

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209360Orig1s000**

**SUMMARY REVIEW**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

**Cross-Discipline Team Leader Review Addendum**

**DATE:** December 21, 2017

**FROM:** Martin Rose, MD, JD, Cross-Discipline Team Leader

**THROUGH:** Norman Stockbridge, MD, PhD, Division Director

**SUBJECT:** Classification of the Type of NDA

**APPLICATION/DRUG:** NDA 209360 / Angiotensin II acetate (LJPC-501)

Although the Pharmacology/Toxicology and the Clinical Pharmacology reviews refer to published literature, upon further review of the NDA, both Drs. Papoian (the lead for Pharmacology/Toxicology) and Dr. Hariharan (the lead for Clinical Pharmacology) conclude that from the standpoint of their review disciplines, the NDA can be approved based solely on safety and effectiveness data submitted in the NDA that were generated by or for the Applicant. The reviewers did review the literature that was submitted with the application, but it was not necessary to rely on this literature because of the characteristics of angiotensin II and the indicated condition, distributive shock. Angiotensin II is an endogenous small peptide that plays a central role in blood pressure regulation in healthy people. It is continuously present in the circulation. It acts directly on arteries to cause vasoconstriction, thereby increasing peripheral resistance and raising blood pressure. This activity is also the mechanism underlying its pharmacologic use to raise blood pressure in patients with distributive shock, who have pathologically reduced peripheral resistance as the cause of their low blood pressure. As a drug, it is given by intravenous infusion and has a 1-minute half-life. Its effects on blood pressure have a very rapid onset and a very rapid offset when the infusion is stopped. The dose is titrated to a target effect. These properties make extensive clinical pharmacology testing not necessary. Also, the drug is used for a short period of time (several hours to several days) in closely-monitored patients in an intensive care unit, where adverse effects are readily observed and patient data are rarely missing. In addition, as explained in my CDTL review, the condition it treats, distributive shock, has a high short-term mortality rate, which makes us tolerant of missing rare adverse events that might have been hinted at in extensive animal testing. All these factors combine to make the well-controlled study conducted by the Applicant in patients with distributive shock, ATHOS-3, adequate to address any aspects of safety and efficacy. Accordingly, these literature reports are not essential to support the approval of the LJPC-501 NDA.

We on the clinical team also conclude that the clinical studies conducted by or for the applicant alone support the clinical safety and effectiveness of the product and support the approval of the NDA. Thus, all 3 non-CMC review disciplines believe that this application could be approved as a 505(b)(1) application. Accordingly, the sponsor has submitted a revised Form 356h designating NDA 209360 as a 505(b)(1) application.

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/s/  
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MARTIN ROSE  
12/21/2017

NORMAN L STOCKBRIDGE  
12/21/2017

## Cross-Discipline Team Leader Review

<b>Date</b>	December 16, 2017
<b>From</b>	Martin Rose, MD JD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # and Supplement #</b>	NDA 209360 (original)
<b>Applicant</b>	La Jolla Pharmaceutical Company, Inc.
<b>Date of Submission</b>	6/29/2017
<b>PDUFA Goal Date</b>	2/28/2018 (NME - priority)
<b>Proprietary Name</b>	Giapreza (FDA review of this name is not complete)
<b>Established or Proper Name</b>	(human) angiotensin II (code name LJPC-501)
<b>Dosage Form(s)</b>	Solution for dilution in 0.9% saline for continuous IV administration, provided as either 1 mL or 2 mL single use vials, each with a concentration of 2.5 mg/mL
<b>Applicant Proposed Indication(s)/Population(s)</b>	"... treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy"
<b>Applicant Proposed Dosing Regimen(s)</b>	Starting dose of 20 ng/kg/min, titrated to goal BP, with maximum dose rate of 80 ng/kg/min in the first 3 hours, then 40 ng/kg/min after that
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	"Brand Name increases blood pressure in adults with distributive shock."
<b>Recommended Dosing Regimen(s) (if applicable)</b>	Same as the Applicant's

### 1. Benefit-Risk Assessment

## Benefit-Risk Assessment Framework

### Benefit-Risk Integrated Assessment

I recommend approval of LJPC-501 (human angiotensin II) for the treatment of distributive shock in adults. I am not recommending a REMS or any PMRs or PMCs other than PMRs for pediatric studies pursuant to PREA (see Secs. 10 and 13). Each discipline involved in this review recommends approval. The clinical reviewers also concur that no REMS or safety-based post-marketing studies are needed.

The drug substance is the acetate salt of chemically synthesized human-sequence angiotensin II. Angiotensin II is an endogenous octapeptide that upregulates blood pressure in humans and other mammals by two mechanisms: direct arterial vasoconstriction and stimulation of aldosterone synthesis and release in the adrenal cortex. Angiotensin II is an important regulator of blood pressure and fluid and sodium balance in health and disease. The LJPC-501 drug product is a 3 mL sterile glass vial containing either 1 mL or 2 mL of a solution of the drug substance in water for injection (2.5 mg/mL in either presentation). The product is intended to be diluted in 0.9% saline for continuous intravenous infusion. A drug product closely related to LJPC-501, bovine angiotensin (Hypertensin<sup>®</sup>, NDA 12-791), which differs from the human version by just one amino acid out of eight, was approved by us for the treatment of hypotension associated with shock in 1962. The NDA was voluntarily withdrawn for reasons unrelated to safety in 2009.

Distributive shock is characterized by tissue hypoperfusion and impaired oxygen utilization with reduced systemic vascular resistance, hypotension, and usually elevated lactate levels. Cardiac output is usually normal or elevated, but can be depressed. About 90% of cases of distributive shock are associated with sepsis. Epidemiologic data on distributive shock are scanty, but data for septic shock are a reasonable substitute. I estimate that there were about 194,000 cases of septic shock in US adults in 2016, based on recently published incidence rates and current census data. The incidence of septic shock appears to be increasing over time. Two large, recent series of patients with septic shock reported mortality at 28 days or in the hospital as ~42% to 50%.

Current treatment guidelines for septic shock recommend use of vasopressors, with norepinephrine as first-line therapy, if mean arterial pressure (MAP) is not raised to at least 65 mmHg following adequate fluid resuscitation. However, not one of the drugs with US labeling for use in sepsis or other forms of distributive shock has labeling indicating that the drug improves mortality or any other clinical outcome. These drugs include: norepinephrine, epinephrine, vasopressin, phenylephrine, ephedrine, dopamine and metaraminol. We have not required applicants to show a benefit other than an increase in blood pressure to support approval of drugs to treat hypotension in the setting of shock. We have accepted the belief prevalent in the medical community that treatment of hypotension in patients with shock will improve tissue perfusion and decrease death and serious morbidity, although this hypothesis has never been rigorously evaluated. However, given the high rate of death in patients with septic shock despite treatment, there is clearly an unmet need for additional safe and effective treatments.

The Applicant's NDA is based almost entirely on a single, multicenter, placebo-controlled RCT in 344 randomized adults with distributive shock and persistent hypotension (mean arterial pressure (MAP) 55 to 70 mmHg) after treatment of specified intensity with fluids and vasopressors (ATHOS-3). ATHOS-3 was performed under a special protocol assessment (SPA). The primary endpoint was the rate of MAP response at hour 3 of treatment with study drug, defined as either a 10 mmHg increase from baseline in MAP or an MAP of at least 75 mmHg. During the first 3 hours after randomization, background vasopressor and fluid dosing were not to be changed to avoid confounding. The analysis plan specified that primary endpoint analysis was to be performed

in the mITT population (all randomized and treated patients). After 3 hours, other vasopressors and fluids could be adjusted. Study drug was to be tapered to discontinuation at hour 48, but could be reinstated within 3 hours if a patient developed a CV SOFA score of 4 or more. No patient could receive more than 7 days of treatment with study drug. Patients were followed for vital status until day 28, regardless of whether they were still in the hospital.

The mITT population included 163 and 158 patients in the angiotensin II and placebo arm, respectively. Results for the primary endpoint of MAP response rate strongly favored angiotensin II, with 114 (70%) vs. 37 (23%) responders in the angiotensin II and placebo arm, respectively (OR=7.95, 95% CI, 4.76, 13.3,  $p=2.54E-15$ ). Results and p values similarly extreme were observed in all the sensitivity analyses performed, including the ITT analysis at 3 hours (N=172 in each arm, OR=6.96, (95% CI, 4.27, 11.3,  $p=7.1E-15$ ). This is compelling evidence of efficacy for effects on blood pressure. Both arms had increases in MAP between baseline and hour 3, but the mean increase in MAP was about 7 mmHg larger in the angiotensin II arm. This analysis was not allocated any alpha error, but the difference was highly statistically significant in the Applicant's analysis. Mortality numerically favored angiotensin II over placebo from Day 1 to the end of the study at Day 28, when there were 75 (46%) vs. 85 (54%) deaths in the angiotensin II and placebo arm, respectively (HR=0.78 (0.57, 1.07), log-rank  $p = 0.12$ ).

While the study results do not show a statistically significant effect on mortality or indeed any other outcome, there is compelling evidence of an effect on blood pressure, and no evidence to support fatal harm. Several of the criteria for finding effectiveness based on one study that are described in FDA's 1998 guidance, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, are present here. ATHOS-3 was a well-conducted placebo-controlled, superiority trial with no important flaws in conduct or baseline imbalances in the study arms. The difference between the study arms for the primary endpoint, the MAP response rate, was large and favored angiotensin II. The p value for this endpoint is extreme — less than  $10^{-14}$ . The p values for the various, prespecified sensitivity tests of that endpoint, including the conservative ITT analysis, are also quite extreme. The study was multicenter and conducted globally, with consistent results across regions. Results across demographic subgroups were likewise consistent. Finally, death rates at 7 and 28 days favored angiotensin II over placebo, although the difference between the study arms did not reach statistical significance. The evidence is strong enough to find that ATHOS-3 provides substantial evidence of the effectiveness of angiotensin II to raise MAP in patients with distributive shock.

The most important risk of angiotensin II compared to placebo in ATHOS-3 was an increased rate of arterial and venous thrombotic events, affecting 21 (13%) vs. 8 (5%) patients in the angiotensin II and placebo arm, respectively. These patients included 7 (4%) vs. 0 with deep vein thrombosis. This risk is consistent with preclinical evidence indicated that angiotensin II was prothrombotic in animals. We are proposing a warning to describe this risk.

The analysis of benefit vs. risk is complicated by comparatively higher rates of in the angiotensin II arm for several adverse events or groups of related events that might reflect either systemic hypoperfusion or hypoperfusion of specific organs. However, these events are common in patients with shock, or in the case of delirium, occur occasionally in the ICU in patients with any condition. These events were delirium, which might be due CNS hypoperfusion (9 patients (6%) vs. 1 (< 1%) and peripheral ischemia, which is very likely related to local hypoperfusion (7 (4%) vs. 4 (2%)). Also, there was an imbalance in AEs relating to acidosis, including lactic acidosis, a sign of systemic hypoperfusion (12 patients (7%) vs. 1 (< 1%)); In support of an increased risk of lactic acidosis with angiotensin II, mean lactate levels, which were obtained systematically during the study, were elevated in both treatment arms at baseline, and fell less during treatment with angiotensin II than with placebo (see Clinical Review, Figure 20). These imbalances may be due to chance, just as we think the results for intracranial hemorrhage favoring angiotensin II over placebo (0 vs. 4 patients in the angiotensin II and placebo arm, respectively) are probably due to chance. If any of them are not, they suggest that some sequelae of hypoperfusion may not be improved in some patients as much with angiotensin II as

with other vasopressors. Finally, there was an imbalance in an event cluster than seems probably unrelated to hypoperfusion: fungal infections, including systemic infections and local candida infections (10 (6%) vs. 1 (< 1%). This finding is not predicted by preclinical findings. Even if any the events favoring placebo described above are not due to chance, which seems reasonably likely for the acidosis finding, the results for death favoring angiotensin II are reassuring.

Accordingly, the clinical review team (including this reviewer) thinks that despite the lack of a confirmed benefit for any outcome other than MAP, the benefits of angiotensin II outweighed its risks in the studied population. This population is representative of patients in the US with distributive shock, so the results of ATHOS-3 can be extrapolated to US patients with distributive shock. Other disciplines have stated no objections to approval. Because there is substantial evidence supporting the effectiveness of angiotensin II and its benefits outweigh its risks, I recommend approval.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>• Distributive shock is a subset of shock marked by decreased systemic vascular resistance, organ hypoperfusion and altered oxygen extraction. Typical manifestations are hypotension and hyperlactatemia. Cardiac output is typically high, but myocardial depression is present in some patients. Distributive shock is due to sepsis in about 90% of cases, with the remainder resulting from anaphylaxis or neurogenic causes such as spinal injury or vagal activation from peritonitis or other GI conditions. (1)</li> <li>• Recent publications of large series of patients with septic shock report in-hospital or 28-day mortality rate of 42% to 50%.</li> <li>• Mortality at 28 days or in the hospital in patients with septic shock was reported as ~42% to 50% in two recent publications.</li> </ul>	<p>Distributive shock, which is in most cases is due to sepsis, occurs in roughly 200,00 US adults each year. It is a frequently fatal condition despite intensive monitoring and treatment. Thus, there is an urgent unmet need for effective therapies.</p>
Current Treatment Options	<ul style="list-style-type: none"> <li>• Current treatment guidelines recommend use of vasopressors such as norepinephrine if mean arterial pressure (MAP) is not raised to at least 65 mmHg following adequate fluid resuscitation. However, not one of the drugs with US labeling for use in sepsis or other forms of distributive shock has labeling that the drug improves mortality or any other clinical outcome. These drugs include: norepinephrine, epinephrine, vasopressin, phenylephrine, ephedrine, dopamine and metaraminol.<sup>1</sup> All but</li> </ul>	<p>While there are several vasoconstrictors that are labeled for treating hypotension in patients with shock, none have been convincingly shown to affect anything other than blood pressure, and a high rate of death persists in patient with this condition despite aggressive treatment.</p>

<sup>1</sup> There is only one metaraminol product (from Fresenius Kabi) listed as currently marketed in the Orange Book. However, no labeling is available on the Dailymed site, and the company's web site does not mention the drug.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>dopamine are indicated for raising blood pressure in patients with hypotension in various settings. Dopamine is approved for correcting “hemodynamic imbalances” in patients with shock syndrome.</p>	<p>Nonetheless, we have not required applicants to show a benefit other than an effect on blood pressure to support approval of drugs to treat hypotension in the setting of shock.</p>
<b>Benefit</b>	<ul style="list-style-type: none"> <li>• The NDA was supported by a well-conducted, randomized, double-blind, placebo-controlled, multicenter pharmacodynamic (PD) study of LJPC-501 (ATHOS-3) in patients with distributive shock and hypotension (MAP 55 – 70 mmHg) despite fluid resuscitation and treatment with one or more vasopressors equal to or greater than levels specified in the protocol. The trial was conducted under a SPA. 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) <math>\geq</math> 75 mmHg. This dosing regimen was based on a published placebo-controlled RCT in 20 patients with shock sponsored by George Washington University using Bachem human angiotensin II that suggested that angiotensin II use was associated with reduced need for catecholamines to maintain BP in the target range.</li> <li>• The primary endpoint was the rate of MAP response after 3 hours of treatment with study drug in the mITT (randomized and treated) population. A MAP response was defined as MAP <math>\geq</math> 75 mmHg or a MAP increase of <math>\geq</math> 10 mmHg from baseline. As we did for the marketed vasopressors used to raise blood pressure in patients with shock, we did not require the Applicant to demonstrate a beneficial effect on assessments other than blood pressure.</li> <li>• Patients in each study arm were similar in terms of demographic and disease-related parameters. About 90% of patients in each arm had sepsis or “potential sepsis”. Depending on the prognostic metric considered, patients had an expected short-term death rate of ~20% (based on mean MELD score), ~ 50% (based on mean norepinephrine equivalent dose at baseline), or &gt; 80% (based on mean total SOFA score).</li> <li>• There were 163 subjects in the LJPC-501 arm and 158 subjects in the placebo arm (mITT population). The primary endpoint of 3-hour MAP response was achieved in 114 subjects (70%) in the LJPC-501 arm and in 37 (23%) in the placebo arm (odds ratio 8,</li> </ul>	<p>Subjects in the ATHOS-3 trial were in critical condition with a high mortality risk based on commonly used ICU metrics. At the time of randomization, patients in each arm had persistent hypotension despite administration of fluids and vasopressors.</p> <p>The trial met its primary endpoint of superiority of LJPC-501 over placebo for the rate of MAP response at hour 3, with an OR of 8 and an extreme p value. This analysis was supported by several pre-specified sensitivity analyses. Mortality trended in favor of active treatment.</p> <p>ATHOS-3 is an adequate and well-controlled study that provides substantial evidence of the effectiveness of LJPC-501 for raising blood pressure in patients with distributive shock. The data are strong enough to support approval as a single study.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>95% confidence interval 5—13, <math>p &lt; 10^{-14}</math>). Various pre-specified sensitivity analyses also favored LJPC-501 and had extreme p values. At 28 days, there were 75 (46%) and 85 (54%) deaths in the LJPC-501 arm, respectively (HR = 0.78, 95% CI 0.57-1.07, log rank <math>p=0.12</math>). No alpha error was assigned to this last analysis.</p>	
Risk	<ul style="list-style-type: none"> <li>• The clinical safety of LJPC-501 in patients with CRH was based entirely on data from ATHOS-3. The size and quality of the safety database is consistent with our expectations at the time of the agreement regarding the SPA. The characteristics of patients in ATHOS-3 are generally adequate to represent the indicated US patient population.</li> <li>• The incidence of known toxicities of currently used 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%)</li> <li>• 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.</li> <li>• The major safety concern for LJPC-501 is the risk of thrombosis:             <ul style="list-style-type: none"> <li>○ 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 &amp; 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 rates of DVT prophylaxis treatment (heparin and related drugs) at baseline.</li> <li>○ A prothrombotic effect of angiotensin II has been demonstrated in animals and healthy volunteers</li> <li>○ Use of anticoagulation during treatment with LJPC-501 should be recommended</li> </ul> </li> </ul>	<p>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 favoring LJPC-501.</p> <p>The totality of evidence suggests that there is a risk of drug-related thrombosis. 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 outcomes, although the mortality results described above are reassuring. The risk of thrombosis should be addressed in the Warnings section of labeling and monitored in the post-market setting. Use of anticoagulation during treatment with LJPC-501 should be recommended.</p> <p>Section 6 should include tabular information from ATHOS-3 on the rates of thromboembolic events and other adverse reactions described in this Risk analysis. There are some mechanistic bases for each of these risks. These risks can be medically</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>in labeling.</p> <ul style="list-style-type: none"> <li>• Other safety topics of interest                             <ul style="list-style-type: none"> <li>○ LJPC-501 is intended for short term use with titration to the target blood pressure in the ICU setting. The half-life of LJPC-501 is about one minute, and the onset and offset of the vasoconstrictive effect are very fast. There is limited evidence to suggest any dose-related toxicity.</li> <li>○ Other safety findings from ATHOS-3 include increased rates of acidosis (including lactic acidosis), delirium, hyperglycemia, and peripheral ischemic events.</li> </ul> </li> </ul>	<p>managed in the ICU setting. As for thrombosis, the concerns about the consequences of these potential risks are alleviated by the observed mortality trend favoring LJPC-501.</p> <p>Current labeling recommends that the maximum dose should not exceed (b) (4). Dose related toxicity was not observed in the pivotal trial, possibly because of the titration regimen used in the trial, the kinetic properties of the drug, and the imposed dosing limits.</p>
<p><b>Risk Management</b></p>	<p>The clinical team believes that toxicities of LJPC-501 and safety concerns (b) (4) of the drug can be managed through proper labeling, including a recommendation for prophylactic anticoagulation to reduce the risk of thrombosis.</p>	<p>Patients with refractory distributive shock who are at risk for thrombosis when treated with LJPC-501 can be managed with adequate prophylactic anticoagulation. A risk evaluation and mitigation strategy is not necessary.</p>

## 2. Regulatory Background

### Introduction

LJPC-501 is human-sequence angiotensin II. The proposed trade name “Giapreza” is still under Agency review. The Applicant’s proposed indication was originally "... treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy," This indication tracks the characteristics of the population that was studied in the single, randomized, placebo-controlled, multicenter, PD trial (ATHOS-3) that is the major source of data supporting both efficacy and safety. However, at our suggestion, they are now proposing a revised indication: “BRAND NAME increases blood pressure in adults with septic or other distributive shock.”

LJPC-501 is a chemically-synthesized 8-amino acid peptide (octapeptide) with a sequence identical to that of human angiotensin II. The drug substance is the acetate salt of angiotensin II. Angiotensin II is an endogenous octapeptide that upregulates blood pressure in humans and other mammals through two mechanisms: by directly stimulating arterial vasoconstriction and by triggering synthesis and release of aldosterone from the adrenal cortex. Both these effects are mediated through binding of angiotensin II with the G-protein coupled angiotensin II receptor Type 1 in target tissues.

### Distributive Shock

Because of limited data on other forms of distributive shock, most of the epidemiologic data discussed below will focus on septic shock, which is by far the most common cause of distributive shock in reported series and in the Applicant’s major trial.

Shock has been defined as “the clinical expression of circulatory failure that results in inadequate cellular oxygen utilization.”(1) Distributive shock is a subset of shock marked by decreased systemic vascular resistance, organ hypoperfusion and altered oxygen extraction. Typical manifestations are hypotension and hyperlactatemia. Cardiac output is typically high, but myocardial depression is present in some patients. Distributive shock is due to sepsis in about 90% of cases (1), with the remainder resulting from anaphylaxis or neurogenic causes such as spinal injury or vagal activation from peritonitis or other GI conditions.

The rate of septic shock in the US increased from 12.6 to 78 cases per 100,000 adults (age adjusted) in the US from 1998 to 2009. Given a current population of about 249 million adults, if the 2009 rate still held, there an expected rate of 194,000 cases of septic shock in the US this year. Septic shock is a condition of the elderly. The mean age of patients with this condition is 69 (2), so rates of septic shock might still be increasing as our population ages. Mortality at 28 days or in the hospital in patients with septic shock was ~42% to 50% in two recent publications, each describing thousands of cases, even though most patients with this condition are now carefully monitored and aggressively managed. (3, 4)

Current treatment guidelines from the Surviving Sepsis Campaign recommend use of vasopressors if mean arterial pressure (MAP) is not raised to at least 65 mmHg following adequate fluid resuscitation.(5) Norepinephrine is first line treatment. However, neither

norepinephrine nor any one of the other drugs with US labeling for use in sepsis or other forms of distributive shock has labeling that the drug improves mortality or another clinical outcome. These drugs include: norepinephrine, epinephrine, vasopressin, phenylephrine, ephedrine, dopamine and metaraminol. All but dopamine are indicated for raising blood pressure in patients with hypotension in various settings. Dopamine is approved for correcting “hemodynamic imbalances” in patients with shock syndrome.

### LJPC-501

No human angiotensin II product has ever been marketed as a drug in the US. However, Hypertensin® (NDA 12-791, Ciba-Geigy (now Novartis)), an octapeptide that is identical in sequence to *bovine* angiotensin II, was approved in the US in 1962 for treatment of shock, but the NDA was withdrawn for reasons unrelated to safety (49 FR 23407-12, May 19, 2009). Bovine angiotensin II differs from the human peptide by one amino acid (valine at position 5 in the bovine peptide instead of isoleucine in the human version). Because of this difference in amino acid sequences between the human and bovine peptides, OPQ considers LJPC-501 to be an NME. There is no foreign marketing history for LJPC-501.

The drug product is supplied in vials for continuous intravenous administration in normal saline. The proposed dosing regimen tracks that used in the Phase 3 trial: LJPC-501 is given IV, diluted in normal saline. The Applicant’s recommended starting dose is 20 ng/kg/min. Blood pressure should be monitored as often as every 5 minutes, and the dose should be titrated [REDACTED] <sup>(b) (4)</sup> ng/kg/min until the desired BP target is attained. The maximum recommended dose in the first 3 hours of treatment is 80 ng/kg/min, and the maximum dose recommended after that is 40 ng/kg/min. Doses as low as 1.25 ng/kg/min may be used.

The critical efficacy and safety information for LJPC-501 comes from the ATHOS-3 trial, described in detail in Sec. 7. ATHOS-3 was performed under a SPA. We accepted the Applicant’s proposed PD primary endpoint, MAP response at hour 3 of randomized treatment. The proposed endpoint was consistent with the blood pressure endpoints that supported approval of other vasopressor agents used to treat shock, none of which had hard clinical outcomes data. These drugs include norepinephrine, epinephrine, vasopressin, phenylephrine, ephedrine, dopamine and metaraminol. All these agents are approved to raise blood pressure, except for dopamine, which is indicated to correct “hemodynamic imbalances” in shock. The Division determined that effects on blood pressure could to support approval of LJPC-501. We also accepted the Applicant's proposal to proceed directly to their confirmatory trial without doing their own Phase 1 or 2 studies in patients with shock. However, there had been a published report of a placebo-controlled RCT in 20 patients with shock sponsored by George Washington University using Bachem human angiotensin II (ATHOS) that suggested that angiotensin II use was associated with reduced need for catecholamines to maintain BP in the target range. (6). The angiotensin II dosing regimen used in ATHOS-3 was based on the regimen used in ATHOS.

ATHOS-3 was performed with no important deviations from the SPA agreement. The trial results, which were largely successful, were published in the NEJM in August of this year (7). Since then we have received several requests from members of the medical community for

emergency use of LJPC-501 in hospitalized patients with shock and hypotension who are unresponsive to available therapy. Septic shock, which constitutes about 90% of cases of distributive shock, has a high mortality rate even though most patients with this condition are treated in an Intensive Care Unit. Although we have granted Priority Review status to this application, we are taking steps so that we can act on this application well before the Priority Review action date of February 28, 2018 so that the drug will be available through commercial channels for use in patients with distributive shock as quickly as possible.

### 3. Product Quality

The product quality team recommends approval, and there are there are no unresolved product quality issues. The team consisted of the following individuals:

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Raymond Frankewich	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Kambhampati Rao	ONDP/DNDPI/NDPBI
Process	Yahong Wang	OPQ/OPF/DPAI/PABI
Facility	Jonathan Swoboda,	OPF/DIA/IABI
Biopharmaceutics	Gerlie Gieser	ONDP/DB/BBI
Microbiology*	Jianli Xue	OPQ/OPF/DMA/MABII
RBPM	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

\* The Microbiology reviewer's recommendations are discussed in Sec. 6 of this review.



The drug product is a sterile solution of the drug substance in water for injection, packaged in a typical container and closure system for sterile, low-volume parenteral products: 3 mL USP Type (b) (4) amber glass bottles fitted with (b) (4) caps. Vials are single-dose. There are two marketed strengths: 2.5 mg in 1 mL and 5.0 mg in 2 mL, each with a concentration of 2.5 mg/mL. All excipients are compendial.

Expiration dating of 18 months is approved for the product when stored at 2°C – 8°C in the proposed commercial container closure system.

Unused drug product remaining in the vial after a single dose is withdrawn is to be discarded. The drug product is to be diluted in 0.9% saline and administered by continuous intravenous infusion. Any diluted drug product not used 24 hours after preparation of the diluted solution should be discarded.

## 4. Nonclinical Pharmacology/Toxicology

The P/T team (Drs. Gowra Jagadeesh and Thomas Papoian) recommends approval. However, they note that extended treatment with angiotensin II promotes vascular inflammation and thrombosis. This seems consistent with the clinical finding ATHOS-3 of an increased risk of thromboembolic events with LJPC-501 as described in Sections 1 and 8 of this review and in the clinical review, and supports the need for the warning that we propose.

It is noteworthy that the P/T review includes a description of the Applicant's *in-vitro* study comparing LJPC-501, human sequence angiotensin II (b)(4) and bovine sequence angiotensin II (b)(4) with respect to their binding to recombinant human angiotensin II receptors expressed in Chinese hamster ovary cells. All 3 peptides bound to the receptors with high affinity, based on 9 experimental runs for each. The two (b)(4) products had similar mean IC50s (~0.5 nM), while the mean IC-50 for LJPC-501 was about half of that of the other two (0.25 nM); i.e., LJPC-501 was more potent. Based on these data, the P/T reviewers determined that non-clinical data from studies of bovine angiotensin II were applicable to human angiotensin II.

## 5. Clinical Pharmacology

The Clinical Pharmacology reviewers, Drs. Pillai and Hariharan, recommend approval for the Applicant's proposed indication, using the proposed intravenous dosing regimen. No PMR or PMC was recommended. They noted no unresolved issues.

The sponsor performed no clinical pharmacology studies, but did submit published literature. The review notes the following:

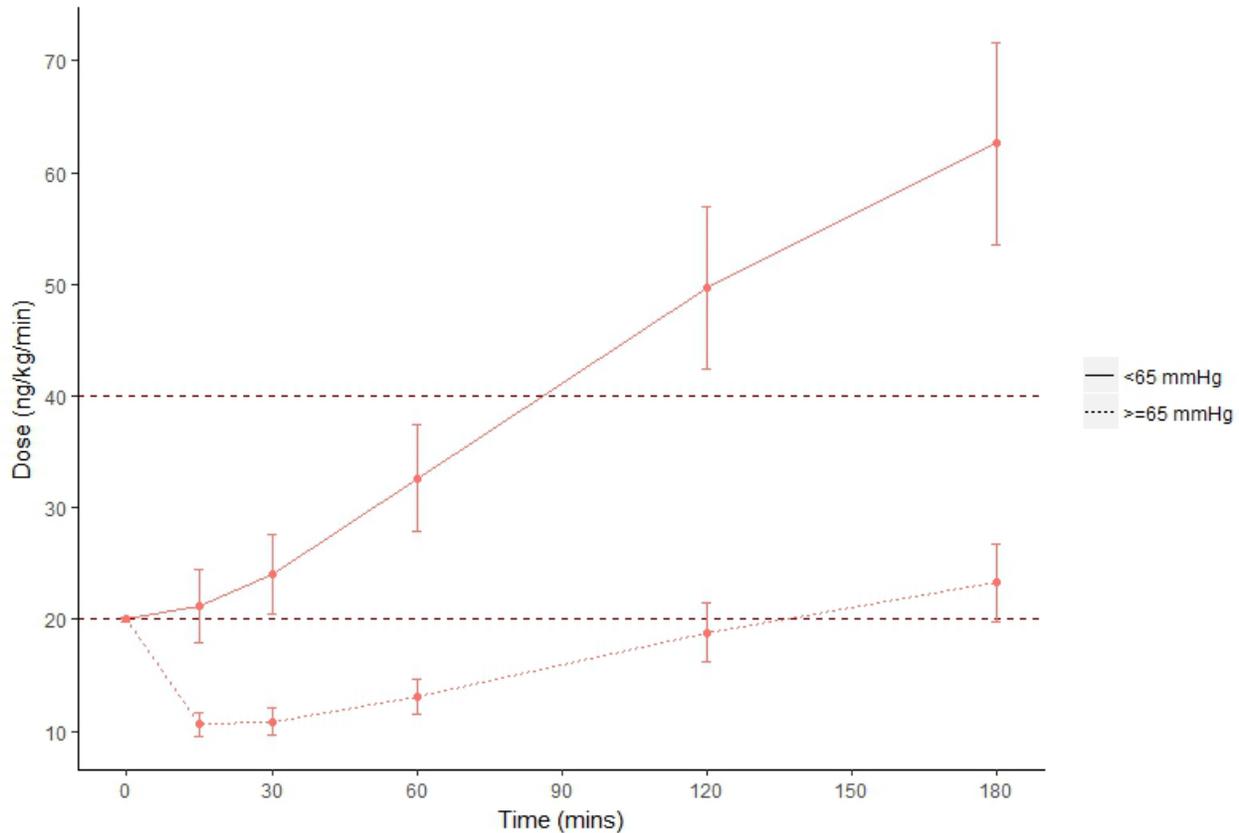
- Bioavailability of the IV solution is 100%.
- Exposure in healthy volunteers was dose-proportional up to 10 ng/kg/min. Escalation beyond that dose was not performed due to drug-induced increases in blood pressure.
- Half-life is < 1 minute. Steady state is reached in 5 minutes.
- Angiotensin II is metabolized by aminopeptidase A to angiotensin 1-7 and by ACE2 to angiotensin 2-8 (angiotensin III). There was no comment on the activity of these metabolites. However, there is rapid offset of the effect on angiotensin II on blood pressure, suggesting that these metabolites are either not active or are rapidly metabolized to inactive compounds.
- Following intravenous infusion of angiotensin II-I<sup>131</sup>, approximately two-thirds of the total blood radioactivity remains in plasma and one-third of radioactivity is present in erythrocytes.
- No drug interaction studies were performed

There was no comment on the effects of angiotensin II on the QT interval.

The reviewers analyzed the administered dose rate of active angiotensin II in the pivotal study vs. time by baseline MAP stratum (< 65 mmHg vs.  $\geq$  65 mmHg).

Results the dose mean and SEM are shown below.

**Figure 1 Angiotensin II Dose Rate vs. Time in ATHOS-3**



Source: Reviewer analysis

The data, which show a mean dose of about 11 ng/kg/min at 15 minutes with a small SEM, suggest that the dose rate in most patients with baseline MAP  $\geq$  65 mmHg was rapidly down-titrated from their initial dose of 20 ng/kg/min. The dose rate in these patients began to increase after minute 30. Given that the BP response to either increases or decreases in angiotensin II dose rate is quite prompt, the current dosing recommendation is not unreasonable. In addition, the mortality results at 7 and 28 days showed no notable difference in the hazard ratios for angiotensin II vs placebo between the subgroups of those with baseline MAP < 65 mm Hg or  $\geq$  65 mm Hg, suggesting that patients with higher levels of baseline MAP were not harmed by the standardized starting dose of angiotensin II, 20 ng/kg/min.

## 6. Clinical Microbiology

The Microbiology reviewer, Jianli Xue, recommends approval. There are no unresolved Microbiology issues.

A microbiological in-use study was performed with LJPC-501 drug product diluted in normal saline IV infusion bags at a concentration of 10,000 ng angiotensin II/mL. This study was used to support diluted drug product concentrations up to the tested concentration. The study was performed at both 2 - 8°C and 20 - 25°C storage temperatures. Testing was performed at 0, 4, 8, 12, 24, 36, and 48 hours. Results demonstrated that the LJPC-501 drug product is microbiologically stable when diluted in 0.9% sodium chloride IV bags (b) (4) after dilution when held at each tested storage temperature range. (b) (4) labeling will (b) (4) recommend discarding a solution of LJPC-501 in normal saline 24 hours after preparation.

## 7. Clinical/Statistical- Efficacy

The applicant conducted one double-blind, placebo-controlled randomized, multicenter trial (LJ501-CRH01, “ATHOS-3”) under a SPA agreement. There were no deviations from the SPA agreement of regulatory importance. Athos-3 qualifies as an adequate and well-controlled clinical investigation. The trial’s results constitute substantial evidence of the effectiveness of LJPC-501 for raising blood pressure in patients with distributive shock. The trial is adequate to support approval as a single trial for reasons that will be described below.

### Study Plan

Athos was conducted at 75 sites in the US, Canada, South America and Europe that enrolled at least one patient. Patients were hospitalized adults ( $\geq 18$  years of age) with “catechol resistant hypotension” (CRH) receiving norepinephrine equivalent dose (NED) of  $> 0.2$  mcg/kg/min (based on the sum of the NED scores for each vasopressor given to the patient) and a MAP of 55 to 70 mmHg for 6 to 48 hours prior to randomization (see the Clinical review for the algorithm for calculating NED). Other disease-specific inclusion criteria included:

- Central venous access and an arterial line present for at least the initial 48 hours of the study.
- 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/m<sup>2</sup>.

Major exclusions were appropriate to enroll a study population with need for urgent additional therapy for distributive shock but unlikely to die acutely of causes other than hypotension and its consequences or to be at high risk of serious ischemic or bleeding complications of vasopressor therapy:

- Burns covering > 20% of total body surface area.
- Cardiovascular SOFA score  $\leq 3$  (increasing scores are associated with worse outcomes).
- Acute coronary syndrome requiring intervention.
- Treatment with ECMO within the last 12 hours.
- Liver failure with a MELD score  $\geq 30$  (increasing scores are associated with worse outcomes).
- History of asthma or currently experiencing bronchospasm requiring the use of inhaled bronchodilators, if not mechanically ventilated.
- Acute mesenteric ischemia, at or prior to study.
- History of, presence of, or highly suspected of having an aortic dissection or abdominal aortic aneurysm.
- Requirement of > 500 mg daily hydrocortisone or equivalent glucocorticoid medication as a standing dose.
- Raynaud's phenomenon, systemic sclerosis or vasospastic disease.
- Expected lifespan < 12 hours.
- Active bleeding and either (1) an anticipated need (within 48 hours of initiation of study) for transfusion of > 4 units of packed red blood cells, or (2) hemoglobin < 7 g/dL or any other condition that would contraindicate serial blood sampling.
- Absolute neutrophil count of < 1000 cells/mm<sup>3</sup>
- Known pregnancy

After consent was obtained from the subject or his/her legal representative, the subject was randomized 1:1 to receive LJPC-501 in normal saline or matching placebo. Randomization strata included screening MAP (< 65 or  $\geq 65$  mmHg) and baseline APACHE score ( $\leq 30$ , 31 to 40, or  $\geq 41$ ). Study drug was infused IV at rate of 20 ng/kg/min initially. As often as every 5 minutes, the dose was titrated up or down to achieve a target MAP of 75 to 84 mmHg using an algorithm (see clinical review). For the first 3 hours, other vasopressors were maintained at their baseline rate and the allowed dosing range for study drug was 2.5 to 200 ng/kg/min. From hour 3 to hour 48, MAP was to be kept in the range of 65-70 mmHg, and the allowed dosing range for study drug were 2.5 to 40 ng/kg/min. During this period, other vasopressors could be down-titrated or stopped. Study drug was to be down-titrated to discontinuation at hour 48 in decrements of up to 10 ng/kg/min every 15 minutes. If within 3 hours of discontinuation, the patient developed a CV SOFA score of 4 or more, study drug could be restarted and given at a maximum rate of 40 ng/kg/min, but no subject was to receive study drug for more than 168 hours.

The primary endpoint analysis was a comparison between active and placebo of the rate of BP response at hour 3 of treatment, with a response defined as MAP of  $\geq 75$  mmHg or an increase from baseline of  $\geq 10$  mmHg, analyzed using logistic regression with pre-defined covariates of baseline MAP, APACHE II score, vasopressin use over the first 6 hours prior to randomization (yes or no), and quantity of catecholamine use (average norepinephrine equivalents in

mcg/kg/min) over the 6 hours prior to randomization. The primary endpoint analysis and other analyses of efficacy were performed in the MITT population unless otherwise specified. This population included all patients who were randomized and received study treatment, with patients assigned to arms to which they were randomized.

Sensitivity analyses of the primary endpoint included the following analyses:

- 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.

In addition, the primary endpoint analysis and several of the sensitivity analyses above were run in the ITT population as a further test of sensitivity.

Secondary endpoints and analyses included:

- Change in cardiovascular SOFA scores 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” analyses included:

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

Revision 3.0 of the statistical plan (the final revision) indicates that if the primary endpoint analysis was successful, alpha of 0.05 would be passed down the following chain of two endpoints, stopping at the first unsuccessful analysis:

- Change in CV SOFA score at hour 48, then
- Change in total SOFA score at hour 48.

All safety analyses were performed in the safety population (all patients who received study treatment, with patients assigned to the arm consistent with their actual treatment).

## **Study Results**

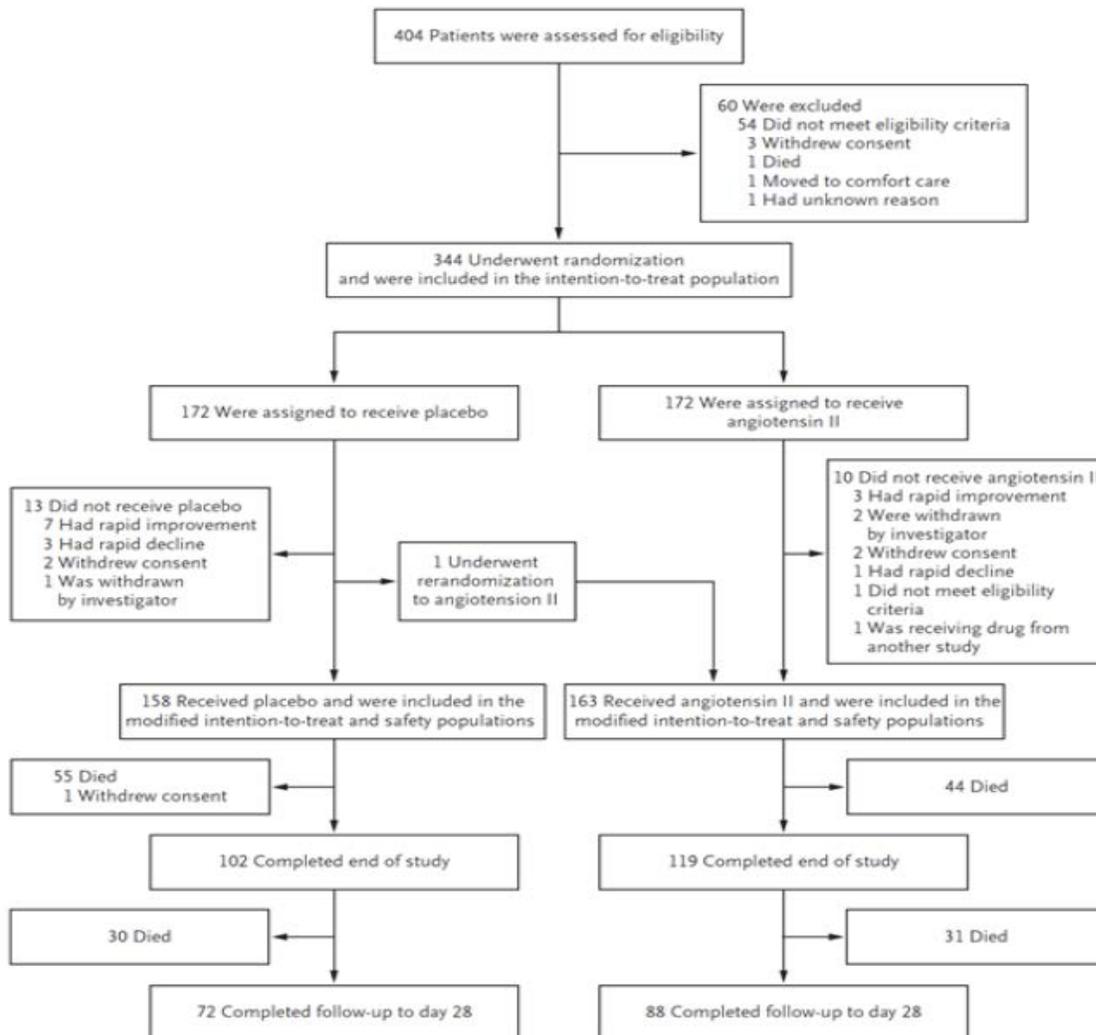
### **Disposition**

There were 172 patients randomized into each of the two treatment arms. Thirteen and 10 patients in the placebo and angiotensin II arm, respectively, did not receive any study drug.

The most common reason for this was rapid improvement following randomization (7 and 3 patients, respectively). Other reasons affecting at least two patients overall were rapid decline, withdrawal of consent, and withdrawal by the investigator. The study report indicates that one patient was randomized to placebo but not treated because of need for a surgical procedure, and then re-randomized to angiotensin II and received treatment. This patient was included in the angiotensin II arm in the MITT and safety population, and in placebo arm in the ITT population. Thus, there were 158 and 163 patients in the placebo and angiotensin II arms, respectively, who received study drug. These patients made up the MITT population.

Patient flow in the study is summarized in [Figure 2](#). Every patient in the study who received study treatment, excluding one in the placebo arm who withdrew consent, was followed to death or the study end at Day 28. The rate of protocol violations in the two arms was 6% - 7%. I agree with clinical reviewers that loss to follow-up or other study conduct issues were few, balanced between the treatment arms, and unlikely to affect interpretation of the trial results.

**Figure 2: 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

Demographic and shock-related characteristics were balanced in the study arms in the mITT population. Mean age in the study was 62, with an SD of 15. About 81% of subject were classified as white, with 10% black or African-American, 4% Asian, and 5% of Hispanic or Latino ethnicity. About 74% of subjects were enrolled in US and Canadian sites. For additional demographic information, see Table 15 in the clinical review.

Overall, 81% of subjects had sepsis as the cause of shock. Another 10% had “potential sepsis.” Vasoplegia was present in 6%, pancreatitis in 1%, and other causes of distributive shock were accounted for the remainder (3%). Screening and baseline values for MAP were quite similar in the treatment arms. The median baseline MAP was 66 mmHg in each arm, and 32% of subjects in each arm had a baseline MAP < 65 mmHg. The treatment arms were

similar to each other in terms of baseline APACHE II score and the MELD score, as well as medical history.

Study inclusion criteria included a requirement of a NED > 0.2 mcg/kg/min at screening. Median NED (range) NED in the 6 hours prior to randomization was identical in the two arms, at 0.4 (0.1-3.0) mcg/kg/min. The median (range) number of standard of care vasopressor medications administered in the 6 hours prior to baseline was 2 (1-4) in each arm. Overall, > 99% of subjects received norepinephrine. Other vasopressors, ordered in decreasing frequency of use, included vasopressin, phenylephrine, epinephrine, metaraminol, dopamine and several others that were each used in ≤ 4 subjects (**Table 1**). The study arms were similar in terms of pre-randomization use of standard of care vasopressors.

**Table 1 Standard of Care Vasopressor Use Prior to Baseline – mITT Population**

	LJPC-501	%	Placebo	%
<b>N (mITT)</b>	163	100%	158	100%
<b>Norepinephrine</b>	163	100%	157	>99%
<b>Dopamine</b>	7	4%	10	6%
<b>Epinephrine</b>	42	26%	38	24%
<b>Ephedrine</b>	1	1%	3	2%
<b>Metaraminol</b>	10	6%	11	7%
<b>Phenylephrine</b>	56	34%	58	37%
<b>Terlipressin</b>	0	0%	1	1%
<b>Vasopressin</b>	117	72%	115	73%

Source: Clinical reviewer’s analysis of study data

**Table 2 Standard of Care Vasopressor During Treatment with Study Drug – mITT Population**

	LJPC-501	%	Placebo	%
N (mITT)	163	100%	158	100%
Norepinephrine	154	94%	144	91%
Dopamine	4	2%	2	1%
Epinephrine	36	22%	24	15%
Ephedrine	1	1%	3	2%
Metaraminol	0	0%	1	1%
Phenylephrine	28	17%	30	19%
Terlipressin	1	1%	1	1%
Vasopressin	72	44%	64	41%

Source: Clinical reviewer’s analysis of study data

Thus, neither missing data nor imbalances in the randomization would be expected to confound the interpretation of the study results.

**Efficacy Results**

The results for the prespecified primary endpoint analysis of MAP response at 3 hours strongly favored angiotensin II over placebo:

**Table 3: Primary Efficacy Endpoint: MAP Response at Hour 3, mITT population**

Primary Endpoint	LJPC-501 (N=163)	Placebo (N=158)	
	<i>n (%)</i>	<i>n (%)</i>	<i>OR (95%CI), p</i>
Responder	114 (70%)	37 (23%)	7.95 (4.76-13.3), p=2.54E-15

Source: Table 14.2.1.1.1, LJ501-CRH CSR.

Response was defined as either MAP ≥ 75 mmHg at 3 hours or an increase from baseline to hour 3 of ≥ 10 mmHg.

Note: From this point forward, p values less than 0.00001 will be described as < 0.00001.

The sensitivity analyses specified in the protocol that were performed in the mITT population have similar results, some with even more extreme p values than the primary endpoint analysis. The analysis of the primary endpoint in the ITT population (172 patients in each arm) also yielded highly favorable results for angiotensin II: response rates of 67% vs. 24%, OR=6.96, (95% CI, 4.27 - 11.3), p<0.00001. Highly significant odds ratios for MAP response favoring angiotensin II over placebo were also observed at hours 1 and 2 in the mITT population (data not shown). In addition, response rates at 3 hours favored angiotensin II over placebo across a range of subgroups based on demographic, geographic, and disease-related characteristics (see clinical review, Figures 6 and 7).

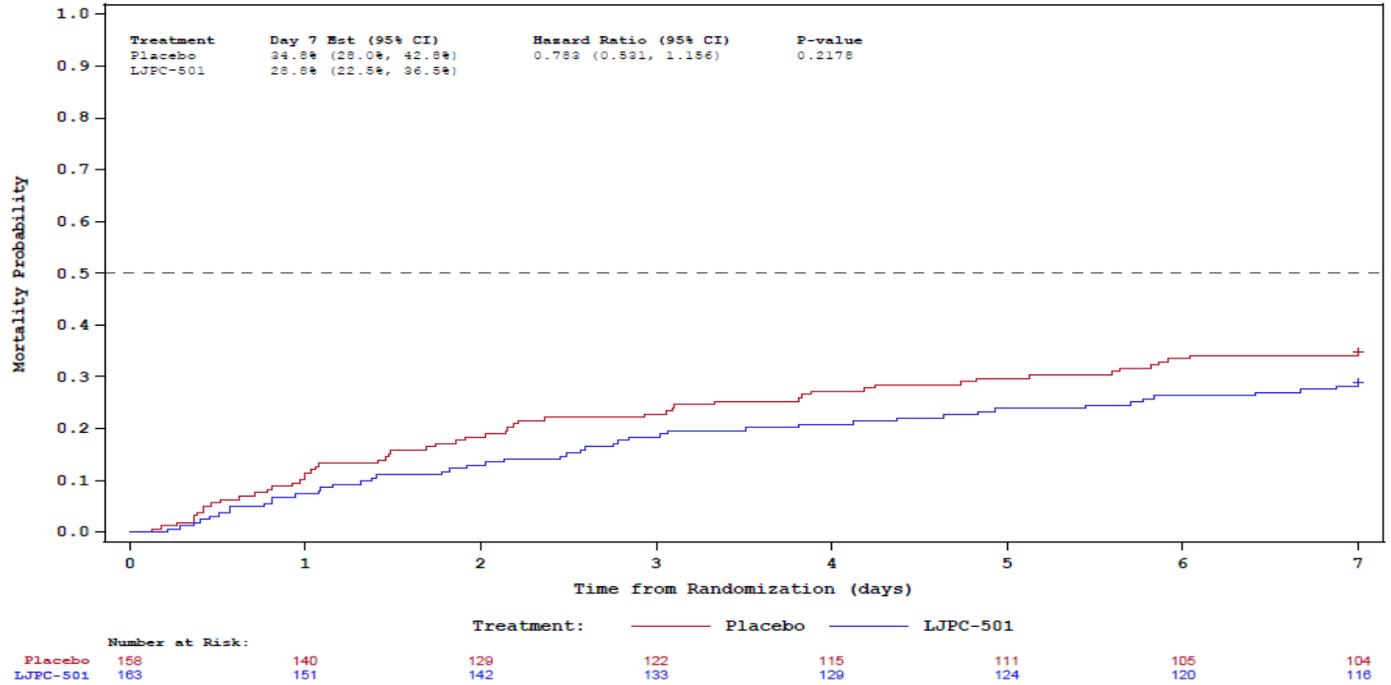
These data support the conclusion that angiotensin II is effective for increasing blood pressure in adult patients with distributive shock. The extreme p values for the primary endpoint

analysis, the ITT population analysis, and for most of the other analyses of MAP response support this conclusion without confirmation from another study. In addition, the pharmacology of human angiotensin II is very similar to that of bovine angiotensin II, providing additional support for the efficacy of human angiotensin II. However, the results of ATHOS-3 are strong enough to stand on their own as support of efficacy.

In ATHOS-3, compared to placebo, angiotensin II treatment was associated with significantly greater reductions in the CV SOFA score from screening at 48 hours analyzed by the van Elteren Wilcoxon (non-parametric) test, which was the first secondary endpoint in the alpha-sparing statistical plan. The mean change was -1.28 and -1.75 units in the placebo and angiotensin II arms, respectively ( $p=0.013$ ). At an earlier time, hour 3, the mean change from screening was -0.01 and -0.13 units, respectively ( $p=0.002$ ). However, because the CV SOFA score is dependent on the dose of specified vasopressors (which do not include angiotensin), one would expect the score to be lower in patients receiving angiotensin II, even if there were no benefit over standard vasopressors. There was no advantage of angiotensin II over placebo for the second secondary endpoint, the total SOFA score at hour 3 or 48.

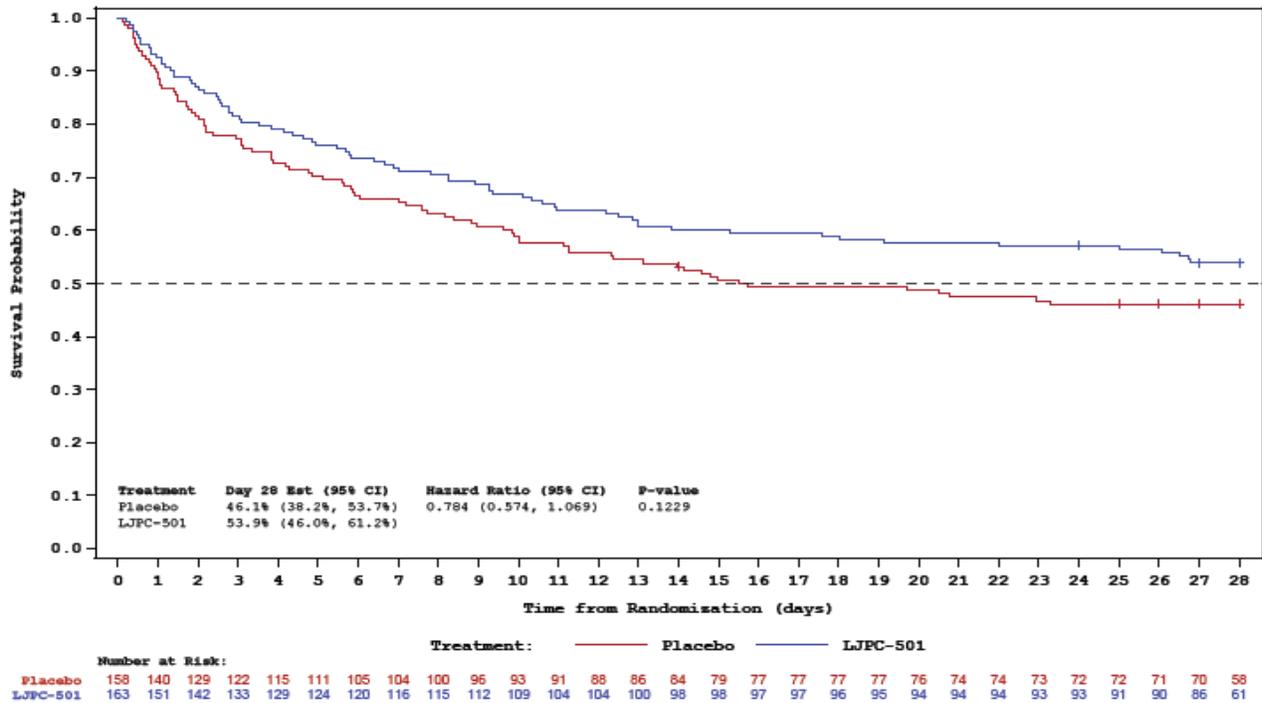
Mortality over the course of the study numerically favored angiotensin II over placebo in the mITT population. By day 7 of treatment, there were 47 (29%) vs. 55 (35%) vs. deaths in the angiotensin II and placebo arm, respectively. (**Figure 3**). By day 28, there were 85 (46%) vs. 85 (54%) deaths, respectively (HR=0.78 (0.57, 1.07), log-rank  $p=0.12$  (**Figure 4**)). While these data do not support a mortality claim, they are reassuring with regard to both the efficacy and safety of angiotensin II.

**Figure 3: 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 4 Survival to Day 28 (mITT Population)**



Source: CSR, Figure 14.2.6.4.2

## **Conclusion**

The results of ATHOS-3 constitute substantial evidence of the effectiveness of angiotensin II for increasing blood pressure in adults with distributive shock. Although the Applicant conducted only one controlled trial, the trial is adequate to demonstrate effectiveness on its own. Several of the criteria for finding effectiveness based on one study that are described in FDA's 1998 guidance, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, are present here. ATHOS-3 was a well-conducted placebo-controlled, superiority trial with no important flaws in conduct or imbalances in the study arms. The difference between the study arms for the primary endpoint, the MAP response rate, was large and favored angiotensin II. The p value for this endpoint is extreme — less than  $10^{-14}$ . The p values for the various, prespecified sensitivity tests of that endpoint, including the conservative ITT analysis, are also quite extreme. The study was multicenter and conducted globally, with consistent results across regions. Results across demographic subgroups were likewise consistent. Finally, death rates at 7 and 28 days favored angiotensin II over placebo, although the difference between the study arms did not reach statistical significance. One might make the argument that efficacy is supported by the efficacy of the previously marketed, closely related bovine angiotensin product, but the strength of the results of ATHOS-3 makes that unnecessary.

## **8. Safety**

Safety data relevant to this application come primarily from the ATHOS-3 trial in patients with the proposed indication. Exposure in that trial included 163 patients treated with angiotensin II and 158 with placebo. All these patients, except one in the placebo arm who withdrew early, were followed to death or the end of the study, 28 days after randomization. About 92% of patients received angiotensin II for 72 hours or less; no patient received it for more than 7 days. The only other study conducted by the Applicant with angiotensin II was a 6-subject single-arm, Phase 1 study in patients with hepato-renal syndrome (HRS), (b) (4)

While the size of the safety database is modest, it is adequate to support approval given the high risk of the underlying condition (distributive shock), the fact that the drug is an endogenous short peptide, the short duration of use, the very short half-life (about one minute), the route of administration (intravenous), the rapid onset and offset of drug activity, the recommended titration scheme (which deters significant overdosing), the and the usual setting of use (the intensive care unit, where patients are monitored closely). Experience with a closely related NDA product now withdrawn from the market for reasons unrelated to safety (Hypertensin®, bovine angiotensin II) is also reassuring of safety, but consideration of this factor is not necessary to support approval.

### **SAEs**

The Applicant's analysis of death is described in Sec. 7. Dr. McDowell did her own analysis, and found 76 (47%) vs. 85 (54%) deaths in the angiotensin II and placebo arms, respectively — one more death in the angiotensin II arm than the Applicant found. This discrepancy arose because the Applicant's analysis of 28-day death was based on deaths occurring in an interval starting with randomization and ending 28 X 24 hours, i.e., 672 hours, later. The one

additional death in the angiotensin II arm found by Dr. McDowell occurred on several hours after the end of the 672-hour interval, but on the same calendar day. The difference in death rates between the two analyses is immaterial to our benefit-risk analysis.

Dr. McDowell's analysis of SAEs (based on the Applicant's table) does not indicate that any specific SAE is notably more frequent with angiotensin II than with placebo (see Clinical Review Table 49). Note that this table lists adverse events, not adverse drug reactions.

### **Discontinuations for AEs**

Discontinuations for AEs (again, the Applicant did not analyze adverse drug reactions) were more frequent in the placebo arm: 34 subjects (22%) vs. 23 (14.1%). The most frequent AE leading to discontinuation was "septic shock" (4 patients (2%) vs. 8 (5%) in the placebo and angiotensin II arm, respectively. Of note, about 90% of study subjects had septic shock or potential septic shock as their reason for treatment, making these data difficult to interpret. No other AE leading to treatment discontinuation had a frequency favoring placebo by a difference of more than 1 subject. We are not including information regarding discontinuations in labeling.

### **Observed Safety Signals**

The rate of patients with events in the "embolic and thrombotic events" SMQ was higher in the angiotensin II arm: 21 patients (12.9%) vs. 8 patients (5.1%). These patients had 25 vs. 8 events in the SMQ. The most common of these events was deep vein thrombosis (DVT), which occurred in 7 vs. 0 patients. Of note, the percentage of patients in the angiotensin II and placebo arms with a history of embolic or thrombotic events at baseline was similar (52% vs. 49%). Among such patients the rate of such events during the study was higher in the angiotensin II arm (67% vs. 50%). Dr. McDowell notes that the standard of care for patients with sepsis includes anticoagulant treatment for prophylaxis, and that anticoagulation during the study with heparin or related drugs was more frequent in the angiotensin II arm (52% vs. 32%), indicating that higher rate of thromboembolic events in the angiotensin II arm was not due to an imbalance in the use of prophylactic anticoagulation. She also notes that the preclinical data indicate that angiotensin II has prothrombotic effects through various mechanisms, and that this safety risk be addressed in labeling. Accordingly, she recommends a warning regarding thrombotic risk along with a recommendation for prophylactic anticoagulation in labeling of angiotensin II. I agree.

The rate of acidosis-related AEs was increased with angiotensin II compared to placebo. There was 1 patient (0.6%) vs. 12 patients (7.4%) with such AEs in the placebo and angiotensin II arm, respectively. Most of these events involved a finding of elevated lactate levels. Lactate levels tend to be high in patients with sepsis, and were elevated to a similar extent in the two arms at screening, but fell to a greater degree with placebo. Likewise, arterial pH was similarly depressed in the two study arms at screening. By day 2, mean levels were similar and near normal in each arm. Given the high frequency of metabolic acidosis in patients with shock and the lack of actionable advice that we can provide in labeling about acidosis, I think we should not have a warning related to this finding. Acidosis terms were combined and included in the table of treatment emergent ADRs.

There were no other actionable safety issues identified in the clinical database.

**Other Safety Information**

We have replaced the Applicant's long list of AEs with a much shorter list of ADRs occurring at rate of at least 4% and 1.5% higher in the angiotensin II arm than the placebo arm (Table 4). We are not distinguishing between events considered serious or non-serious. In the context of patients with shock in an ICU, this distinction is often arbitrary. The Applicant has agreed to our approach, although labeling has not been finalized.

**Table 4: Adverse Reactions Occurring in ≥ 4% of Patients in Either Treatment Arm with a Risk Difference ≥ 1.5% (placebo as the reference) in ATHOS-3**

Adverse Event	BRAND NAME N=163	Placebo N=158
Thromboembolic events <sup>a</sup>	21 (12.9%)	8 (5.1%)
Deep vein thrombosis	7 (4.3%)	0 (0.0%)
Thrombocytopenia	16 (9.8%)	11 (7.0%)
Tachycardia	14 (8.6%)	9 (5.7%)
Acidosis	12 (7.4%)	1 (0.6%)
Delirium	9 (5.5%)	1 (0.6%)
Hyperglycemia	7 (4.3%)	4 (2.5%)
Peripheral ischemia	7 (4.3%)	4 (2.5%)

<sup>a</sup> Including arterial and venous thromboembolic events  
Source: Dr. Unger’s analysis

**9. Advisory Committee Meeting**

There are no issues that require consideration by an AC, and no AC meeting has been scheduled.

**10. Pediatrics**

The Applicant has an agreed PSP that proposes 2 pediatric trials in patients with (b)(4). The first will be in patients >2 to 17 years old (b)(4). The second will be in those ≤2 years old (N is not stated), but it will not start until a study in (b)(4) is completed.

Only brief synopses of the clinical studies have been submitted to us. Both are open-label, (b)(4) trials. In each study, the primary goal is to evaluate the effect of LJPC-501 infusion on mean arterial pressure. Secondary goals are to (b)(4)

Dosing regimens of LJPC-501 are not specified.

The PERC has agreed to the content of the iPSP, but has recommended that we negotiate a more accelerated timetable for the studies. The current timetable is reproduced below.

### Study in Pediatric patients > 2 years old

- Estimated protocol submission date: No later than Apr 2017
- Estimated study initiation date: No later than Aug 2017
- Estimated final report submission date: No later than Feb 2022

### Nonclinical toxicology study

- Estimated protocol submission date: No later than July 2018
- Estimated study initiation date: No later than Nov 2018
- Estimated final report submission date: No later than Mar 2019

### Pediatric patients ≤ 2 years old

- Estimated protocol submission date: No later than Apr 2019
- Estimated study initiation date: No later than May 2019
- Estimated final report submission date: No later than Mar 2024

The study in pediatric patients ≤ 2 years old will take place contingent upon review of the nonclinical toxicology study by the FDA.

PERC recommends that we move up the date of the protocol of the non-clinical study to January of this year and the initiation date to May of this year. This will allow an earlier start to the study in children up to 2 years old.

## 11. Other Relevant Regulatory Issues

There were no clinical site inspections. Financial disclosure by investigators was adequate and there were no issues. There are no other outstanding regulatory issues.

## 12. Labeling

Discussions between FDA and the Applicant regarding labeling are at an advanced stage, and we have reached agreement on many parts of the label. Division and Office management have been involved. Discussions are continuing. As of the date of this review, the following aspects of labeling are notable:

-  (b) (4)  
We believe that the indication should  (b) (4) state that the product is indicated to increase blood pressure in adult patients with distributive shock. The refractory nature of the enrolled patients in ATHOS-3 would be described in Section 14. The Applicant has agreed with our approach.
- Dosing is consistent with the Applicant's proposal, which is based on dosing in ATHOS-3.
- We have added a warning regarding risk for arterial and venous thrombosis. The Applicant has accepted this warning. There are no other warnings and no contraindications at this time.

### **13. Postmarketing Recommendations**

There is no need for a REMS, PMC, or safety-based PMR. There should PMRs for the PREA-required preclinical study and two clinical studies in children (see Sec. 10).

### **14. Recommended Comments to the Applicant**

There are none.

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MARTIN ROSE  
12/16/2017