatic disorders - comprehensive search (SMQ)	23 (14.1%)	21 (13.3%)
Transaminases increased	1 (0.6%)	5 (3.2%)
Ascites	4 (2.5%)	2 (1.3%)
Ischaemic hepatitis	2 (1.2%)	4 (2.5%)
Liver function test abnormal	4 (2.5%)	0 (0.0%)
Alanine aminotransferase increased	2 (1.2%)	1 (0.6%)
Hyperammonaemia	2 (1.2%)	1 (0.6%)
Hepatic failure	2 (1.2%)	1 (0.6%)
International normalised ratio increased	1 (0.6%)	1 (0.6%)
Aspartate aminotransferase increased	1 (0.6%)	1 (0.6%)
Hepatic function abnormal	1 (0.6%)	1 (0.6%)
Blood bilirubin increased	1 (0.6%)	1 (0.6%)
Acute hepatic failure	0 (0.0%)	2 (1.3%)
Gamma-glutamyltransferase increased	1 (0.6%)	0 (0.0%)
Hepatic lesion	1 (0.6%)	0 (0.0%)
Liver disorder	1 (0.6%)	0 (0.0%)
Hepatic cancer	1 (0.6%)	0 (0.0%)
Liver injury	1 (0.6%)	0 (0.0%)
Ammonia increased	1 (0.6%)	0 (0.0%)
Hepatic encephalopathy	1 (0.6%)	0 (0.0%)
Hypoalbuminaemia	1 (0.6%)	0 (0.0%)
Hepatic enzyme increased	0 (0.0%)	1 (0.6%)
Hyperbilirubinaemia	0 (0.0%)	1 (0.6%)
Hypocoagulable state	0 (0.0%)	1 (0.6%)

Table 78 Incidence of acute renal injury-related AEs

SMQ/Preferred term	AE	
	LJPC-501 N = 163	Placebo N=158
Acute renal failure (SMQ, broad)	14 (8.6%)	18 (11.4%)
Acute kidney injury	8 (4.9%)	10 (6.3%)
Renal impairment	2 (1.2%)	2 (1.3%)
Oliguria	1 (0.6%)	2 (1.3%)
Renal failure	1 (0.6%)	1 (0.6%)
Urine output decreased	1 (0.6%)	1 (0.6%)
Anuria	1 (0.6%)	1 (0.6%)
Renal tubular necrosis	0 (0.0%)	1 (0.6%)
Blood creatinine increased	0 (0.0%)	1 (0.6%)

13.6. Renal-related efficacy endpoints

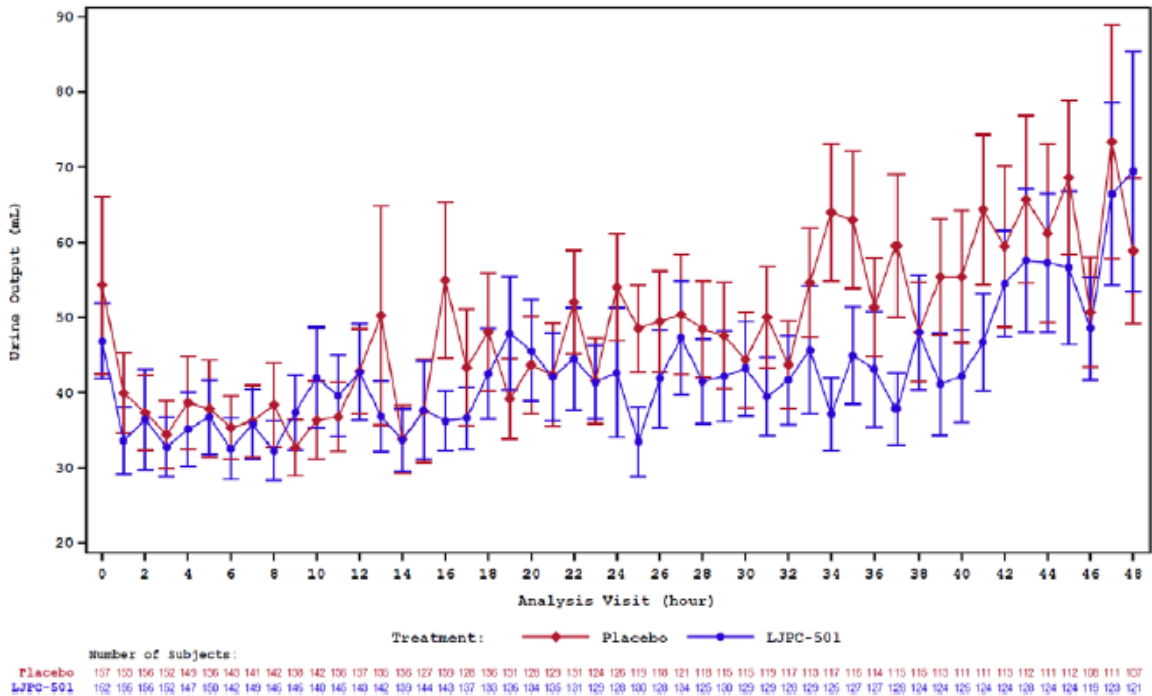
Urine output was an exploratory efficacy endpoint and was measured at screening, Day 1 (0 to 3 hours), Day 1 (3 to 24 hours) and Day 2 (24 to 48 hours). Overall, urine output was similar between the arms.

Table 48: Urine Output by Study Period (mITT Population)

Time Point/Period Statistic (mL/h)	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Baseline^a	(N = 157)	(N = 162)	(N = 319)
Mean (SD)	54.3 (148.19)	46.8 (63.96)	50.5 (113.40)
Median (range)	19.2 (0.0 – 1750.0)	23.0 (0.0 – 339.2)	20.0 (0.0 – 1750.0)
Hour > 0 to Hour 3	(N = 158)	(N = 161)	(N = 319)
Mean (SD)	38.5 (58.12)	36.0 (58.00)	37.3 (57.98)
Median (range)	16.3 (0.0 – 358.3)	19.0 (0.0 – 393.3)	18.3 (0.0 – 393.3)
Change from Baseline	(N = 157)	(N = 160)	(N = 317)
Mean (SD)	-15.8 (132.72)	-11.1 (57.28)	-13.4 (101.75)
Median (range)	0.0 (-1571 – 165.8)	-2.5 (-286.7 – 393.3)	-1.7 (-1571 – 393.3)
p value	p = 0.0207		
Hour > 3 to Hour 48	(N = 155)	(N = 161)	(N = 316)
Mean (SD)	48.1 (64.55)	43.2 (61.92)	45.6 (63.17)
Median (range)	20.8 (0.0 – 370.5)	22.6 (0.0 – 540.0)	21.4 (0.0 – 540.0)
Change from Baseline	(N = 154)	(N = 160)	(N = 314)
Mean (SD)	-6.8 (139.79)	-4.0 (60.99)	-5.3 (106.97)
Median (range)	0.0 (-1641 – 175.5)	-0.1 (-222.4 – 390.0)	0.0 (-1641 – 390.0)
p value	p = 0.2743		
Change from Hour 3	(N = 155)	(N = 159)	(N = 314)
Mean (SD)	8.9 (44.56)	7.2 (51.91)	8.1 (48.35)
Median (range)	0.5 (-174.7 – 203.8)	1.1 (-244.3 – 340.0)	0.8 (-244.3 – 340.0)
p value	p = 0.7830		

Source: CSR p127

Figure 23: Mean (SE) Urine Output by Hour to Hour 48 (mITT Population)



Source: CSR p128

There was also no significant differences between the arms on SOFA scores in the renal system.

Table 51: SOFA Score by System at Screening and Hour 48 (mITT Population)

	Timepoint Statistic	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Respiratory System	Screening	(N = 158)	(N = 163)	(N = 321)
	Mean (SD)	2.32 (1.118)	2.24 (1.099)	2.28 (1.107)
	Median (range)	2.0 (0 - 4)	2.0 (0 - 4)	2.0 (0 - 4)
	Day 2, Hour 48	(N = 158)	(N = 163)	(N = 321)
	Mean (SD)	2.49 (1.230)	2.23 (1.184)	2.36 (1.212)
	Median (range)	3.0 (0 - 4)	2.0 (0 - 4)	2.0 (0 - 4)
	Change from Screening	(N = 158)	(N = 163)	(N = 321)
	Mean (SD)	0.17 (1.227)	-0.01 (1.354)	0.08 (1.294)
	Median (range)	0 (-3 - 4)	0 (-4 - 4)	0 (-3 - 4)
	p-value	p = 0.4725		
Nervous System	Screening			
	Mean (SD)	2.60 (1.321)	2.18 (1.496)	2.39 (1.426)
	Median (range)	3.0 (0 - 4)	2.0 (0 - 4)	3.0 (0 - 4)
	Day 2, Hour 48			
	Mean (SD)	2.66 (1.329)	2.48 (1.509)	2.57 (1.424)
	Median (range)	3.0 (0 - 4)	3.0 (0 - 4)	3.0 (0 - 4)
	Change from Screening			
	Mean (SD)	0.06 (1.290)	0.29 (1.457)	0.18 (1.380)
	Median (range)	0 (-4 - 4)	0 (-3 - 4)	0 (-4 - 4)
	p-value	p = 0.3198		
Liver	Screening			
	Mean (SD)	1.10 (1.185)	0.78 (0.972)	0.94 (1.094)
	Median (Range)	1.0 (0 - 4)	0.0 (0 - 3)	0.0 (0 - 4)
	Day 2, Hour 48			
	Mean (SD)	1.64 (1.577)	1.38 (1.411)	1.51 (1.498)
	Median (range)	2.0 (0 - 4)	1.0 (0 - 4)	1.0 (0 - 4)
	Change from Screening			
	Mean (SD)	0.54 (1.138)	0.62 (1.241)	0.58 (1.190)
	Median (range)	0.0 (-1 - 4)	0.0 (-2 - 4)	0.0 (-2 - 4)
	p-value	p = 0.5445		

	Timepoint Statistic	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Coagulation	Screening	(N = 158)	(N = 162)	(N = 320)
	Mean (SD)	0.99 (1.154)	0.91 (1.042)	0.95 (1.098)
	Median (range)	0.5 (0 – 4)	1.0 (0 – 4)	1.0 (0 – 4)
	Day 2, Hour 48	(N = 158)	(N = 163)	(N = 321)
	Mean (SD)	1.89 (1.542)	1.92 (1.388)	1.91 (1.463)
	Median (range)	2.0 (0 – 4)	2.0 (0 – 4)	2.0 (0 – 4)
	Change from Screening	(N = 158)	(N = 162)	(N = 320)
	Mean (SD)	0.90 (1.303)	1.02 (1.233)	0.96 (1.267)
	Median (range)	1.0 (-2 – 4)	1.0 (-1 – 4)	1.0 (-2 – 4)
p-value	p = 0.4721			
Renal System	Screening	(N = 158)	(N = 162)	(N = 320)
	Mean (SD)	1.70 (1.208)	1.65 (1.363)	1.68 (1.287)
	Median (range)	2.0 (0 – 4)	2.0 (0 – 4)	2.0 (0 – 4)
	Day 2, Hour 48	(N = 158)	(N = 163)	(N = 321)
	Mean (SD)	2.35 (1.708)	2.44 (1.663)	2.40 (1.683)
	Median (range)	3.0 (0 – 4)	3.0 (0 – 4)	3.0 (0 – 4)
	Change from Screening	(N = 158)	(N = 162)	(N = 320)
	Mean (SD)	0.65 (1.547)	0.78 (1.516)	0.72 (1.530)
	Median (range)	0.0 (-3 – 4)	0.0 (-3 – 4)	0.0 (-3 – 4)
p-value	p = 0.2054			

Source: CSR p131-132

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13.7. Adverse events from literature

Table 15: Adverse Events in Published Studies of Angiotensin II in Hypotensive Shock

Preferred Term	Number (%) of Patients				
	Singh 1966		Chawla 2014		Combined
	NE (N = 25)	Val ⁵ -Ang II (N = 25)	Placebo added to NE (N = 10)	Ile ⁵ -Ang II added to NE (N = 10)	Any Ang II (N = 35)
Cardiac disorders					
Atrial fibrillation	--	--	0	2 (20.0%)	2 (5.7%)
General disorders & administration site conditions					
Flushing	4 (16.0%)	2 (8.0%)	--	--	2 (5.7%)
Tachyphylaxis	15 (60.0%)	8 (32.0%)	--	--	8 (22.9%)
Drug effect increased	0	1 (4.0%)	--	--	1 (2.9%)
Multiorgan failure	--	--	3 (30.0%)	2 (20.0%)	2 (5.7%)
Investigations					
Urine output decreased	--	--	1 (10.0%)	3 (30.0%)	3 (8.6%)
Metabolic & nutrition disorders					
Acidosis	--	--	3 (30.0%)	2 (20.0%)	2 (5.7%)
Alkalosis	--	--	0	4 (40.0%)	4 (11.4%)
Musculoskeletal & connective tissue disorders					
Soft tissue necrosis	10 (40.0%)	0	--	--	0
Nervous system disorders					
Headache	6 (24.0%)	5 (20.0%)	--	--	5 (14.3%)
Renal & urinary disorders					
Acute kidney injury	--	--	2 (20.0%)	0	0
Vascular disorders					
Thrombophlebitis	14 (56.0%)	1 (4.0%)	--	--	1 (2.9%)
Hypertension	--	--	0	2 (20.0%)	2 (5.7%)
Hypotension	--	--	1 (10.0%)	2 (20.0%)	2 (5.7%)
Respiratory, thoracic, & mediastinal disorders					
Respiratory failure	--	--	3 (30.0%)	1 (10.0%)	1 (2.9%)
Wheezing	--	--	0	1 (10.0%)	1 (2.9%)

Abbreviations: Ang II = angiotensin II; Ile⁵-Ang II = angiotensin II with isoleucine as 5th amino acid; NE = norepinephrine; Val⁵-Ang II = angiotensin II with valine as 5th amino acid and amide group on 1-aspartate.

Source: ISS, p38

Clinical Review
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 505(b)(2) NDA 209360
 Angiotensin II

Table 16: Adverse Events Reported in Published Studies of Angiotensin II in Healthy Volunteer Subjects

System Organ Class Preferred Term	Number (%) of Subjects					
	Brod 1969 (N = 15)	Broughton Pipkin 1981 (N = 2)	Hausdorf 1987 (N = 30)	Lim 2007 (N = 13)	Sluiter 1987 (N = 12)	Overall N = 72
General disorders & administration site conditions						
Facial flushing	--	--	--	--	2 (16.7%)	2 (2.8%)
Chest pressure sensation	4 (26.7%)	--	--	--	--	4 (5.6%)
Retrosternal chest pain	--	2 (100%)	--	--	--	2 (2.8%)
Chest tightness	--	2 (100%)	--	--	--	2 (2.8%)
Chest heaviness	--	1 (50.0%)	--	--	--	1 (1.4%)
Oppression	--	--	1 (3.3%)	--	--	1 (1.4%)
Feeling of warmth	--	--	--	--	2 (16.7%)	2 (2.8%)
Nervous system disorders						
Headache	2 (13.3%)	1 (50.0%)	--	1 (7.7%)	2 (16.7%)	6 (8.3%)
Cardiac disorders						
Palpitations	--	--	--	--	1 (8.3%)	1 (1.4%)
Orthostatic dizziness	--	--	--	--	1 (8.3%)	1 (1.4%)
Respiratory, thoracic & mediastinal disorders						
Shortness of breath	1 (6.7%)	--	--	--	--	1 (1.4%)

Source: ISS, p40

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/s/

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