27 June 2019
EMA/508753/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Giapreza

International non-proprietary name: angiotensin II

Procedure No. EMEA/H/C/004930/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Giapreza
Applicant:	La Jolla Pharmaceutical II B.V. Herengracht 500 1017 CB Amsterdam NETHERLANDS
Active substance:	Angiotensin II acetate
International Non-proprietary Name/Common Name:	Angiotensin II
Pharmaco-therapeutic group (ATC Code):	Cardiac therapy, other cardiac stimulants (C01CX09)
Therapeutic indication(s):	Giapreza is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	2.5 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial (1ml) and 1 vial (2 ml)

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List of abbreviations

DMF	Dimethylformamide
ESI-MS	Electrospray Ionization Mass Spectrometry
Fmoc	fluorenyl-methyloxycarbonyl
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
MAA	Marketing Authorisation Application
NMT	Not more than
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PTFE	Polytetrafluoroethylene
RP	Reverse Phase
SPPS	Solid Phase Peptide Synthesis
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TFA	Trifluoroacetic acid
TYMC	Total Combined Yeasts/Moulds Count
uHPLC	ultra-high performance liquid chromatography
XR(P)D	X-Ray (Powder) Diffraction

ACE:	angiotensin-converting enzyme
ACEi:	angiotensin-converting enzyme inhibitor
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
APACHE II:	Acute Physiologic Assessment and Chronic Health Evaluation II
ARB:	angiotensin II receptor type 1 blocker
ARDS:	acute respiratory distress syndrome
Arg:	arginine
Asp:	aspartate
AST:	aspartate aminotransferase
AT1:	receptor angiotensin II receptor type 1
CI:	confidence interval
CO:	cardiac output
CRH:	catecholamine-resistant hypotension
CSR:	clinical study report
CTCAE:	Common Terminology Criteria for Adverse Events
CV:	cardiovascular
CVP:	central venous pressure
DBP:	diastolic blood pressure
DSMB:	data safety monitoring board
ECG:	electrocardiogram
ECMO:	extracorporeal membrane oxygenation
FDA:	United States Food and Drug Administration
FiO_2:	fraction of inspired oxygen
GCP:	Good Clinical Practice
His:	histidine
ICF:	informed consent form
ICH:	International Conference on Harmonisation
ICU:	intensive care unit
IEC:	independent ethics committee
Ile:	isoleucine

Ile5:	isoleucine at amino acid position 5
IRB:	institutional review board
ITT:	intent-to-treat
IV:	intravenous(ly)
La Jolla:	La Jolla Pharmaceutical Company (the sponsor)
LJPC-501:	angiotensin II acetate for intravenous use
MAP:	mean arterial pressure
mcg:	microgram; µg
MCH:	mean corpuscular hemoglobin
MCV:	mean corpuscular volume
MedDRA:	Medical Dictionary for Regulatory Activities
MELD:	Model for End-stage Liver Disease
mITT:	modified intent-to-treat
NCI:	National Cancer Institute
NED:	norepinephrine-equivalent dose
ng:	nanograms
OR:	odds ratio
PaO_2:	partial pressure or arterial oxygen
Phe:	phenylalanine
PP:	per protocol
Pro:	proline
QTc:	QT interval corrected by heart rate
QTcB:	QT interval corrected by heart rate, Bazett's formula
QTcF:	QT interval corrected by heart rate, Fridericia's formula
RAAS:	renin-angiotensin-aldosterone system
RDW:	red cell distribution width
RR:	relative risk
SA:	scientific advice
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SOC:	system organ class
SOFA:	sequential organ failure assessment
SPA:	Special Protocol Assessment
TEAE:	treatment-emergent adverse event
Tyr:	tyrosine
UK:	United Kingdom
ULN:	upper limit of normal/reference range
US:	United States
Val:	valine
Val5:	valine at amino acid position 5

1. Background information on the procedure

1.1. Submission of the dossier

The applicant La Jolla Pharmaceutical II B.V. submitted on 30 May 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Giapreza, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2017.

The applicant applied for the following indication: treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0130/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0130/2918 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance angiotensin II acetate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice on 14 September 2017 (EMEA/H/SA/3618/1/2017/SME/III) and 26 April 2018 (EMEA/H/SA/3618/1/FU/1/2018/SME/II) for the development programme supporting the indication granted by the CHMP. The Scientific advice pertained to the following quality, non-clinical and clinical aspects:

- Specification and characterisation of drug substance and drug product. Acceptability of proposed comparability exercise in order to bridge nonclinical and clinical literature data to the product.
- Completeness of performed safety pharmacology (including QT assessment) and toxicology studies.
- Adequacy of the already performed, single pivotal Phase 3 study LJ501-CRH01, as well as supportive safety and efficacy information from the literature, to support the submission of an MAA, including design, patient population, dosing, primary and secondary endpoints, safety, PK/PD.
- In a follow-up advice the applicant queried whether available data could support a submission for full marketing approval, and an accelerated assessment. Acceptability of a proposed post-authorisation, randomized, placebo-controlled study in at least 450 adult patients with advanced acute kidney injury (AKI) requiring renal replacement therapy (RRT) associated with severe vasodilatory shock to generate additional safety data and further demonstrate the relationship between improvement in MAP and resolution of organ failure, and including all-cause mortality at day 28 as a secondary endpoint.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Joseph Emmerich

The application was received by the EMA on	30 May 2018
The procedure started on	21 June 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	11 September 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	11 September 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 September 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	18 October 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 January 2019
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at two investigator sites: one in Australia between 12 and 16 November 2018 and one in New Zealand between 7 and 9 November 2018 and at the Sponsor site in the Unites States between 17 and 20 December 2018. The outcome of the inspection carried out was issued on	18 January 2019

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	6 March 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 March 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 March 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 May 2019, 23 May 2019, 12 June 2019, 21 June 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Giapreza on	27 June 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The claimed indication for Giapreza (angiotensin II) is the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

There is no universal consensus definition of distributive or vasodilatory refractory shock, and the causes of shock may be diverse. Therefore, the target population is difficult to define. The most common causes of distributive shock are sepsis, inflammation, vasoplegia, and severe drug reactions (Armstrong et al 2017). Distributive shock requires immediate treatment to ensure organ perfusion through the re-establishment of adequate blood pressure while the underlying cause of shock is identified and treated.

Distributive shock is characterised by peripheral vasodilation and reduced blood pressure despite preserved cardiac output (Armstrong et al 2017). Proposed definitions include failure to achieve a BP goal despite vasopressor therapy, need for rescue vasopressor therapy, or need for high vasopressor doses [Jentzer et al. Chest 2018;154:416-426]. A reasonable definition of refractory shock would be an inadequate response to high-dose vasopressor therapy (defined as ≥ 0.5 mg/kg/min norepinephrine-equivalent dose) [Bassi et al, Crit Care Pract. 2013654708].

2.1.2. Epidemiology

The applicant has estimated that the number of patients who are hypotensive and do not respond to fluid or currently available vasopressor therapy is approximately 280,000 individuals in the United Kingdom, Germany, France, Italy and Spain per year based on epidemiological data on septic shock (Source: Epidata). In the Rapporteur's calculation, based on a 3 to 5/10.000 inhabitants prevalence of septic shock (i.e.: 30% to 44% of patients with sepsis) [Bouza et al. *BMC Infect Dis.* 2014;14:3863.2014; Fleischmann et al. *Deutsches Ärzteblatt International*. 2016;113:159-166], and considering 513 million inhabitants in the EU, the target population with septic shock could be approximately 154,000 to 156,000 EU subjects per year. Anyway, given the lack of specific epidemiological data on patients with distributive shock who have refractory hypotension, all available estimates are derived from different sources and assumptions, and therefore are subject to high imprecision.

Observational studies suggest that, using the definition of inadequate response to high-dose vasopressor therapy (defined as ≥ 0.5 mg/kg/min norepinephrine-equivalent dose), 6% to 7% of critically ill patients may develop refractory shock [Jentzer et al. Chest 2018;154:416-426].

As sepsis is the main cause of refractory vasodilatory/distributive shock (i.e.: about 90% of patients recruited into the single pivotal trial ATHOS-3 had septic shock), the target population could roughly correspond in most cases to patients with septic shock with cardiovascular organ failure that do not respond to vasopressor therapy. The prevalence of severe sepsis in Europe is around 1% of all hospital admissions [Bouza et al, 2014; BMC Infect Dis. 2014;14:3863.2014], with a prevalence around 9/10.000 inhabitants and 44% mortality as reported consistently in two recent Spanish and German studies [Bouza et al. BMC Infect Dis. 2014;14:3863.2014; Fleischmann et al. Deutsches Ärzteblatt International. 2016;113(10):159-166]. Among these patients with severe sepsis, about one third of them (30%-44%) (3/10.000 to 5/10.000 prevalence) will develop septic shock, with an estimated 47-63% mortality in those patients with two or more organ dysfunctions (CV, respiratory, renal, hematologic). That prevalence is considered low and in the borderline of the definition of an orphan disease, although in practice, with a broad indication requested, the population may be significantly higher.

2.1.3. Biologic features

A central pathophysiologic feature of refractory shock is the impairment of vascular response to catecholamine stimulation. Reduced catecholamine responsiveness and uncontrolled pathologic vasodilation (vasoplegia) can occur because of changes in receptor signaling, metabolic derangements, and depletion of endogenous vasoactive hormones [Jentzer et al. Chest 2018;154:416-426].

Inappropriate vasodilation typically occurs from the effects of inducible nitric oxide synthase (iNOS), which produces excessive amounts of vasodilatory nitric oxide (NO). NO increases vascular levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate to trigger vasodilation.

Angiotensin II is one of the four vasoconstrictive hormones secreted in response to shock in order to defend blood pressure (together with epinephrine, norepinephrine and vasopressin). Absolute or relative deficiencies of endogenous vasoactive hormones, such as cortisol, vasopressin, and angiotensin II, can develop in shock states, further decreasing vasopressor responsiveness. The combination of pathologic vasodilation with vasoconstriction from vasopressor drugs produces heterogeneous effects on different vascular beds, leading to maldistribution of blood flow despite acceptable systemic hemodynamic parameters [Jentzer et al. Chest 2018;154:416-426].

2.1.4. Clinical presentation, diagnosis

The first step in the evaluation of refractory shock is to exclude factitious BP measurements and identify the primary cause and reversible secondary contributors, such as hypovolemia, uncontrolled vasodilation, pump failure, or obstructive shock [Jentzer et al. Chest 2018;154:416-426].

Bedside diagnostic testing for patients with refractory shock may include a combination of hemodynamic, laboratory, and imaging parameters. Empiric broad-spectrum antibiotics are often considered until sepsis can be excluded.

An objective assessment of cardiac output is critical to help guide clinical management, including surrogate measures such as Doppler-derived estimates, minimally invasive pulse contour analysis, and central venous oxygen saturation. Low cardiac output or central or mixed venous oxygen saturation requires further testing to differentiate into hypovolemic, cardiogenic, or obstructive shock. Elevated central or mixed venous oxygen saturation levels and high cardiac output typically indicate vasodilatory shock. Despite lack of evidence supporting a survival benefit in critically ill patients, a pulmonary artery catheter can be considered when the hemodynamic state remains uncertain despite other testing.

Patients with inadequate cardiac output should be assessed for fluid responsiveness, and objective measures of fluid responsiveness should be used to guide resuscitation. Measures of fluid responsiveness frequently require patients to undergo mechanical ventilation at 8 to 10 mL/kg ideal body weight and be in sinus rhythm, which might not always be possible. A controlled fluid challenge can be considered in the absence of fluid overload, particularly when measures of fluid responsiveness are indeterminate. After addressing contributing causes and fluid responsiveness, initiation and optimization of vasopressor therapy should be considered [Jentzer et al. Chest 2018;154:416-426].

It was agreed during Scientific Advice (EMA/CHMP/SAWP/581080/2017) that distributive shock failing to respond adequately to standard of care can be characterised as the presence of a high cardiac output shock [cardiac index > 2.3 L/min/m2 or a central venous oxygen saturation > 70% coupled with central venous pressure of > 8 mmHg, with a mean arterial pressure (MAP) between 55 mmHg and 70 mmHg high-dose], requiring vasopressors at > 0.2 µg/kg/min of NE, or the equivalent dose of another vasopressor, ie, patients with a cardiovascular (CV) Sequential Organ Failure Assessment (SOFA) score of 4. The applicant's Phase 3 clinical trial enrolled subjects meeting these criteria.

Hypotension and consequent organ hypo-perfusion are cardinal signals of shock, associated with organ dysfunction and mortality (Xu et al 2015). Vasodilatory shock requires immediate treatment to re-establish adequate blood pressure and maintain adequate organ perfusion while the underlying cause is identified and treated (Corrêa 2014, Thooft 2011, Boerma 2010).

Even short durations of hypotension (i.e., 1-5 minutes) may be associated with an increased frequency of potentially life-threatening morbidity such as myocardial infarction, stroke, and acute kidney injury (AKI) (Walsh et al 2013). In distributive shock, despite fluid and aggressive vasopressor therapy, a significant proportion of patients fail to reach blood pressure targets, and will die. A review of existing evidence (Bassi et al 2013) suggests that at least 50% of patients requiring aggressive vasopressor therapy, usually NE at doses ≥ 0.2 µg/kg/min, will succumb to the underlying disease, most commonly septic shock, in large part due to failure to achieve haemodynamic targets, coupled with the adverse effects of high-dose catecholamines (Dünser et al 2009, Schmittinger et al 2012, Stolk et al 2016).

2.1.5. Management

The treatment of distributive shock includes the treatment of the underlying causes (e.g.: infections in septic shock, etc.), fluid resuscitation and vasopressors.

As per international consensus definitions, adequate fluid resuscitation should be defined by at least 30 ml/kg (Levy & al. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions conference, Crit Care Med 2003). Adequate fluid resuscitation is a prerequisite according to the CHMP for the successful and appropriate use of vasopressors in patients with septic shock. With regard to this, a minimum of 30 ml/kg of crystalloids (1.5-3 litres) is advised for most patients to qualify as adequate fluid resuscitation.

Inadequate response to adequate fluid resuscitation means that that hypotension persists after 30 mL/kg crystalloid. In addition, hypoperfusion is most often defined as hypotension after a challenge with IV fluid (2 liters crystalloid has been suggested for volume-replete patients), and/or blood lactate ≥ 4 mmol/L. When an appropriate fluid challenge fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be started.

Angiotensin II is one of the four vasoconstrictive hormones secreted in response to shock in order to defend blood pressure (together with epinephrine, norepinephrine and vasopressin). In Europe, where consensus guidelines are widely adopted, the most commonly recommended and used first-line vasopressors in this setting are catecholamines, particularly norepinephrine (Annane 2018, Avni 2015, Damiani 2015, van Zanten 2014, Ferrer 2013, Prucha 2013, Tromp 2011, Boussekey 2010, Reinhart 2010, Póvoa 2009, Varpula 2007, Pottecher 2006a, Pottecher 2006b). Since their introduction, application of these guidelines has been shown to have improved patient outcomes including reducing mortality (Herrán-Monge 2017, Sánchez 2017, Ferrer 2008).

Second-line vasopressors include the posterior pituitary hormones vasopressin and arginine vasopressin (argipressin). Vasopressin is not authorised across all EU countries and is not commonly used to treat vasodilatory shock in Europe. In countries where vasopressin has a national marketing authorisation for any indication (e.g., the Netherlands), its use is reserved for off-label 'rescue' treatment in patients who fail to achieve an adequate MAP response with catecholamines. Empressin (argipressin or arginin-vasopressin) is another vasopressin analogue that is authorised in several EU countries "for the treatment of catecholamine refractory hypotension following septic shock in patients older than 18 years." Therefore, angiotensin II may become the third approved second-line vasopressor drug (behind vasopressin and argipressin) for this patient group in the EU.

Both catecholamines and vasopressin have narrow therapeutic windows with toxic effects at higher doses (Dünser 2017, Dünser 2009), including cardiac and digital ischaemia with norepinephrine (Russell 2018, Russell 2008) and ischaemic skin lesions with vasopressin (Dünser 2003). It can be difficult to titrate vasopressin to achieve and maintain the desired MAP, and since it is not fast-acting (peak effect at 15 minutes; Vasostrict Prescribing Information), this may further complicate its use (Malay 2004) and leave patients hypotensive for longer. Only 45% of patients with vasodilatory shock who receive vasopressin have a blood pressure response (Sacha 2018), therefore there remains a significant unmet need for catecholamine resistant hypotension (CRH) patients who are also resistant to vasopressin.

A recent review (Bassi 2013) indicates patients requiring high dose vasopressors have a > 50% all-cause mortality. These data demonstrate that CRH remains an intractable disease and one of the most deadly inpatient diagnoses in the developed world. For the past two decades the treating physician has had only two vasopressor drug classes available for the management of vasodilatory shock. Thus, a significant unmet medical need exists for effective vasopressor therapies in patients with vasodilatory shock who remain hypotensive despite fluid and current standard of care vasopressor therapy. A vasopressor with a different mechanism of action compared with existing therapies would be a valuable addition to the protocols used to restore adequate MAP in these patients, provided that its efficacy and safety are demonstrated.

Although the applicant has identified vasopressor therapies available, considering the heterogeneous and ambiguous population included in the indication for any kind of vasodilatory/distributive refractory shock, other rescue therapies available in refractory shock should have had to be taken into account as well. In a recent review, signed by members of the Company, among other authors, glucocorticoid therapy is mentioned among rescue therapies available in refractory shock [Jentzer JC, et al. Chest. 2018;154:416-426]. Glucocorticoid receptors augment vascular alpha-adrenergic responsiveness and reduce inflammation-mediated vasodilation. Hydrocortisone has both glucocorticoid and mineralocorticoid actions, and has been studied in a number of studies. Although glucocorticoid therapy in shock remains controversial with conflicting evidence regarding a mortality benefit, there is consistent and recent evidence supporting a more rapid resolution of shock [Annane D, et al. N Engl J Med 2018;378:809-18; Venkatesh et al. N Engl J Med. 2018; DOI: 10.1056/NEJMoa1705835]. Therefore, they can also be considered among rescue therapies available in refractory shock.

About the product

Angiotensin II, an endogenous octapeptide whose effects were first recognised in the 1930s and which was subsequently isolated in the 1940s (reviewed in Basso 2001, de Gasparo 2000), is the key biologically active vasopressor peptide in the renin-angiotensin-aldosterone system (RAAS). The RAAS is the third system, alongside the sympathetic nervous system and the vasopressin system, which is active in regulating blood pressure. Angiotensin II raises blood pressure by direct vasoconstriction, increased aldosterone release, and renal control of fluid and electrolyte balance.

Direct action of angiotensin II on the vessel wall is mediated by binding to the G-protein-coupled angiotensin II receptor type 1 on vascular smooth muscle cells which stimulates Ca^{2+}/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction (Balakumar 2014). Angiotensin II also appears to have inotropic properties via the β-arrestin pathway, which is stimulated by the AT1 receptor independent of G proteins and leads to increased myocyte contractility (Shenoy 2005, DeWire 2011). This response has been demonstrated in nonclinical studies, however, the magnitude of this effect as compared to classical inotropes, including milrinone and dobutamine, has not been established in humans.

LJPC-501 is a novel formulation of synthetic Ile5-angiotensin II (human sequence). Ile5-angiotensin II has not previously been authorised in the European Union. Angiotensin II in Giapreza (Ile5-Angiotensin II) has no current ATC code assigned. Even so, there is a significant body of clinical research data in which the pharmacokinetics (PK) and pharmacodynamics (PD) of Ile5-angiotensin II (generally a clinical grade peptide supplied by Bachem AG) have been reported.

An earlier product, marketed under the invented name Hypertensin® (Ciba-Geigy, acquired by Novartis and no longer marketed), and which contained a derivative of bovine angiotensin II (Val5-angiotensin II amide) as drug substance, is also well characterised in the literature. It corresponds to the active substance with ATC code called angiotensinamide (ATC code: C01CX06; Therapeutic group C01CX: other cardiac stimulants). Hypertensin(R) was authorised for the treatment of shock and circulatory collapse by various national competent authorities in Europe; however, Hypertensin is no longer marketed in Europe after withdrawal from its last market (Germany) in 1992. Hypertensin was removed from the market in the United States for reasons unrelated to safety in 2008 (Giapreza, FDA Summary Review).

The applicant states that totality of the literature across these various forms of angiotensin II provides an extensive account of its pharmacological, metabolic, and toxicological properties. Clinically, angiotensin II has a long history of being administered safely to healthy subjects, children, pregnant women, and patients with a broad range of medical conditions comprising cardiovascular, renal, hepatic, and pulmonary diseases, endocrine and metabolic disorders, traumatic injuries, and shock. A recent comprehensive, systematic literature review identified 1,124 studies published in English between 1941 and 2016, in which more than 31,000 subjects were exposed to angiotensin II administered by intravenous (IV) infusion (Busse 2017). It has to be pointed out that the mentioned review has several limitations. Most of the studies used one of two synthetic forms of ATII, an amide derivative of the bovine amino acid sequence or an acetate salt of the human sequence. No comparative studies are available to conclude whether the results are applicable to different synthetic forms of ATII. The vast majority of subjects were not representative of the intended use (i.e.: most subjects were healthy volunteers and the dosing regimens tested are unlikely to correspond to those tested in the ATHOS-3 trial). In addition, most studies were conducted several decades ago, thus being unlikely to be representative of current practice.

Finally, the applicant's contention that raising blood pressure by a mechanism of action different from available vasoconstrictors used in current clinical practice has to be considered itself as a therapeutic innovation was not endorsed in the applicant's request for accelerated assessment (see also section 2.4).

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the applicant's failure to show sufficient strength of evidence to support fulfilment of unmet need in patients with vasodilatory/distributive shock refractory to vasopressors.

The applicant has not requested a conditional marketing authorisation.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 2.5 mg/ml of angiotensin II. The product contains the acetate salt of angiotensin II.

Other ingredients are: mannitol, water for injections, sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

The product is available in Type I glass vial with an aluminium over-seal, stopper (elastomeric), and plastic cap.as described in section 6.5 of the SmPC.

Active substance

General information

Angiotensin II is a linear octapeptide containing 8 natural L-amino acids that is produced synthetically. The chemical name of angiotensin II acetate is L-aspartyl-L-arginyl-L-valyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine, acetate salt corresponding to the molecular formula: C50H71N13O12 • (C2H4O2)n (n= number of acetate molecules; theoretical n = 3). The molecular mass of the free peptide is 1045.5 g/mol (monoisotopic mass).

Both the N- and the C-terminus of the amino acid sequence are unmodified. The active substance is isolated as the acetate salt form of the peptide with some residual water as a natural constituent. Only natural L-amino acids are used in the synthesis of angiotensin II acetate. The structure of angiotensin II acetate is shown in Figure 1.

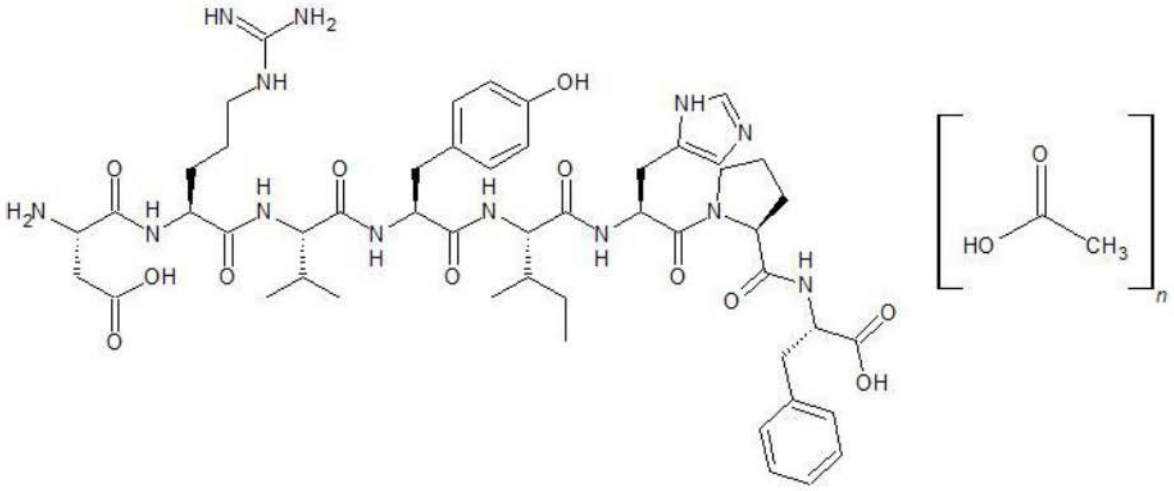


Figure 1: structure of angiotensin II acetate

The structural formula is: L-aspartyl-L-arginyl-L-valyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine, acetate salt, which corresponds to a molecular formula. The molecular mass of the free peptide is 1045.5 g/mol (monoisotopic mass)

Only natural *L*-amino acids are present in angiotensin II acetate. The active substance exhibits stereoisomerism due to the presence of nine stereocentres in the molecule, eight of which are in the peptide backbone; the remaining stereocentre is on the sidechain of the isoleucine residue. The molecule is synthesized as a single diastereomer with all chiral centres of pre-defined stereochemistry.

Each protected amino acid is tested for enantiometic purity and enantiomeric purity is controlled routinely specific optical rotation in the active substance specification.

The structure of the active substance is determined by the solid phase peptide synthesis (SPPS) process described in the next section, which proceeds sequentially by addition of each well-characterized and stereochemically defined protected amino acid to a growing peptide chain bound to a resin. The chemical structure of angiotensin II acetate was elucidated by a combination of chemical and spectroscopic techniques summarized in Table 1.

Table 1. Chemical and spectroscopic tests supporting the proposed structure.

Test Attribute	Analytical Procedure
Molecular mass of the peptide free base form of the drug substance	ESI-MS
Sequence of amino acids for the peptide free base form of the drug substance	Tandem MS/MS
Identity and ratio of the individual amino acids in the peptide free base form of the drug substance	Amino acid analysis
Identity and chirality of the individual amino acids in the peptide free base form of the drug substance	Chiral amino acid analysis by GC-MS
Identity and quantity of the drug substance counter ion	RP-HPLC
Molecular structure identification	1D ^{1}H and 2D $^{1}H/^{1}H$ TOCSY and NOESY NMR

Angiotensin II acetate is a reversibly hygroscopic white to off-white powder, which is freely soluble in water and saline (100 mg/ml) and insoluble in acetonitrile and methanol. The pH of angiotensin II acetate drug substance dissolved in water at a concentration of 40 mg/mL was determined to be 4.54.

Since the peptide is isolated by lyophilisation, no crystalline or polymorphic forms are expected and, to date, none have been observed. X-ray powder diffraction (XRPD) analysis confirmed that the active substance is completely amorphous. No crystalline forms were observed. The active substance is fully solubilized during formulation of the finished product, so the solid-state form of the active substance is not considered critical to the performance of the finished product.

The specific optical rotation was also determined. The angiotensin II molecule contains three basic groups (the N-terminal alpha-amino group, the guanidine group on the side chain of the arginine residue and the imidazole group on the side chain of the histidine residue) and two acidic groups (the C-terminal carboxyl group and the carboxyl group on the side chain of the aspartic acid residue), resulting in a net positive charge of +1 at neutral pH. This results in a calculated isoelectric point of 7.54.

Manufacture, characterisation and process controls

Angiotensin II acetate active substance is synthesized at by conventional solid-phase peptide synthesis (SPPS) chemistriesprotected amino acids, having appropriate side chain protection, as building blocks in the assembly of the peptide.

The synthesis is considered a key step of the manufacturing process as it ensures that the correct sequence is assembled and that the cleaved crude material obtained in the next processing step is of sufficient purity to achieve the target yield. Amino acid starting materials are tested for enantiomeric purity with validated analytical methods to confirm chirality prior to use and racemization of chiral centers is controlled through Fmoc chemistry.

The angiotensin II acetate active substance manufacturing process consists of the major process steps, as outlined below, using commercially available well defined starting materials with acceptable specifications. These include the resin and derivatised amino acids.

Step 1: Solid-phase peptide synthesis (SPPS),

Step 2: Cleavage of the angiotensin II peptide from the resin and deprotection,

Step 3: Purification

Step 4: Reconstitution (wet pooling), filtration, and lyophilisation, and

Step 5: Jar milling and packaging.

Briefly, the synthesis is initiated using an insoluble support to which the terminal amino acid in the sequence is attached Theprotected amino acids are attached sequentially to the peptide chain resulting in a fully protected peptide attached to the solid support resin. The crude peptide is obtained by simultaneous cleavage of the peptide from the resin and removal of the side chain protecting groups through acidolysis resulting in the terminal acid form of the fully deprotected peptide. The resin is then removed by filtration.

The crude angiotensin II peptide is purified and converted to the final acetate salt form . Isolation by lyophilisation yields the final angiotensin II acetate active substance with appropriate purity and quality. After lyophilisation the active substance is jar milledLyophilized angiotensin II acetate active substance that does not fulfil relevant acceptance criteria as established in the active substance specification may be subjected to repurification or relyophilization.

The manufacturing process for angiotensin II acetate is described with sufficient details in terms of raw materials and process parameters. Target quantity is described for each raw material used at a given step. The proposed ranges for the process parameters are acceptable.

The active substance is packaged in amber glass containers. The container closure system is a USP <660>/Ph. Eur. 3.2.1 compliant Type III soda-lime, amber glass container, which is fitted with a Teflon-lined polypropylene

screw cap with a foam-backed Teflon (PTFE) liner. The polypropylene screw cap lid does not come into contact with the drug substance. The PTFE liner is the only material that comes into contact with the active substance. The container closure system provides some protection from moisture and light. The cap and the cap liner comply with European Regulation 10/2011/EC.

The products obtained in each step of the synthesis are stored at specific temperature conditions for a time period.

The hold time study was performed using a commercial scale batch produced according to the manufacturing process described. The qualified hold times listed in the dossier for each process step are supported by manufacturing process history for registration and validation lots of active substance. However, the CHMP recommends performing an additional hold time study post-approval on one additional batch of active substance to further support the qualified hold times for each process step.

Critical steps in the synthesis of the active substance have been identified and their potential impacts on the quality attributes of the active substance have been suitably addressed.

Appropriate in-process controls are established to monitor the completeness of the reaction using suitable visual tests for the coupling reactions with protected amino acid and/or by monitoring the reaction time for the cleavage of the peptide from the resin. Suitable acceptance criteria based on batch results The specifications and control methods for intermediate products, starting materials and reagents have been presented.

No aseptic or sterilisation process is performed in the manufacture of angiotensin II acetate.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. A comprehensive evaluation of the actual and potential peptide related impurities of the Angiotensin II acetate that could be introduced via the manufacturing process or from degradation pathway has been conducted. Characterisation of specified related substances has been presented. No residual solvent has been observed above ICH Q3C recommended limits in the active substance batches. Only the solvents used in the last purification steps of the commercial process are routinely controlled. The carry-over of non-peptide related organic compounds used or generated during the process can be considered very unlikely given the whole process that includes many washes of the resin and the purification. A suitable elemental impurities risk assessment was conducted on Angiotensin II acetate active substance following the principles outlined in ICH Q3D. No metal catalysts are used in the commercial process. Absence of genotoxic impurity discussion is acceptable as ICH M7 guideline excludes peptides from consideration.

The angiotensin II acetate manufacturing process at the proposed commercial site has remained fundamentally the same for all lots of active substance manufactured to date. An overview of the angiotensin II acetate batches manufactured with a description and rationale of manufacturing process changes has been provided. These were minor and were based on a series of quality risk assessments, process development work, process experience, and process scale-up. The in-process control limits were tightened during development as process capabilities improved. Changes introduced have been presented in sufficient detail and have been justified. It has been demonstrated that the changes did not have a significant impact on the quality of the product. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

In support of the MAA, the applicant has presented literature studies conducted with Hypertensin® (Ciba Geigy) and angiotensin II product manufactured by Bachem (not approved for marketing in any country). Quality data have been provided to justify bridging to the proposed substance. A comparability study of angiotensin II acetate manufactured by the proposed commercial site to other sources and forms of angiotensin II has been

provided. The angiotensin II acetate active substance used to manufacture Giapreza is produced synthetically in the Ile^5-angiotensin II form. Angiotensin II manufactured by the proposed manufacturer and angiotensin II manufactured by Bachem are of the same amino acid sequence. The bovine angiotensin II (Val^5-angiotensin II) and Hypertensin (Val^5-angiotensin II amide) are similar save for the amide group in Hypertensin. Based on analytical comparability data, the peptide contained in Giapreza and that from Bachem can be considered as equivalent from analytical point of view. Bovine Angiotensin II (Val^5-angiotensin II) and Hypertensin (Val^5-angiotensin II amide) are not of the same amino acid sequence of angiotensin II acetate from the proposed manufacturer and thus cannot be considered as equivalent from a chemical point of view.

Specification

The active substance specification includes tests for appearance (visual), identification by mass spectrometry (RP-HPLC/ESI-MS), identification by peptide sequencing (RP-HPLC/MS-MS), identification by amino acid analysis (Ph. Eur.), purity (RP-HPLC), related substances (RP-HPLC), assay (net peptide content by elemental analysis, % nitrogen), water content (Ph. Eur.), acetic acid content (USP), residual TFA content (USP), mass balance, residual solvents (GC), elemental impurities (Ph. Eur.), specific rotation (Ph. Eur.) bacterial endotoxins (Ph. Eur.) and microbial enumeration (Ph. Eur.).

The current specifications for angiotensin II acetate are acceptable for the manufacture of the finished product. The proposed limits for peptide related substances (specified and unspecified) are set in line with recommendations published in Ph. Eur. monograph 2034. Suitable toxicological data are submitted for the setting of the acceptance criteria for residual TFA. The limits proposed for residual solvents are those given in ICH guideline and are therefore acceptable. The risk assessment and the control strategy proposed for elemental impurities in the active substance are considered as satisfactory. Given the pharmaceutical use, the active substance is suitably tested for residual bacterial endotoxins and microbial enumeration.

The applicant has included a justification for not including test for pH testing. pH has been omitted since angiotensin II acetate is a solid. This is acceptable.

In the original submission, the applicant presented a justification for the omission of specific rotation.

As mentioned above angiotensin II acetate active substance is manufactured as a single diastereomer with high diastereomeric and enantiomeric purity with all amino acids of the L-configuration. Control of chiral quality has been established by applying limits to the appropriate starting materials.

The applicant has however been asked to implement the specific rotation as part of the routine control

In the original submission, the applicant also presented a justification for the omission of a control for benzene in the active substance specification. This solvent was not detected in three validation batches. However, considering a maximum daily dose of angiotensin II (5.2 mg) and the worse scenario (current limits for each solvent and their purity), the maximum potential exposure to benzene was calculated . Given the maximum daily dose of angiotensin II (5.2 mg), the maximum exposure to benzene should be not higher than 0.0104 µg per day. In order to ensure a residual level of benzene in angiotensin II in line with ICH Q3C(R6), a test for benzene was added. The method validation is on-going and the CHMP recommends providing the supporting validation report in the upcoming type IA variation (annual report).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH Q2(R1) guideline. The appearance method was not validated since it is qualitative in nature. The mass balance method was not validated since it is the sum of the assay, acetic acid content, and water content results.

Satisfactory information regarding the reference standards for used for assay and impurities testing has been presented.

Information on all lots of angiotensin II acetate active substance manufactured to date has been presented. These include three pilot scale and three commercial scale batches. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three pilot scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market (same material but smaller size-15 mL) for up to 48 months under long term conditions (-20 ± 5ºC) and for up to 6-12 months under accelerated conditions (5 ± 3ºC or 25 ± 2°C/60 ± 5% RH) according to the ICH guidelines were provided. The three registration stability lots were manufactured at a scale that is at 10% scale or up to 50% scale according to a process that is representative of the commercial process (same synthetic route only minor changes in reagents and solvents were made in some batches to improve process capability and increase efficiency of purification step during scale-up).

Supportive stability data from three commercial scale batches stored for 18 months under long-term conditions (-20 ± 5ºC) were also presented.

Samples were tested for appearance, identification by mass spectrometry, water content, assay (net peptide content), purity and related substances.

The analytical procedures used to evaluate the stability of the registration stability lots are the same as those proposed in the specification with the exception that for part of the duration of the stability studies, a different purity and related substances method was in place. The applicant performed a bridging study to support the change in method from the original development purity and related substances method to the intended commercial method.

No significant changes are observed for the angiotensin II acetate drug substance when stored at -20 ± 5°C. All lots met the specification acceptance criteria.

After 12 months of storage at 5 ± 3°C, no significant change in appearance, water content, purity, or total related substances was observed for any of the two lots tested. The primary degradation product of the active substance was identified. It started to slightly increase during the 12-month study,.

Stability studies at a stress storage condition of 25 ± 2°C/60 ± 5% RH were performed for the three registration lots and one supportive stability lot. After three months of storage, a decrease in purity and a subsequent increase in the level of total related substances was observed in all lots. This increase in total related substances was attributed to the increase of the primary degradation product of the active substance. After six months, the level of the degradation product exceeded its specification. The water content also increased during this six month study, but still met the specification

The accelerated stability data support short term excursions outside the proposed label storage condition of -20 ± 5°C.

A photostability study was conducted on one batch of angiotensin II acetate as per ICH Q1B. The sample was tested for appearance and HPLC purity/related substances and compared to a dark control. The changes observed were negligible. Based on these results, angiotensin II acetate active substance is considered photostable.

Forced degradation studies were performed on angiotensin II acetate active substance during validation of the HPLC method for related substances. The peptide was exposed to acid, base, oxidation and thermal conditions. The active substance was stable when exposed to acidic and basic conditions with only minor degradation observed and is very stable when exposed to oxidative conditions with no significant degradation observed. The active substance showed significant degradation when exposed to high temperatures, mainly due to the formation of the primary degradation product.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months stored at -20 ± 5°C in the proposed container.

2.2.2. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product (also known as LJPC-501) is a sterile, aqueous solution containing 2.5 mg/ml angiotensin II as active substance and is supplied in single-dose vials as a concentrate for solution for infusion.

Two presentations are proposed: 2.5 mg angiotensin II/vial and 5 mg angiotensin II/vial (nominal fill volume of 1 ml and 2 ml, respectively), with no differences in the formulation or container closure system. Each 3 ml vial of drug product contains 0.2 ml overfill to achieve sufficient excess volume in the vial to achieve the desired extracted volume.

The finished product has to be diluted in 0.9% (v/v) sodium chloride solution prior to administration by intravenous infusion and is titrated to effect.

The composition of the finished product is provided in Table 3. The excipients used in the manufacture of the finished product include mannitol USP/Ph. Eur. as tonicity modifier, and water for injection (WFI) USP/Ph. Eur. Trace amounts of sodium hydroxide (NaOH) NF/Ph. Eur. and hydrochloric acid (HCl) NF/Ph. Eur. are also added, as needed, to adjust the pH .

Table 2: composition of the finished product (2.5 mg/vial and 5 mg/vial Presentations)

Component	Quality Standard	Function
Angiotensin II Acetate[b]	In-house	Active Ingredient
Mannitol	USP/Ph. Eur.	Tonicity Modifier
WFI	USP/Ph. Eur.	Solvent
1 N NaOH[c]	NF/Ph. Eur.	pH Adjustment
0.05 N HCl[d]	NF/Ph. Eur.	pH Adjustment

NF = National Formulary; Ph. Eur. = European Pharmacopeia;
USP = United States Pharmacopeia; WFI = water for injection;
b Amounts reported in the table reflect angiotensin II acetate salt, which is equivalent to 2.5 mg peptide (angiotensin

II) content free of base salt.
c The 1 N NaOH solution is prepared from NF/Ph. Eur. sodium hydroxide pellets and USP/Ph. Eur. WFI.
d The 0.05 N HCl solution is prepared from NF/Ph. Eur. grade hydrochloric acid and USP/Ph. Eur. WFI.

The aim of the pharmaceutical development was to develop a formulation for intravenous infusion. Since both the N- and the C-terminus of the peptide sequence are unmodified, and the molecule does not contain any complex bonds and thus is very stable, even in an aqueous solution, a liquid formulation that would be simple to manufacture in a cGMP environment and that would show good stability when stored long-term at frozen or refrigerated storage conditions and could tolerate excursions to room temperature was pursued. A target concentration of 2.5 mg/ml of angiotensin II net peptide content was selected as this amount would efficiently be dissolved in the solvent, WFI, and would support the range of peptide doses required during clinical administration.

The physicochemical properties of the active substance that could influence the performance of the finished product and its manufacturability (solubility, crystal properties) have been identified and discussed. As indicated in the active substance section, angiotensin II acetate is a linear octapeptide isolated as acetate salt and comes in the form of an amorphous powder. All chiral centres are of predefined stereochemistry and angiotensin II acetate is synthesized as a single diastereomer. The active substance is amorphous, with no crystalline material observed. It is slightly soluble in water at pH 7 and freely soluble in water at pH 2 and 9. Since angiotensin II acetate is fully solubilized in water during formulation, the crystalline form of the active substance is not considered critical.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The compatibility of angiotensin II acetate with the excipients can be considered demonstrated by stability results.

The physicochemical and biological properties of the formulation relevant to product performance include appearance, pH, osmolality, subvisible particulates, bacterial endotoxins, and sterility. These are tested at release and on stability.

During early development, a 5 mg/vial presentation with a nominal 2 ml fill volume per vial was selected because this presentation would be most suitable for further dilution in the planned clinical study and in clinical practice in general. During the conduct of the Phase 3 clinical study, it was noted that most patients did not utilize the full contents of the vial and excess remained. Thus, a second presentation was added to the proposed commercial drug product (2.5 mg/vial [2.5 mg/ml]). There are no differences in formulation or container closure system in the two presentations. The only difference between the two presentations aside from the colour of the button on the seal, is the headspace and surface to volume ratio of the product in the vials. The surface to volume ratio is not expected to impact the quality of the finished product. Although the increased headspace in the vial has the potential to expose the drug product to more oxidative stress, none of the amino acids sensitive to oxidation –namely, methionine (Met), tryptophan (Trp), and cysteine (Cys)-, are present in the primary sequence of angiotensin II. As a result, oxidative degradation is not considered to be a significant degradation pathway for this active substance. Furthermore, forced degradation studies presented in the active substance section confirm this. This was also supported by stability data from vials of the two presentations stored in the upright and inverted orientations for 12 months under long-term storage condition (5°C) and for 6 months under accelerated storage condition (25°C/60% RH) which showed comparable results. Thus, comparability of the drug product in the 2.5 mg/vial and 5 mg/vial is demonstrated.

The method of sterilization for the finished product was also evaluated as part of the manufacturing process development. The potential to perform terminal sterilization was investigated. Briefly, samples for LJPC-501

finished product in the intended commercial container closure system were cycled three times in an autoclave at 121°C for 30 minutes. After each cycle, samples were held at 5°C until analysis. A control sample was also stored at 5°C until analysis. Samples were tested for appearance, assay and related substances. After the first autoclave cycle the total related substances increased and after the third cycle they reached a higher level demonstrating that angiotensin II peptide is sensitive to heat. These conditions were too hard and the applicant was requested to try sterilization by moist heat at 121ºC for 15 minutes and, if the product is degraded, sterilization by moist heat with F0 ≥ 8 minutes achieving SAL of ≤ 10^{-6}, in accordance to EMA Guideline: Decision trees for the selection of sterilization methods (CPMP/QWP/054/98), the Annex to the Note for guidance on development pharmaceutics (CPMP/QWP/155/96). These studies were conducted and after the respective autoclave cycles were completed, the sample vials were tested for appearance by visual inspection and assay and related substances by HPLC. After 15 minutes exposure the assay and related substances results did not meeting the specification. In the second study (F0=8), the assay result fell to a just inside the specification limit; however, the individual and total impurities did not meet the specification requirements. Therefore, the results from these studies justify the selection of sterile filtration for the manufacture of the finished product.

During product development, three different finished product manufacturers were involved, but there were no changes made to the finished product formulation throughout clinical development. Changes to the manufacturing process between manufacturing sites were minor and limited to those necessary to adapt to the new manufacturing site and an increase in scale. A comparison of the manufacturing processes at each site has been provided. The results of analysis of the manufacturing unit operations, specifications and batch analysis data among the three manufacturers involved in development showed comparability of the finished product manufactured at the three sites.

The finished product manufacturing process allows for the bulk drug product solution to be held after the final concentration step, prior to sterile filtration.

The applicant conducted hold time studies to establish the maximum hold time of the bulk finished product solution. The in-process hold time was formally validated as part of finished product process validation.

Prior to finished product manufacturing, an initial study to evaluate compatibility of the formulation with the components in the manufacturing process was performed with various contact surfaces utilized during the manufacturing process. An extractables and leachables materials assessment for the equipment used in the production was also performed. Based on this evaluatuion the risk of extractables and leachables was considered to be low.

To support the MAA, a comprehensive finished product comparability assessment of Giapreza (LJPC-501) finished product and Bachem angiotensin II acetate product was executed. The active substance, angiotensin II acetate, used to produce LJPC-501 is the same form of angiotensin II that was used in many clinical studies over the past two decades (Ile^5-angiotensin II, manufactured by Bachem). The comparability assessment conducted lead to a conclusion that both products are equivalent in terms of analytical chemistry characterization and properties. The container closure system consists of a clear 3 mL USP/Ph. Eur. Type 1 borosilicate glass vial with a 13 mm ph. Eur. elastomeric stopper, sealed with an aluminium closure and a plastic flip-off cap. A blue plastic flip-off cap is used for the 2.5 mg/vial presentation and a green plastic flip-off cap is used for the 5 mg/vial presentation. The secondary packaging consists of an individual paperboard carton for each vial. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product

A rationale for the selection of the container closure system has included. The choice of materials for primary packaging is justified. The risk for potential delamination of the Type I glass vials was evaluated, concluding that

the risk is low. Adsorption, extractables and leachables studies were performed on the stopper and the complete container closure system. The extractables and leachables risk from labels was also evaluated. It is concluded that the physical and chemical properties of container are suitable for use with the formulation and present no safety risk to the patient. Stability test results to date confirm the absence of any significant leakage, water sorption, or evaporation of aqueous solvent for the container closure system. Throughout clinical development, container closure integrity studies via dye ingress were conducted to challenge the seal formed by capping operations.

As indicated above, the finished product has to be diluted in normal saline (0.9% sodium chloride) solution prior to administration by intravenous infusion and is titrated to effect. The diluted drug product solution may be stored at room temperature or refrigerated. Diluted finished product solution should be discarded after 24 hours.

The applicant conducted an in-use study to evaluate the compatibility of the product with the normal saline (0.9% sodium chloride) solution and typical administration components.

Two concentrations of the finished product diluted in normal saline were used, 5,000 ng angiotensin II/ml (equivalent to 1 mL LJPC-501 finished product in 500 mL IV bag) and 10,000 ng angiotensin II/ml(equivalent to 1 mL LJPC-501finishe product in 250 ml IV bag), in two types of IV infusion bags (PVC and non-PVC) at 25°C/60% RH. The two concentrations were selected to support the range of expected clinical administration concentrations. Two types of IV infusion tubing sets were also included in the study, one type containing [di-(2-ethylhexyl)phthalate (DEHP)] and one type DEHP-free. Bags were connected to the two types of IV infusion tubing sets (DEHP DEHP-free). Samples were stored for up to 36 hours at 25°C/60% RH. The 36-hour point is a period beyond the intended maximum holding time for the diluted drug product. Samples were tested for appearance, pH, assay, related substances and osmolality. All test results met protocol specification requirements and support a 24-hour hold period of diluted finished product at 25°C/60% RH.

The applicant also conducted a microbiological in-use study to evaluate the microbiological stability of the finished product and the ability of diluted finished product solution in normal saline to support microbiological growth. Finished product after dilution in normal saline (0.9% sodium chloride) IV infusion bags to a concentration of 10,000 ng angiotensin II/mL was evaluated for up to 48 hours at 2 - 8°C and 20 - 25°C storage temperatures. Results demonstrate that the drug product is microbiologically stable for up to 48 hours under the conditions tested. Therefore, the results of the microbiological in-use study support a 24-hour hold period of the drug product diluted in normal saline (0.9% sodium chloride) at concentrations ≤ 10,000 ng/ml at 2-8°C and 20-25°C storage temperatures. This supports the SmPC recommendation for the diluted solution: “Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature and 2 – 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 °C or 25 °C”.

Two studies were conducted to investigate potential interactions between angiotensin II and the other vasopressors norepinephrine, epinephrine, vasopressin, dopamine and phenylephrine. As terlipressin is an analog of vasopressin, the results achieved with vasopressin are expected to be representative of what would be seen with terlipressin and it was therefore omitted from the study. Studies were designed to simulate intravenous line mixing of multiple commercial vasopressors along with angiotensin II to determine if any drug interactions are observed. These two independent studies showed no evidence of interaction between angiotensin II and five commercial vasopressors. The stability of solutions of angiotensin II, individual and combined vasopressors were evaluated by visual observation, HPLC and Isothermal Titration Calorimetry.

Manufacture of the product and process controls

Giapreza consists of a sterile, aqueous solution supplied in single-dose vials. The manufacturing process is a standard aseptic filling process employing a system of two serially arranged filters. The process steps used to manufacture Giapreza include: formulation of bulk product solution, sterile filtration, aseptic filling, labelling and secondary packaging.

As indicated above, the product is supplied in two presentations: 2.5 mg angiotensin II/vial (2.5 mg/ml) and 5 mg angiotensin II/vial (2.5 mg/ml). There are no differences in the formulation or container closure system used for packaging for the two presentations. The 2.5 mg/vial is provided with a nominal fill volume of 1 ml per vial and the 5 mg/vial is provided with a nominal fill volume of 2 ml per vial.

Since aseptic manufacturing processes are inherently critical, process parameters involved during the sterile filtration and aseptic filling have been identified as critical. The sterilizing filter was validated for its use in the drug product manufacturing for a maximum product contact time, maximum process flow rate , and a maximum filtration volume.

The process validation covers both manufactured presentations. Validation data on production scale batches has been presented Terminal sterilization and depyrogenation of the primary packaging used during aseptic processing of the finished product is performed. The sterilization methods are described and validation of these methods is included in the dossier. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification by mass spectrometry (RP-HPLC/ESI-MS), identification (HPLC), assay (HPLC), related substances (HPLC), pH (Ph. Eur.), sub-visible particles (Ph. Eur.), extractable volume/volume of injection in containers (Ph. Eur.), osmolality (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.).

Parameters included in the specification are considered the critical ones for guaranteeing finished product safety and efficacy. The acceptance criteria have been established based on manufacturing capability, stability data, ICH guidelines and compendial requirements. Limits proposed for the specification are considered justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

During the stability studies, some oscillating values in assay were observed, suggesting that there was a problem in the inherent variability of the assay method, and a question was raised. The applicant identified two potential sources contributing to the analytical variability of the assay method. First, the method demonstrates some baseline noise that presents itself intermittently. Second, the quantitative reference standard is a lyophilized powder aliquoted to single-use vials. Vial to vial variability of the reference standard can also contribute to method variability. The applicant developed a UHPLC assay method to replace the current HPLC assay method. The UHPLC method has reduced the baseline noise, which lessens any effect on the quantitative results. The UHPLC method also utilizes a liquid reference standard to address vial to vial variability present with the current, lyophilized reference standard. This UHPLC method has recently been validated, but not yet implemented (validation report). The applicant is preparing a bridging study to transition from the HPLC method to the UHPLC method. Therefore, the CHMP recommends submitting the updated UHPLC assay method to

replace the current HPLC assay method for release and stability testing of the commercial batches prior to commercial launch of the product in the EU.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. It included information supplied by drug substance and excipient manufacturers and data generated by the applicant. Known and potential sources of elemental impurities are identified: active substance, water, mannitol, manufacturing equipment (an extractables and leachables assessment is performed) and container closure system (an extractables and leachables assessment is performed). Batch analysis data (2.5 mg/vial and 5 mg/vial batches) using a validated method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A justification for the exclusion of residual solvents from the commercial release specification for the finished product has also been presented and is acceptable. Residual solvents are controlled are controlled as part of the release active substance specification. The supplier of the excipient, mannitol, certifies that no Class 1, 2, 3, or other solvents are used in the manufacture or purification of the excipient. The only solvent used in the manufacture of the finished product is water and no organic solvents are used.

Results from an important number of batches manufactured at each development site and the proposed manufacturing site and with different use (process validation, clinical, development or registration) have been provided. The lots manufactured by the proposed manufacturer were released per the proposed finished product release specification and evaluated using the proposed analytical methodologies. Batch results are sufficient and acceptable. They confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from twelve (three commercial scale) batches of finished product stored for up to 36 months (5 mg/vial) or 24 months (2.5 mg/vial) presentations under long term conditions (5 ± 3°C) and for up to 6 months under accelerated conditions (25 ± 2°C/60 ± 5% RH) according to the ICH guidelines were provided. The batches of Giapreza are identification those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for all parameters included in the finished product specification except from identification by mass spectrometry. Samples were tested in both the upright and inverted orientation. The analytical procedures used are stability indicating. The analytical procedures used to evaluate the stability of the registration lots are the same as those proposed for routine use with the exception that for part of the duration of the stability studies, a different assay and related substances method was in place. The applicant performed a bridging study to support the change in method from the original development assay and related substances method to the intended commercial method.

All results met the specification in place at the time of analysis when stored at 5 ± 3°C for up to 36 months and no trends were observed.

At accelerated storage condition, all results met the proposed specification and no trends were observed, except for the degradation product. where a significant change was observed, exceeding its specification. However, after one month, this degradation product was within specification, which supports short-term excursions of the finished product outside the label storage condition of 5 ± 3°C.

No discernable difference was observed between the upright and inverted orientations under both long-term and accelerated storage conditions.

A freeze/thaw study was conducted on one batch. Samples were cycled three times between freezing (-20°C) and 25°C/60% RH. After each cycle, samples were withdrawn for testing. Samples were tested for appearance, assay, related substances, pH, and particulate matter. All results met the specification. Based on these results, it is concluded that Giapreza can withstand exposure to freezing conditions.

A photostability study was conducted on one batch of Giapreza as per ICH Q1B StabilityTesting: Photostability Testing of New Drug Substances and Products. The sample was tested for appearance and HPLC assay/degradation products and compared to a dark control that had been wrapped in foil. No changes were observed and therefore it is concluded that Giapreza is photostable.

Based on available stability data, the proposed shelf-life for both the 2.5 mg/vial and 5 mg/vial presentations of 36 months stored at 2 - 8°C as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.3. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.5. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

i) performing an additional hold time study post-approval on one additional batch of active substance to further support the qualified hold times for each process step;

ii) providing the supporting validation report for the GC method for benzene included in the active substance in the upcoming type IA variation (annual report);

iii) submitting the updated UHPLC assay method to replace the current HPLC assay method for release and stability testing of the commercial batches prior to commercial launch of the product in the EU, as per the commitment provided.

2.3. Non-clinical aspects

2.3.1. Introduction

Giapreza contains active substance angiotensin II (also referred to as LJPC-501). Angiotensin II is the key biologically active vasopressor endogenous octapeptide in the renin angiotensin aldosterone system (RAAS). Angiotensin II raises blood pressure by direct vasoconstriction, increased aldosterone release, and renal control of fluid and electrolyte balance.

LJPC-501 is a novel formulation of synthetic Ile^5-angiotensin II (human sequence). Ile^5 angiotensin II has not previously been authorised in the European Union.

The non-clinical package contains data obtained with the proposed product and literature studies conducted with **Ile^5-angiotensin II** (generally a clinical grade peptide supplied by Bachem AG) and Hypertensin® (Ciba-Geigy, acquired by Novartis and no longer marketed), and which contained a derivative of bovine angiotensin II (**Val^5 angiotensin II amide**) as drug substance. There is also a part of the literature for which the source of angiotensin II is unknown.

Scientific Advice was given by EMA (EMEA/H/SA/3618/1/2017/SME/III) in 2017. The advice included the following conclusions/recommendations regarding nonclinical issues:

While the approach to investigate the cardiovascular safety pharmacology aspects is considered to be acceptable to support marketing authorisation, there are issues with respect to the potential effects on the respiratory and central nervous systems which require further consideration. It is anticipated that no further non-clinical studies are required despite the final comparability conclusion. Absence of data on potential effects on reproduction could be justified considering the target population. The applicant should thoroughly discuss the existing non-clinical and clinical data which demonstrate any potential effects on reproduction, with a view to demonstrating how the deficiencies could be addressed by way of the SmPC and the risk management plan. Notwithstanding, the feasibility of conducting a reproduction toxicity study should be explored/discussed.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The angiotensin II in LJPC-501 is identical to the human amino acid sequence, with isoleucine at the 5-position (Ile5-angiotensin II). Some of the non-clinical studies from the literature used alternative forms of angiotensin II based on the bovine sequence, either **Val5-angiotensin II amide (Hypertensin®, manufactured by Ciba-Geigy Pharmaceutical Co)** or **Val5-angiotensin II (non-amide, multiple manufacturers);** or research **grade Ile5-angiotensin II (multiple manufacturers, including Bachem)**. A comparative sequence analysis of LJPC-501 and other forms of angiotensin II is provided in Figure 4. Some studies did not report the sequence or source of angiotensin II used.

LJPC-501[a]	**Asp**^{1}-Arg-Val-Tyr-**Ile**^{5}-His-Pro-Phe^{8}	(Ile^{5}-angiotensin II)
Ile^{5}-angiotensin II (Bachem)	**Asp**^{1}-Arg-Val-Tyr-**Ile**^{5}-His-Pro-Phe^{8}	(Ile^{5}-angiotensin II)
Hypertensin®	**Asn**^{1}-Arg-Val-Tyr-**Val**^{5}-His-Pro-Phe^{8}	(Val^{5}-angiotensin II amide)
Bovine	**Asp**^{1}-Arg-Val-Tyr-**Val**^{5}-His-Pro-Phe^{8}	(Val^{5}-angiotensin II)

[a] Ile^{5}-angiotensin II used to manufacture LJPC-501 is identical to the endogenous human form of angiotensin II.

Figure 2 Comparative Sequence Analysis of Angiotensin II in LJPC-501 (Ile5-angiotensin II), Ile5-angiotensin II (Bachem), Hypertensin® (Val5-angiotensin II amide), and Bovine (Val5-angiotensin II)

The mechanism of action and pressor efficacy of angiotensin II has been evaluated across multiple species and in a number of non-clinical models of hypotension, as well as in human studies. Because angiotensin II has been extensively studied over decades, a review of selected appropriate open literature publications has been used to support the proposed clinical indication.

In order to bridge LJPC-501 to other forms of angiotensin II described in the literature, the Applicant has carried out a number of *in vitro* studies in order to stablish the receptor binding and functional activity of both angiotensin II receptor subtypes AT_1 and AT_2 comparison.

Binding affinity for AT_1 and AT_2 was measured and summary reports were provided. TR 0265 includes discussion of the results obtained from TR 0266 while TR-0207 summarizes the results obtained from TR-0205 and TR-0206. In studies TR-0265 and TR-0207, AT_1 and AT_2 receptor-expressing Chinese hamster ovary (CHO-KI) cell lines were utilised to assess the binding of angiotensin II test compounds to the AT_1 receptor (TR-0265) and the AT_2 receptor (TR-0207), respectively, by comparing binding affinities. It should be noted that the original studies have not been provided. The missing reports were submitted in the responses for clarification. In addition, it appears that there is a three and two-fold difference in binding affinity for AT_1 and AT_2 respectively between LJPC-501 and human angiotensin II. The company argues that the values obtained are due to variation in the assay and are within normal values, nonetheless the differences reported in the mean IC_{50} values are too high to be considered as normal variations in the assay, therefore the applicant was requested to further discuss and clarify this issue. The receptor binding assays submitted are indicative of a certain degree of variability between LJPC-501 (Ile-5 angiotensin II) and Bachem Ile5-angiotensin II. However, there was no significant difference in the IC50 values provided. The applicant indicates that the cell assay membranes employed, assess binding of human angiotensin II and LJPC-501 to the respective receptors and do not reflect actual functional potency.

Only functional endpoints were measured for receptor AT_1 and the applicant has been unable to develop a workable functional assay for the AT_2 receptor. The studies performed to measure the functional assay for this receptor (TR-0183 and TR-0271) have been included in the clinical part of the CTD.

It has been published that the AT_2 receptor is not coupled to classical second messengers such as cAMP therefore measurements of cAMP expression would not be relevant (Singh and Karnik, 2016). Furthermore, the Applicant was asked to justify the rationale for not including neuronal cells and study of pathways involved in neurite outgrowth and neuronal differentiation. The Applicant has carried out a relevant attempt to clarify the issue by reviewing published related literature and also by carrying planning and carrying out *in vitro* studies. Although the Applicant has not been successful to find a adequate test to assess AT_2R functionality, it is acknowledged the Applicant's proposal to tackle this issue by addressing efficacy of LJPC-501 mostly by titrating the infusion to the potential effective dose. The assessors also conclude that this issue is not crucial for a final authorization bearing in mind the above discussion.

The data provided related to pharmacodynamic studies in both small and large animal models of sepsis and hypotension suggest that exogenous angiotensin II restored systemic mean arterial pressure (MAP), and increased urinary output and creatinine clearance, at concentrations similar to those that are effective in humans with shock.

Secondary pharmacodynamic studies

Angiotensin II has been shown to can affect glucose via stimulation of glucogenesis and impairment of insulin sensitivity. It should be noted that in clinical trials with LJPC-501, the incidence of hyperglycaemia was higher in patients who received LJPC-501 compared to placebo. However, based on cumulative evidence from literature, pre-clinical data, randomized clinical trials and postmarketing safety surveillance, there was insufficient evidence for a causal relationship between LJPC 501 and hyperglycaemia. Therefore, "hyperglycaemia" has been removed as an adverse reaction from the product information. With regards to CNS the applicant has not included a relevant discussion regarding secondary pharmacology. It may be argued that the product does not cross the BBB, but AT2 receptors are present in the brain and vasodilatory shock and sepsis are associated with disruption of the BBB. Similarly no information was found reported angiotensin II effects in the immune system. Since non-clinical data is considered inconclusive and bearing in mind that it is covered by clinical outstanding issues, this concern is being dealt with in the clinical AR.

Safety pharmacology programme

A cardiovascular safety pharmacology was carried out assessed effects of LJPC-501 on cardiac contractility, haemodynamic, respiratory, pharmacokinetic, and electrocardiogram (ECG) parameters in anaesthetised normotensive dogs (TR-0095). LJPC-501 significantly increased MAP, heart rate, systemic vascular resistance, left ventricular systolic and diastolic pressure, and PR interval. No QTc prolongation has been reported.

No dedicated measurements of effect on respiratory system and CNS with LJPC-501 were performed. Clinical and non-clinical data, when taken together reveals a limited risk of respiratory events associated with the product administration. Delirium, agitation and 1 case of cerebral infarction have been observed in patients in clinical trial with LJPC-501. Relation between LJPC-501 and these central effects could not be established as central effects are a frequent complication in patients due to their pathologic conditions or administrated psychoactive medications. A potential impact of administration of exogenous angiotensin II on BBB integrity and potential toxic consequences could not be discarded from nonclinical point of view. A clinical monitoring and management are particularly important.

Pharmacodynamic drug interactions

Taking into account the target population and the product, no relevant pharmacodynamic interactions should be expected.

In conclusion, pharmacology studies from literature or performed by the applicant have demonstrated that LJPC-501 is relevant to the proposed indication, treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

2.3.3. Pharmacokinetics

No stand-alone PK studies with LJPC-501 were conducted by the Applicant. Extensive non-clinical studies are reported in the literature on exogenously administered angiotensin II that provide a comprehensive understanding of its pharmacokinetic (PK) profile. Animal PK profile was characterized by high blood clearance rate, short half-life, low volume of distribution and low plasma protein binding. Angiotensin II showed dose-proportional systemic exposures over a wide range of dose level. About half to three-quarters of angiotensin II was eliminated in one circulation in all vascular beds giving an estimated half-life of approximately 15 sec in dogs. In rats, half-life was approximately 15 sec and apparent volume of distribution was 18 ml/kg. In sheep, half-life was approximately 45 sec and blood clearance after IV infusion 100 L/hr. The protein binding was estimated approximately at 50%. Angiotensin II was eliminated mainly by metabolism by end terminal cleavage (at both the amino and carboxyl termini) in a variety of tissues, including erythrocytes, plasma and many of the major organs (i.e., kidney, liver, heart and lung). Three endogenous angiotensin II active metabolites were identified: angiotensin III (amino acids 2-8), angiotensin IV (amino acids 3-8), and the carboxy terminal cleavage product des-8-angiotensin (amino acids 1-7). Renal excretion played a negligible role in the elimination of angiotensin II.

Moreover, PK information was collected from cardiovascular safety pharmacology with LJPC-501 (TR-0095) and a toxicity study of angiotensin II in neonatal sheep (TR-0237). It is noted that the blood samples collected in dogs and in lambs were not stabilized during the blood collection, but they were stabilized only at the bioanalysis site. The loss was estimated to be close to 90%; consequently, the bioanalytical results and the toxicokinetic evaluations could not be considered relevant. Long-term stability studies were performed for unstabilized samples in order to bridge the missing data; however, no results were submitted. The applicant was requested to submit the missing long-term stability results on unstabilized plasma and discussed the relevance of these results. PK data from study TR 0095 can only be interpreted as qualitative, no quantitative extrapolation can be raised from it. The observed PD activity in treated animals is indeed suitable to confirm the systemic exposure. There was a discrepancy between study report TR 0267 where it was reported stabilization during blood collection and the module 2.6.5.2 where it was reported that the blood were not stabilized. The responses confirm that the study samples were stabilized during the blood collection in the study TR 0267.

In accordance with the data showed by the applicant, pharmacokinetic drug interactions would not be expected with LJPC-501.

2.3.4. Toxicology

Single dose toxicity

Single dose experiments were conducted by Byrom using Val^5-angiotensin II amide, which was given to normotensive albino rats by intravenous (IV) injection (Byrom 1964). Angiotensin II in doses of 1 to 100 µg were administered using several different protocols such as a single administration, two administrations (separated by 10 minutes) or multiple infusions given at 30-minute intervals for periods of 2.5 to 7 hours. IV injections of very large doses of angiotensin II cause acute medial necrosis of large renal arteries in the rat. The necrosis appears to be an immediate result, direct or indirect, of the double physical stress imposed on the arteries by overstimulation and excessive filling tension. Repeated doses of angiotensin II occasionally cause focal glomerular necrosis, which is derived from capillary aneurysms by a process of thrombosis.

To evaluate the relationship between myocardial damage and angiotensin II levels, Kremer *et al* infused Val^5-angiotensin II amide continuously via a jugular catheter at rates of 0.001 to 0.5 µg/kg/min for 24 hr to normotensive rabbits (Kremer 1981). Myocardial and renal toxicity was then determined from the histopathological examination of multiple sections of each tissue. Arterial pressure and plasma urea concentrations were increased in proportion to arterial angiotensin II concentrations. Ischemic necroses were found in the proximal, distal, and collecting tubules of kidneys from angiotensin II treated rabbits. Angiotensin II myocardial necroses were primarily seen in the left ventricle, while right ventricle effects were only observed at the highest angiotensin II dosages. Even at the highest doses of angiotensin II, no effects were seen in the endocardium, arteries, or arterioles. The infused angiotensin concentrations were closely correlated to blood pressure and cardiac toxicity as measured histopathologically. It was concluded that the damage to the left ventricle resulted from the systemic hypertension.

Repeat dose toxicity

Repeat-dose Toxicity Study of Angiotensin II by Intravenous Administration in Rodents

In a study by Hu *et al*., normotensive Sprague Dawley rats received an IV infusion of 10 ng/kg/min of angiotensin II for 14 days (Hu 2004). Angiotensin II treatment resulted in a pronounced increase in MAP accompanied by a small increase in the cardiac arterial wall thickness. Angiotensin II alone caused MAP to increase in two separate phases. MAP increased by 22 mmHg the first day of angiotensin II administration and by an additional 6 mmHg on the second day of angiotensin II administration, remaining at 28 mmHg above baseline through the fourth day. Mean arterial pressure then increased again during Days 5 to 9 by another 25 mmHg and remained constant for the final 5 days of the angiotensin II infusion at about 53 mmHg above baseline. No other evidence of vascular, cardiac or kidney toxicity due to angiotensin II treatment was observed using immunohistochemistry.

Repeat-dose Toxicity Study of Angiotensin II by Intravenous Administration in Rabbits

Li *et al* examined whether elevated plasma concentrations of Ile^5-angiotensin II induce coronary events in Watanabe heritable hyperlipidaemic (WHHL) rabbits (Li 2016).

Angiotensin II or saline was infused as follows:

Experiment 1 tested an acute increase of angiotensin II in circulation by infusion of angiotensin II or saline at rates of 100 ng/kg/min (low-Ang II) or 200 ng/kg/min (high-Ang II) for 4 weeks.

Experiment 2 tested a gradual increase of angiotensin II in circulation by two different doses (from low- to high-dose- infusion) at escalating doses of either 50 ng/kg/min (low-Angiotensin II) for the first 4 weeks followed by 100 ng/kg/min for the second 4 weeks, or 75 ng/kg/min (high-Angiotensin II) for the first 4 weeks followed by 150 ng/kg/min for the second 4 weeks of the experiment, *versus* a control group treated with saline.

In experiment 1, rapid infusion of angiotensin II resulted in mortality rates of 50% and 92% in the low- and high-Angiotensin II groups, respectively, whereas there were no deaths in the vehicle group. Surviving rabbits in the low- and high-Angiotensin II groups at 4 weeks had high blood pressure along with an increased number of blood neutrophils and monocytes compared with the vehicle group. Plasma lipids were unchanged between the low- and high-Angiotensin II groups and the vehicle group. Autopsy examinations revealed that all dead rabbits in both low- and high-Angiotensin II groups had severe pulmonary oedema, congestion, and haemorrhage, which was not present in any of the surviving rabbits that were euthanized at 4 weeks. There were no abnormalities in other organs (ie, liver, kidneys, brain, adrenals, stomach, or intestines). The pulmonary pathological features suggest that the death of WHHL rabbits was caused by acute left heart failure. Histological examinations revealed that 80% of low-Angiotensin II and 100% of high-Angiotensin II groups exhibited histological features of fresh myocardial infarction (MI), including myocardial eosinophilic degeneration, disappearance of striation, coagulation necrosis, oedema, neutrophil infiltration, and haemorrhage. MI changes were observed in one rabbit in the vehicle group. Coronary erosion/rupture and thrombosis were found in both the low-and high-Angiotensin II groups but not in the vehicle group.

In experiment 2, all rabbits survived until 4 weeks and received another infusion of angiotensin II for an additional 4 weeks. Similar to experiment 1, the blood pressure of (both angiotensin II groups) and blood leukocytes (high-Angiotensin II group) were significantly higher compared with the vehicle group, while plasma lipids were unchanged. After changing to high doses of angiotensin II after 4 weeks, 71% of rabbits died in the high-Angiotensin II group and 1 rabbit died in the low-Angiotensin II group, while none of the rabbits in the vehicle group died. Pathological examinations revealed that pulmonary oedema, pulmonary haemorrhage, and MI were present in both low- and high-Angiotensin II groups, which was similar to the findings of experiment 1. Similar to experiment 1, coronary plaque rupture/erosion and thrombosis were found in both low- and high-Angiotensin II groups, while coronary stenosis in the angiotensin II groups was not significantly different from the vehicle group. When the protocol was applied to wild-type Japanese white rabbits (non-hyperlipidaemic), elevation of blood pressure was similar, but there was no discernible atherosclerosis in aortas or coronary arteries and no MI.

A study by Gavras *et al* in rabbits demonstrated acute renal failure, tubular necrosis, and MI after IV infusion of Val5-angiotensin II amide at 0.9 to 1.8 µg/kg/min for 3 days (Gavras 1971). Five normotensive rabbits received no sodium supplementation during the angiotensin II infusion period and a negative sodium balance was observed while five normotensive rabbits received sodium supplementation (subcutaneous (SC) injection of 10 to 50 mEq) and maintained a positive sodium balance. In both angiotensin II-treated groups a greater than 4-fold increase in serum urea was observed as was a potassium deficit. The ratio of urine/serum urea and creatinine also decreased for both groups. Blood pressure was initially increased in both groups but returned to normal by the end of the experiment. Kidney tubular necrosis was observed in most rabbits whether they received angiotensin II with or without sodium supplementation. These effects were in both the proximal and distal tubules with the glomeruli and arterioles being unaffected. Most of the rabbits examined had widespread focal MI although no arterial lesions were seen. No changes in serum urea were observed and no renal and cardiac lesions were observed in control furosemide-treated animals.

Genotoxicity

No dedicated studies have been carried out. This approach is endorsed since this product is analog to a naturally synthesized molecule.

Carcinogenicity

No carcinogenicity studies were conducted to assess the carcinogenic potential of LJPC 501, as it is a naturally occurring peptide and is intended for short–term clinical use.

Reproduction Toxicity

There have been no formal reproductive or developmental studies conducted with LJPC-501 or with exogenously administered angiotensin II. This is supported considering the target population. In a juvenile toxicity study performed in neonatal lambs (<1-week-old) with a 48-hour continuous intravenous administration, the nominal dose rates of 4, 12 and 40 ng/kg/min were well tolerated. No treatment-related abnormalities were observed.

2.3.5. Ecotoxicity / environmental risk assessment

LJPC-501 is a peptid consisting of naturally occurring amino acids, therefore ecotoxicity/environmental risks are not expected.

2.3.6. Discussion on non-clinical aspects

In studies TR-0265 and TR-0207, AT_1 and AT_2 receptor-expressing Chinese hamster ovary (CHO-KI) cell lines were utilised to assess the binding of angiotensin II test compounds to the AT_1 receptor (TR-0265) and the AT_2 receptor (TR-0207), respectively, by comparing binding affinities. It should be noted that the original studies have not been provided. In addition, it appears that there is a three and two-fold difference in binding affinity for AT_1 and AT_2 respectively between LJPC-501 and human angiotensin II. The company argues that the values obtained are due to variation in the assay and are within normal values, nonetheless the differences reported in the mean IC_{50} values are too high to be considered as normal variations in the assay, therefore the Applicant was requested to further discuss and clarify this issue. The receptor binding assays submitted are indicative of a certain degree of variability between LJPC-501 (Ile-5 angiotensin II) and Bachem Ile5-angiotensin II. However, there was no significant difference in the IC50 values provided. The applicant indicates that the cell assay membranes employed, assess binding of human angiotensin II and LJPC-501 to the respective receptors and do not reflect actual functional potency.

Only functional endpoints were measured for receptor AT_1 and the applicant has been unable to develop a workable functional assay for the AT_2 receptor. The studies performed to measure the functional assay for this receptor (TR-0183 and TR-0271) were not available in the non-clinical CTD since the information was included in the clinical section.

It has been published that the AT2 receptor is not coupled to classical second messengers such as cAMP therefore measurements of cAMP expression would not be relevant (Singh and Karnik,2016). The Applicant was asked to justify the rationale for not including neuronal cells and study of pathways involved in neurite outhgrowth and neuronal differentiation. The Applicant has carried out a relevant attempt to clarify the issue by reviewing published related literature and also by carrying planning and carrying out in vitro studies. Although the applicant has not been successful to find a adequate test to assess AT2R functionality, it is acknowledged the applicant's proposal to tackle this issue by addressing efficacy of LJPC-501 mostly by titrating the infusion to the potential effective dose. The assessors also conclude that this issue is not crucial for a final authorization bearing in mind the above discussion.

With regards to CNS the applicant has not included a relevant discussion regarding secondary pharmacology. It may be argued that the product does not cross the BBB, but AT2 receptors are present in the brain. Similarly no information was found reported angiotensin II effects in the immune system. Since non-clinical data is considered inconclusive and bearing in mind that it is covered by clinical outstanding issues, this concern is being dealt with in the clinical AR.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view GIAPREZA can be considered as approvable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

This marketing authorisation application concerns the use of Giapreza (angiotensin II) in the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy. The evidence data presented for Giapreza comprises a single pivotal study. Pivotal controlled Phase 3 study LJ501-CRH01 (ATHOS-3) was conducted to determine the safety and efficacy of angiotensin II.

Table 3 Description of Efficacy Study of LJPC-501 versus Placebo in Patients with Catecholamine-resistant shock.

Study ID	No. of Study Centres Location(s)	Study start date Enrolment status, date Total Enrolment / Enrolment goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	Study Object-ive	No. Subjects by Arm Entered/ Treated/ completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
LJ501-CRH01	75 sites enrolled patients Australia, Belgium, Canada, Finland, France, Germany, New Zealand, United Kingdom, United States	Started 06 May 2015 Completed 09 Feb 2017 344/315	Phase 3, randomised, double-blind, parallel group, multicentre Placebo-controlled	LJPC-501 IV titrated to effect (Hours 0-3: 1.25–200 ng/kg/min; Hours 3-48: 1.25-40 ng/kg/min) versus Placebo (saline, volume matched titration)	Efficacy and Safety	LJPC-501: 172/163/119 Placebo: 172/158/100	Treatment: 48 hours with option of up to 7 days Patient participation: 7 to 32 days	195/126 64 years (22-89)	Catecholamine-resistant hypotension ≥ 18 years old, requiring >0.2 µg/kg/min NED to maintain MAP 55-70 mmHg with adequate volume resuscitation; clinical features of high-output shock.	Primary: MAP response at Hour 3 in mITT population Secondary: Change in CV and Total SOFA scores from Baseline to Hour 48 in mITT population Exploratory: Mortality to Day 7 and Day 28 Change in vasopressor doses over time

Source: LJ501-CRH01 CSR

Abbreviations: CV=cardiovascular; F=female; IV=intravenous; M=male; MAP=mean arterial pressure; mITT=modified intent-to-treat (randomised and treated); NED=norepinephrine-equivalent dose (sum of all vasopressors); SOFA=Sequential Organ Failure Assessment.

A request for GCP inspection has been adopted for the single pivotal study supporting this application: **LJ501-CRH01** [ATHOS III: A phase 3, placebo-controlled, randomized, double-blind, multicenter study of LJPC-501 in patients with catecholamine-resistant hypotension (CRH)]. The integrated inspection report (EMEA/H/C/004930 AEMPS: BPC/18-0194 La Jolla Pharmaceutical Company) is dated 21 January 2019. Despite some GCP breaches observed at this inspection, the proposed corrective action preventive action (CAPA) seems to be sufficient for solving those issues and that the trial has been carried out with an acceptable level of GCP compliance and international standards.

2.4.2. Pharmacokinetics

There is a significant body of clinical research data in which the pharmacokinetics (PK) and pharmacodynamics (PD) of Ile5-angiotensin II (generally a clinical grade peptide supplied by Bachem AG) have been reported. An earlier product, marketed under the invented name Hypertensin® (Ciba-Geigy, acquired by Novartis and no longer marketed), and which contained a derivative of bovine angiotensin II (Val5-angiotensin II amide) as drug substance, is also well characterized in the literature. This product was authorized for the treatment of shock and circulatory collapse by various national competent authorities in Europe The totality of the literature across these various forms of angiotensin II provides an extensive account of its pharmacological, metabolic, and toxicological properties. Clinically, angiotensin II has a long history of being administered safely to healthy subjects, children, pregnant women, and patients with a broad range of medical conditions comprising cardiovascular, renal, hepatic, and pulmonary diseases, endocrine and metabolic disorders, traumatic injuries, and shock. A recent comprehensive, systematic literature review identified 1,124 studies published in English between 1941 and 2016, in which more than 31,000 subjects were exposed to angiotensin II administered by intravenous (IV) infusion (Busse 2017).

The Summary of Clinical Pharmacology presents PK and PD data from the Phase 3 study LJ501-CRH01 and from studies of angiotensin II in the scientific literature to support the use of LJPC-501 in the proposed indication. For the bibliography part, studies were selected that best represented the cumulative knowledge of angiotensin II pharmacokinetics, metabolism, and pharmacodynamics following administration to humans, including studies that described interactions with intrinsic and extrinsic factors. The majority were basic research studies conducted in human volunteers.

Statement on GCP compliance and bio-analytical audits are given. The pre-study validation of the analytical method is satisfactory. The calibration standards of the in-study validation were acceptable. Study samples were not stabilized during the blood collection at the clinical site as per the clinical protocol. The validated assay SOP ANI 11286.01 requires stabilization. The applicant agreed that the samples were not stabilized at the time of collection, and for this reason the sponsor performed the additional investigation into stability for incurred samples (TR 0326). There were 611 samples that were stabilised by the analytical laboratory before analysis, which occurred from 98 to 667 days following collection. Eighteen samples out of 611 (3%) were stored for less than 114 days before stabilisation, which is the preferred time described in the stability study report (TR 0326). Given the small number of samples that were stored for less than 114 days prior to stabilisation, an additional analysis of only these samples will not provide any meaningful information. This is especially true considering the large inter-variability of these data.

The plasma half-life of IV administered angiotensin II is less than one minute. It is metabolized by end terminal cleavage (at both the amino and carboxy termini) in a variety of tissues including erythrocytes, plasma and many of the major organs (i.e., intestine, kidney, liver and lung). And any metabolites of LJPC-501 that retain pharmacological activity are expected to have the same activity as the metabolites of endogenous angiotensin II. These metabolites act through the RAAS.

In the phase 3 Study LJ501-CRH01 Angiotensin I and angiotensin II concentrations were measured in serum at Baseline and Hour 3 using the bioanalytical methods assessed above. At Hour 3, angiotensin II levels reflect both endogenous angiotensin II and exogenous LJPC-501. Since LJPC-501 was titrated to effect, inter-patient variability of the PK of LJPC-501 was observed and expected. The median LJPC-501 dose at the Hour 3 PK draw was 10 ng/kg/min, with a range from 0 to 200 ng/kg/min, and a coefficient of variation exceeding 100%. From individual serum levels, the ratio of angiotensin I to angiotensin II at Baseline was calculated as a measure of the endogenous conversion of angiotensin I to angiotensin II (Chawla 2016). A lower ratio may indicate that more angiotensin I is being converted to angiotensin II while a higher ratio may indicate that less angiotensin I is being converted to angiotensin II. Post-baseline assessments indicate the effect of exogenous LJPC-501 on this ratio. There were no significant differences in the baseline endogenous levels of angiotensin I, angiotensin II, or their ratio between the placebo and LJPC-501 treatment groups. At Hour 3, there were no significant changes from baseline in angiotensin I, angiotensin II, or their ratio in the placebo group. In the LJPC-501 group, there was a significant decrease in angiotensin I concentration ($p < 0.0001$) and the angiotensin I/II ratio decreased significantly from a geometric mean of 2.6 at baseline to 1.4 at Hour 3 ($p < 0.0001$), ie, away from a relative low angiotensin II state. The change in the angiotensin I/II ratio in the LJPC-501 group was driven by the drop in the angiotensin I concentration. There was an increase in angiotensin II concentration from baseline to Hour 3 in the LJPC-501 group (from 279 pg/ml to 309 pg/ml at hour 3).

Absorption

No dedicated pharmacokinetic studies have been conducted. Bioavailability following intravenous administration is expected to be 100%.

Distribution

No specific studies have been conducted to investigate the distribution of Giapreza. LJPC-501 contains the endogenous human octapeptide Ile5-angiotensin II as drug substance. Plasma protein binding is not expected, and therefore no study reports are provided.

Elimination

The plasma half-life of IV administered angiotensin II is less than one minute. It is metabolized by end terminal cleavage (at both the amino and carboxy termini) in a variety of tissues including erythrocytes, plasma and many of the major organs (ie, intestine, kidney, liver and lung). And any metabolites of LJPC-501 that retain pharmacological activity are expected to have the same activity as the metabolites of endogenous angiotensin II. These metabolites act through the RAAS.

Dose proportionality and time dependencies

LJPC-501 exhibits less-than-dose proportional increase in plasma angiotensin II exposure, even considering that pharmacokinetics in study LJ501-CRH01 were limited to snapshot angiotensin II concentration data at Baseline (just prior to study drug initiation) and at Hour 3 (the time of the primary efficacy evaluation) and that the half-life of LJPC-501 is very short. Similarly to other vasopressors such as catecholamines, the hemodynamic response to LJPC-501 will be monitored to effect via titration.

Special populations

On the basis of literature data, it could be anticipated that the Giapreza PK is not influenced by age, gender or impaired renal and hepatic function. However, the applicant has generated some PK data in the pivotal trial in which some elderly patients and patients with renal or hepatic impairment were recruited. Therefore, the Company was asked to show the pharmacokinetic data available in these subgroups of subjects in the Phase 3 study. In response the applicant has shown that there were no significant differences in angiotensin I or angiotensin II concentrations or the ratio between them at Baseline or Hour 3 when comparing patients less than 65 or less than 75 years of age to older patients, so assessors agree that doses were similar regardless of age.

Regarding patients with renal impairment, there was a tendency to require higher doses of LJPC-501; however, despite these differences in LJPC-501 doses administered when comparing subgroups by renal function, there were no significant differences in angiotensin I or angiotensin II concentrations or the ratio between them at Baseline or Hour 3.

Data from patients with hepatic impairment had shown that mean infusion rates of LJPC-501 were similar in patients with Grade 2 to 4 bilirubin compared with patients with Grade 0 to 1 bilirubin and that there were no significant differences between these 2 bilirubin subgroups in angiotensin I, angiotensin II, or the angiotensin I/II ratio at baseline or at Hour 3 or in the changes from baseline to Hour 3.

The CHMP agrees that these data support the applicant's position that the starting dose of LJPC-501 should be the same regardless of age, renal function, or hepatic function, and that LJPC-501 dose should be titrated to effect on MAP individually for each patient. It is possible that patients with renal impairment requiring renal replacement therapy may require higher doses during treatment than patients with normal renal function, but this can be accommodated by titrating to effect on MAP after initiating treatment at the same starting dose.

The applicant states that no dose-adjustment may be needed in special populations, as angiotensin II will be titrated to effect and administered in a controlled clinical setting where haemodynamic variables are frequently monitored. So, dose regimen of LJPC-501 will be adjusted individually. The issue of the more appropriate starting dose is discussed under clinical efficacy.

Some of the articles provided by the applicant to describe the PK of angiotensin II dealt with patients (e.g. Admiraal 1993), other dealt with healthy subjects (e.g. Donato 1972) but no comparison was performed by the applicant. The applicant provided literature and a comparison table on normotensive subjects, hypertensive subejcts, and pregnant women. This comparison is sparse, but so are available data, and it should not impact clinical use of Giapreza.

Table 4 Study Drug Administration and Exposure by Age (mITT Population)

Variable	LJPC-501 Arm (N = 163)			
	Age < 65 years	Age ≥ 65 years	Age < 75 years	Age ≥ 75 years
Duration of exposure, hours	(N = 90)	(N = 73)	(N = 122)	(N = 41)
Mean (SD)	45.1 (24.97)	49.2 (29.56)	44.5 (23.63)	54.3 (34.85)
Median	48.0	48.2	48.0	48.5
Range	4.0 – 168.0	3.5 – 164.5	3.5 - 168.0	9.7 - 164.5
Duration of exposure, n (%)				
> 0 to < 3 hours	0	0	0	0
3 to < 45 hours	34 (37.8%)	27 (37.0%)	49 (40.2%)	12 (29.3%)
45 to < 51 hours	44 (48.9%)	33 (45.2%)	59 (48.4%)	18 (43.9%)
51 to < 72 hours	7 (7.8%)	5 (6.8%)	7 (5.7%)	5 (12.2%)
≥ 72 hours	5 (5.6%)	8 (11.0%)	7 (5.7%)	6 (14.6%)

Variable	LJPC-501 Arm (N = 163)			
	Age < 65 years	Age ≥ 65 years	Age < 75 years	Age ≥ 75 years
Overall time-averaged dose, ng/kg/min [a]	(N = 90)	(N = 73)	(N = 122)	(N = 41)
Mean (SD)	20.75 (22.781)	20.98 (19.594)	21.31 (22.955)	19.51 (15.791)
Median	12.76	16.59	14.20	14.30
Range	1.34 – 111.61	1.33 – 123.70	1.34 - 123.70	1.33 - 68.32
Dose at sample collection, ng/kg/min [b]	(N = 85)	(N = 64)	(N = 110)	(N = 39)
Mean (SD)	34.4 (49.91)	33.0 (47.34)	35.5 (51.79)	29.0 (38.70)
Median	10.0	10.0	10.0	10.0
Range	1.3 – 200.0	0.0 – 200.0	0.0 – 200.0	1.3 – 180.0
Hour 0-3 time-averaged dose, ng/kg/min [c]	(N = 85)	(N = 64)	(N = 110)	(N = 39)
Mean (SD)	25.9 (33.26)	22.5 (27.90)	26.1 (33.53)	19.9 (22.19)
Median	10.7	10.2	10.3	10.2
Range	2.2 - 152.5	0.6 – 129.4	0.6 - 152.5	3.1 - 109.7

Source: Study LJ501-CRH01 Table 14.2.10.2.2, Day 120 Table 55.2[a] Over the full duration of exposure.
[b] At the actual time of Hour 3 sample collection[c] From the time of initiation of study drug to the actual time of Hour 3 sample collection

Consequences of possible genetic polymorphism

Data from literature have shown that some genetic polymorphisms have the potential to affect the RAAS. It is agreed that no consequences of genetic polymorphism will be relevant for LJPC-501 because it will be titrated to effect and administered in a controlled clinical setting.

The applicant provided literature data on inter and intra-individual variability of Angiotensin II, showing inter-individual variability around 170% and intra-individual variability (three hours difference) of 23%.

Pharmacokinetic interaction studies

The applicant has not performed *in vitro* or *in vivo* studies to directly assess induction or inhibition of cytochrome P450s or interaction with membrane transporters (eg, P-glycoproteins, breast cancer resistance protein, organic anion/cation transporters). These studies are not deemed necessary for an endogenous peptide that is not metabolised through the cytochrome P450 system.

2.4.3. Pharmacodynamics

Mechanism of action

Angiotensin II, the active ingredient of Giapreza, is a well-characterised endogenous vasopressor that raises blood pressure by vasoconstriction, increased aldosterone release and renal control of fluid and electrolyte balance.

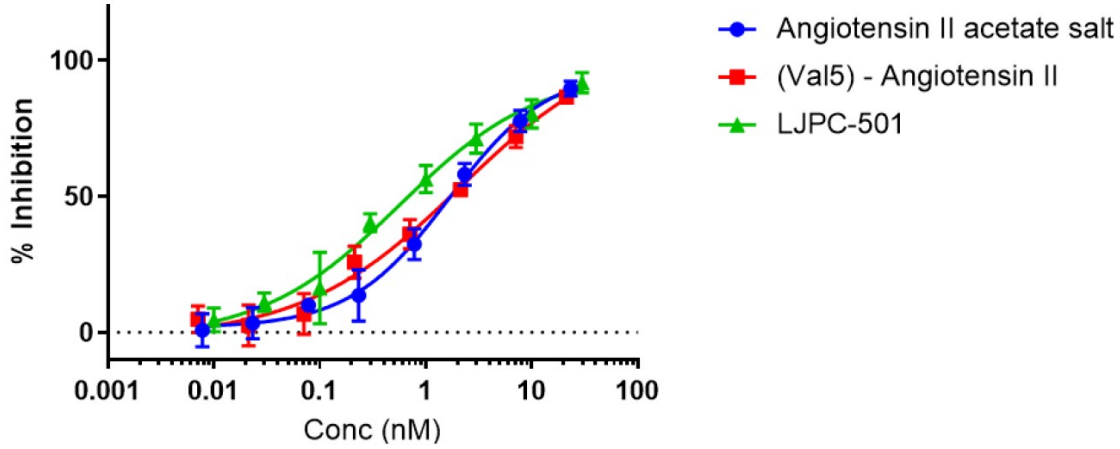
It is agreed that the literature provides a comprehensive understanding of the PD of exogenously administered angiotensin II and that specific dedicated studies are not needed. However, PD parameters were measured during the phase III ATHOS-3 pivotal clinical trial (section 2.5). In addition, there is an extensive body of clinical literature that describes and provides a full understanding of its pharmacological actions and mechanism of action.

Primary and Secondary pharmacology

Direct action of angiotensin II on the vessel wall is mediated by binding to the G-protein-coupled angiotensin II receptor type 1 on vascular smooth muscle cells which stimulates Ca^{2+}/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction. Angiotensin II also appears to have inotropic properties via the β-arrestin pathway, which is stimulated by the AT1 receptor independent of G proteins and leads to increased myocyte contractility (Shenoy 2005, DeWire 2011).

The human body leverages 3 major counter-regulatory systems in blood pressure homeostasis including the sympathetic nervous system and the vasopressin system. The mechanism of action of LJPC-501 (human angiotensin II), which modulates the RAAS, differs from, and complements the other two systems, and the commercially available vasopressors that influence them. Patients who remain hypotensive, despite fluid and vasopressor therapy, may benefit from this additional, currently unavailable, class of vasopressor.

In order to compare the different forms of angiotensin II use in the literature and in the phase 3 study for Giapreza the applicant have conducted in vitro studies demonstrating that LJPC-501 induced similar functional activity and receptor binding activity as human and bovine angiotensin II at the AT1 receptor and similar receptor binding activity as human and bovine angiotensin II at the AT2 receptor.



Source: TR-0265, Figure 1.
Note: Angiotensin II acetate salt = Bachem AG human Ile^5-angiotensin II; (Val^5)-Angiotensin II = Bachem AG bovine Val^5-angiotensin II; LJPC-501 = Ile^5-angiotensin II
Abbreviations: AT_1=angiotensin II receptor type 1; conc=concentration

Figure 3 Percent Inhibition of Radioligant Binding to AT_1 as a Function of Concentration of Various Angiotensin II Analogues: Study TR-0265

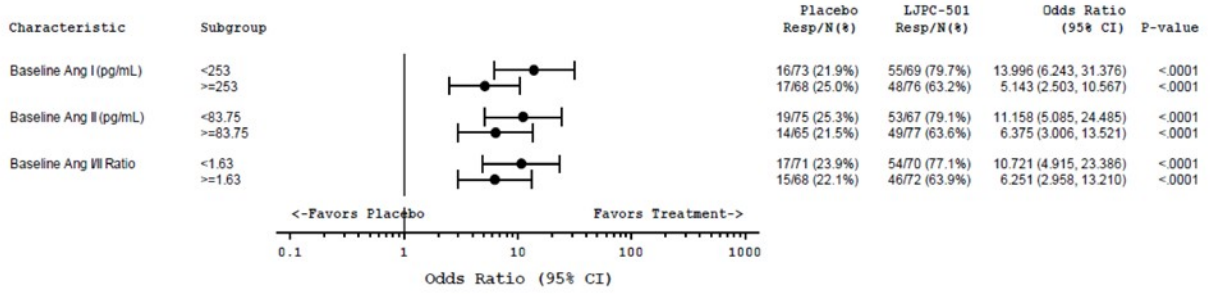
The data provided confirm the acceptability of bridging between LJPC-501 and Bachem AG Ile5-angiotensin II and Bachem AG Val5-angiotensin II (and Hypertensin by extrapolation) for the supportive clinical data reported in the scientific literature.

In the pivotal study, achieving a MAP response to LJPC-501 at Hour 3 was more likely in patients with lower Baseline concentrations of angiotensin I and II, but this did not preclude a robust treatment effect of LJPC-501 on MAP response in patients with Baseline concentrations above the median (see also efficacy section).

Table 5 Effects of Baseline Angiotensin II on MAP at Hour 3 and Treatment Effect (mITT Population)

Outcome Subgroup	Placebo	LJPC-501	Comparison	Statistic	95% CI	p value
Baseline Angiotensin I	**n/N (%)**					
< 253 pg/mL	16/73 (21.9%)	55/69 (79.7%)	LJPC-501 to placebo	OR = 14.0	6.24 – 31.4	< 0.0001
≥ 253 pg/mL	17/68 (25.0%)	48/76 (63.2%)	LJPC-501 to placebo	OR = 5.14	2.50 – 10.6	< 0.0001
Across treatment arms			LJPC-501 to placebo, stratified	OR = 8.27	4.84 – 14.1	< 0.0001
Within treatment group	OR = 0.84	OR = 2.29				
95% CI	0.39 - 1.84	1.08 - 4.85				
p value	0.6658	0.0282				
Baseline Angiotensin II	**n/N (%)**					
< 83.75 pg/mL	19/75 (25.3%)	53 /67 (79.1%)	LJPC-501 to placebo	OR = 11.2	5.08 – 24.5	< 0.0001
≥ 83.75 pg/mL	14/65 (21.5%)	49/77 (63.6%)	LJPC-501 to placebo	OR = 6.38	3.01 – 13.5	< 0.0001
Across treatment arms			LJPC-501 to placebo, stratified	OR = 8.42	4.89 – 14.5	< 0.0001
Within treatment group	OR = 1.24	OR = 2.16				
95% CI	0.56 – 2.72	1.02 - 4.58				
p value	0.5978	0.0417				
Angiotensin I/II ratio	**n/N (%)**					
< 1.63 pg/mL	17/71 (23.9%)	54/70 (77.1%)	LJPC-501 to placebo	OR = 10.7	4.91 - 23.4	< 0.0001
≥ 1.63 pg/mL	15/68 (22.1%)	46/72 (63.9%)	LJPC-501 to placebo	OR = 6.25	2.96 - 13.2	< 0.0001
Across treatment arms			LJPC-501 to placebo, stratified	OR = 8.17	4.76 - 14.0	< 0.0001
Within treatment group	OR = 1.11	OR = 1.91				
95% CI	0.50 - 2.45	0.91 - 3.98				
p value	0.7919	0.0836				

Source: Table 14.2.9.1.1 (univariate analyses)
Note: Subgroups included patients with < median value or ≥ median value for each variable.



Source: Modified from LJ501-CRH01 CSR, Figure 14.2.6.2.1
Note: Odds ratio and 95% CIs with Chi-square test p values. The cut-off values for subgroups by angiotensin I and II levels and I/II ratio are median values.
Abbreviations: Ang=angiotensin; CI=confidence interval; MAP=mean arterial pressure; Resp=responders; N=total number in subgroup

Figure 4 Univaries Analysis of MAP at Hour 3 by Baseline Angiotensin I and Angiotensin II (mITT Population)

Anyway, there were geographic differences in angiotensin II concentrations, with the lowest ones reported in North-America. Since it is well understood Afro-American population has lower circulating renin levels and a less significant fall in blood pressure in response to RAS inhibitors.

A subset of patients (37, 22.7%) appeared to be particularly sensitive to the effects of LJPC-501 and had an increase in MAP to above 100 mmHg (range: 101.3 to 142.0 mmHg) within the first 15 minutes; a similar observation was also made in the earlier pilot study (Chawla 2014). This overshoot of target MAP was rapidly corrected through down-titration of LJPC-501 (and in some cases also concomitant vasopressors). However, it seems that at least a part of the initial exagerated effect could be related to the use of a too high angiotensin II starting dose (20 ng/kg/min) for most patients (see also efficacy section).

Regarding secondary pharmacology, a thorough QT study was not conducted for LJPC-501. However, an effect on QT prolongation can be reasonably ruled out on the basis of *in vitro* studies, non-clinical studies and ECG assessments and adverse events from the ATHOS-3 pivotal trial. In other hand, among the different effects related to the activation of AT2 by angiotensin II, it has been described that angiotensin produce pro-coagulant and pro-inflammatory effects.

The main expected PD interactions of angiotensin II is with drugs targeting the renin-angiotensin-aldosterone system. Other PD interactions with other medicines are unlikely to have a material effect on the use of LJPC-501 in clinical practice, given the drug will be titrated to PD effect. Product information is appropriate in this respect.

2.4.4. Discussion on clinical pharmacology

The applicant has not conducted specific PK studies with LJPC-501, but measurement of angiotensin concentrations was made during the ATHOS-3 pivotal trial (LJ501-CRH01). The literature provides a comprehensive understanding of the PK of exogenously administered angiotensin II. The pharmacological profile of angiotensin II is well-established. The plasma half-life of IV administered angiotensin II is less than one minute. It is metabolized by end terminal cleavage (at both the amino and carboxy termini) in a variety of tissues including erythrocytes, plasma and many of the major organs (ie, intestine, kidney, liver and lung). And any metabolites of LJPC-501 that retain pharmacological activity are expected to have the same activity as the metabolites of endogenous angiotensin II. These metabolites act through the RAAS. The applicant provided literature data on inter and intra-individual variability of angiotensin II, showing inter-individual variability around 170% and intra-individual variability (three hours difference) of 23%.

In the phase 3 Study LJ501-CRH01 Angiotensin I and angiotensin II concentrations were measured in serum at Baseline and Hour 3 using the bioanalytical methods assessed above. At Hour 3, angiotensin II levels reflect both endogenous angiotensin II and exogenous LJPC-501. Since LJPC-501 was titrated to effect, inter-patient variability of the PK of LJPC-501 was observed and expected. The median LJPC-501 dose at the Hour 3 PK draw was 10 ng/kg/min, with a range from 0 to 200 ng/kg/min, and a coefficient of variation exceeding 100%. From individual serum levels, the ratio of angiotensin I to angiotensin II at Baseline was calculated as a measure of the endogenous conversion of angiotensin I to angiotensin II (Chawla 2016). A lower ratio may indicate that more angiotensin I is being converted to angiotensin II while a higher ratio may indicate that less angiotensin I is being converted to angiotensin II. Post-baseline assessments indicate the effect of exogenous LJPC-501 on this ratio. In the LJPC-501 group, there was a significant decrease in angiotensin I concentration ($p < 0.0001$) and the angiotensin I/II ratio decreased significantly from a geometric mean of 2.6 at baseline to 1.4 at Hour 3 ($p < 0.0001$), ie, away from a relative low angiotensin II state. The change in the angiotensin I/II ratio in the LJPC-501 group was driven by the drop in the angiotensin I concentration. There was an increase in angiotensin II concentration from baseline to Hour 3 in the LJPC-501 group (from 279 pg/ml to 309 pg/ml at hour 3).

LJPC-501 exhibits less-than-dose proportional increase in plasma angiotensin II exposure, even considering that pharmacokinetics in study LJ501-CRH01 were limited to snapshot angiotensin II concentration data at Baseline (just prior to study drug initiation) and at Hour 3 (the time of the primary efficacy evaluation) and that the half-life of LJPC-501 is very short.

The PK data available in special populations are scarce. There were no significant differences in angiotensin I or angiotensin II concentrations or the ratio between them at Baseline or Hour 3 when comparing patients less than 65 or less than 75 years of age to older patients, or in subgroups by renal function, or in subgroups with Grade 2 to 4 bilirubin compared with patients with Grade 0 to 1 bilirubin. These data support that the starting dose of LJPC-501 should be the same regardless of age, renal function, or hepatic function. It is possible that patients with renal impairment requiring renal replacement therapy may require higher doses during treatment than patients with normal renal function, but this can be accommodated by titrating to effect on MAP after initiating treatment at the same starting dose.

The applicant was requested to correlate PK concentrations and adverse event data available from the pivotal study ATHOS-3 and to discuss about the relationship between Giapreza concentrations and adverse effects. There was little relationship between angiotensin II concentration at Hour 3 of LJPC-501 administration and TEAE incidence. Thrombotic TEAEs did not occur more frequently in patients with higher angiotensin II at Hour 3. These analyses have several limitations. LJPC-501 was titrated to effect on MAP as needed and the plasma concentration was only measured at Hour 3. Therefore, plasma concentration at hour 3 is not necessarily indicative of the concentration over the entirety of the study. As such, an analysis of plasma concentration at Hour 3 to all adverse events in the study is not meaningful and it is difficult to draw conclusions based upon these data.

Angiotensin II raises blood pressure by vasoconstriction, increased aldosterone release and renal control of fluid and electrolyte balance. Direct action of angiotensin II on the vessel wall is mediated by binding to the G-protein-coupled angiotensin II receptor type 1 on vascular smooth muscle cells which stimulates Ca^{2+}/calmodulin-dependent phosphorylation of myosin and causes smooth muscle contraction. Angiotensin II also appears to have inotropic properties via the β-arrestin pathway, which is stimulated by the AT1 receptor independent of G proteins and leads to increased myocyte contractility (Shenoy 2005, DeWire 2011).

In the pivotal study, achieving a MAP response to LJPC-501 at Hour 3 was more likely in patients with lower Baseline concentrations of angiotensin I and II, but this did not preclude a robust treatment effect of LJPC-501 on MAP response in patients with Baseline concentrations above the median (see also efficacy section). Anyway, there were geographic differences in angiotensin II concentrations, with the lowest ones reported in North-America. Since it is well understood Afro-American population has lower circulating renin levels and a less significant fall in blood pressure in response to RAS inhibitors, the applicant was invited to discuss whether there may be racial differences in response to angiotensin-II. Ancillary univariate and multivariate analyses were provided comparing treatment effects in White and non-White subgroups, which showed that MAP response and mortality at Day 7 or Day 28 did not vary significantly by race. A subset of patients (37, 22.7%) appeared to be particularly sensitive to the effects of LJPC-501 and had an increase in MAP to above 100 mmHg (range: 101.3 to 142.0 mmHg) within the first 15 minutes. It seems that at least a part of the initial exagerated effect could be related to the use of a too high angiotensin II starting dose (20 ng/kg/min) for most patients (see also efficacy section). Regarding secondary pharmacology, a thorough QT study was not conducted for LJPC-501. However, an effect on QT prolongation can be reasonably ruled out on the basis of in vitro studies, non-clinical studies and ECG assessments and adverse events from the ATHOS-3 pivotal trial. The main expected PD interactions of angiotensin II is with drugs targeting the renin-angiotensin-aldosterone system. Other PD interactions with other medicines are unlikely to have a material effect on the use of LJPC-501 in clinical practice, given the drug will be titrated to PD effect. Product information is appropriate in this respect.

Finally, relevant PD markers, like sensitive measures of glomerular filtration, cardiac function, intestinal perfusion, global and vital organ oxygen extraction, etc, were not measured during the pivotal trial. Organ perfusion will be measured in the requested Post-authorisation efficacy study (PAES) (section 4).

Some of the articles provided by the applicant to describe the PK of angiotensin II dealt with patients (e.g. Admiraal 1993), other dealt with healthy subjects (e.g. Donato 1972) but no comparison was performed by the applicant. The applicant provided literature and a comparison table on normotensive subjects, hypertensive subejcts, and pregnant women. This comparison is sparse, but so are available data, and it should not impact clinical use of Giapreza.

The only compounds that would, a priori, be expected to alter the PK of LJPC-501 would be any that altered angiotensin-converting enzyme 2 (ACE2) or aminopeptidase A activity (affecting the metabolic clearance rate) or altered the expression of AT1 receptor (affecting receptor-mediated endocytosis of angiotensin II). This equates to treatment with ACE inhibitors (ACEi) or AT1 receptor blockers (ARBs). Although some patients in vasodilatory shock will have been receiving drugs in these classes at diagnosis, clinically it would be expected that they would be discontinued for the duration of their severe hypotensive episode.

2.4.5. Conclusions on clinical pharmacology

The Applicant has not been conducted specific PK or PD studies with LJPC-501, but measurement of angiotensin concentrations and PD parameters (i.e.: MAP) was made during the ATHOS-3 pivotal trial (LJ501-CRH01). The literature provides a comprehensive understanding of the PK of exogenously administered angiotensin II. The pharmacological profile of angiotensin II is well-established. The plasma half-life of IV administered angiotensin II is less than one minute. It is metabolized by end terminal cleavage (at both the amino and carboxy termini) in a variety of tissues including erythrocytes, plasma and many of the major organs (ie, intestine, kidney, liver and lung). Any metabolites of LJPC-501 that retain pharmacological activity are expected to have the same activity as the metabolites of endogenous angiotensin II. These metabolites act through the RAAS.

Angiotensin II raises blood pressure by vasoconstriction, increased aldosterone release and renal control of fluid and electrolyte balance. The mechanism of action of LJPC-501 (human angiotensin II), which modulates the RAAS, differs from, and complements the other two systems, and the commercially available vasopressors that influence them. Patients who remain hypotensive, despite fluid and vasopressor therapy, may benefit from this additional, currently unavailable, class of vasopressor. Regarding secondary pharmacology, a thorough QT study was not conducted for LJPC-501. However, an effect on QT prolongation can be reasonably ruled out on the basis of in vitro studies, non-clinical studies and ECG assessments and adverse events from the ATHOS-3 pivotal trial. The main expected PD interactions of angiotensin II is with drugs targeting the renin-angiotensin-aldosterone system. Other PD interactions with other medicines are unlikely to have a material effect on the use of LJPC-501 in clinical practice, given the drug will be titrated to PD effect. Product information is appropriate in this respect.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No phase II company-sponsored studies are available. However, a study sponsored by George Washington University (NCT01393782; ATHOS pilot trial) in 20 patients with high output shock compared Ile5-angiotensin II (Bachem) (n=10) to placebo (n=10) when added to ongoing norepinephrine and other vasopressors is available as publication [Chawla et al. Crit Care. 2014;18:534]. The main investigator of this phase II study, Dr. Lakhmir S. Chawla (working at that time at the Division of Intensive Care Medicine and Division of Nephrology, Veterans Affairs Medical Center, Washington, DC, USA), is nowadays the Chief Medical Officer of La Jolla Pharmaceutical BV. Therefore, this study can be considered as the phase II pilot study for this drug. The acronym ATHOS means Angiotensin for High-Output Shock (ATHOS proof of concept dose-finding study, and ATHOS-3).

Study drugs were titrated to effect with a goal of maintaining MAP at approximately 65 mmHg while reducing the norepinephrine dose over a 6-hour period. The initiation of an angiotensin II infusion in patients receiving norepinephrine for high output shock resulted in a decrease in norepinephrine doses. The authors suggest that initial dosing ranges are most likely between 2 and 10 ng/kg/min, but should be titrated as needed given the potential for a variable response.

Of interest, there were 2 highly sensitive patients (exaggerated effect) to angiotensin II, thus making necessary a careful dose titration.

2.5.2. Main study

The evidence data presented for Giapreza comprises a single pivotal study. Pivotal controlled Phase 3 study LJ501-CRH01 (ATHOS-3) was conducted to determine the safety and efficacy of angiotensin II. The study design and choice of control group was agreed upon after discussion with the FDA, and the study was conducted in the US as part of the Special Protocol Assessment. Since eligible patients received standard-of-care fluid resuscitation prior to study drug treatment and continued to receive standard-of-care catecholamine and/or other vasopressor treatment during study drug treatment, placebo was considered to be a safe choice of control in a parallel treatment group.

Title: LJPC-501 (ANGIOTENSIN II) LJ501-CRH01 A PHASE 3, PLACEBO-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY OF LJPC-501 IN PATIENTS WITH CATECHOLAMINE-RESISTANT HYPOTENSION (CRH)

Study phase: Phase 3

First patient enrolled: 06 May 2015; **Last patient completed:** 09 February 2017

Release date of report: 21 June 2017

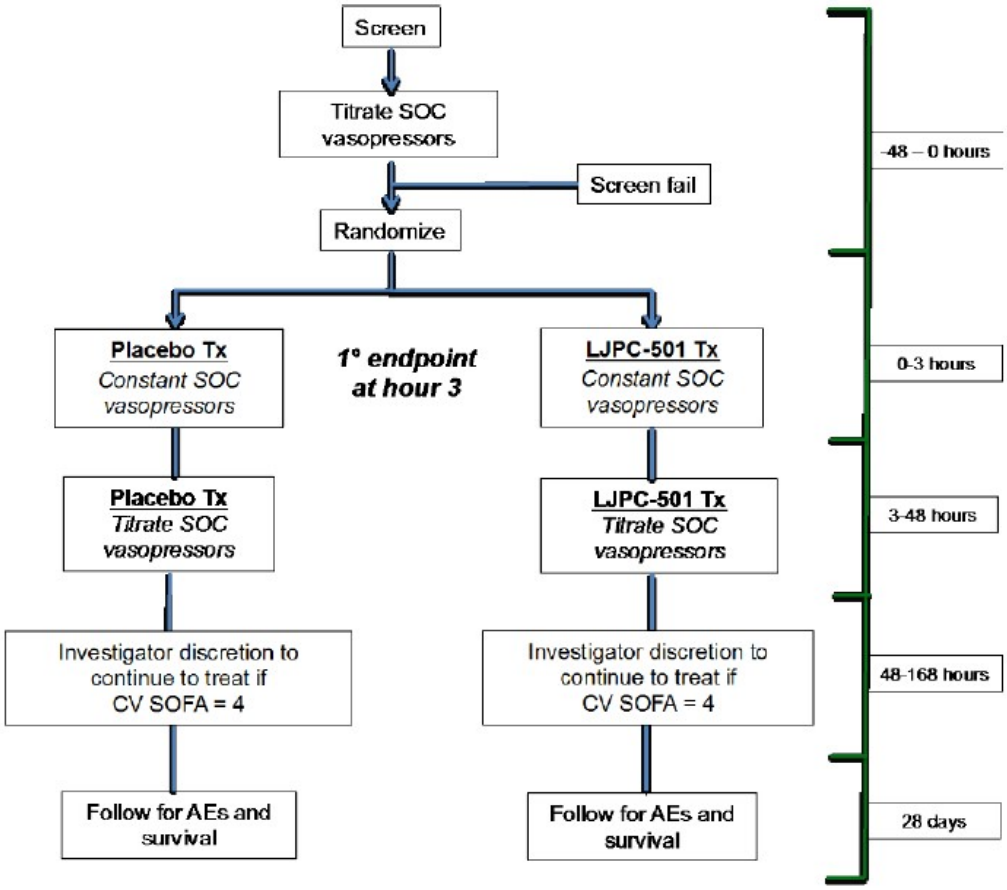
Methods

LJ501-CRH01 was a multicenter, randomized, double-blind, placebo-controlled, parallel 2-arm study that enrolled adult patients with CRH who were hospitalized in an intensive care setting.

The study comprised 4 active stages:

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

Figure 7 displays the overall study plan. End-of-study assessments occurred on Day 7 (168 hours ± 12 hours) or at least 3 days after end of treatment; these included recording of concomitant medications and standard-of-care vasopressor doses, a limited physical examination, vital signs (including MAP), and adverse event (AE) assessments. A safety assessment was performed at a follow-up phone call or chart review on Day 28.



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

Figure 5 ATHOS-3 Study Flow Chart

Study Participants

Inclusion Criteria

Each patient was required to meet **all** the following inclusion criteria to be enrolled in the study:

1. Adult patients ≥ 18 years of age with CRH, defined as those who require a total sum catecholamine dose of > 0.2 mcg/kg/min for a minimum of 6 hours and a maximum of 48 hours, to maintain a MAP between 55-70 mmHg.
2. Patients are required to have central venous access and an arterial line present, and these are expected to remain present for at least the initial 48 hours of study.
3. Patients are required to have an indwelling urinary catheter present, and it is expected to remain present for at least the initial 48 hours of study.
4. Patients must have 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.

5. Patients **must have clinical features of high-output shock by meeting one of the following criteria**.

    a. Central venous oxygen saturation > 70% (either by oximetry catheter or by central venous blood gas) and central venous pressure (CVP) > 8 mmHg.

6. **OR**

    a. Cardiac index > 2.3 L/min/m2

7. Patient or legal surrogate is willing and able to provide written informed consent and comply with all protocol requirements.

Exclusion Criteria: The study protocol had 19 exclusion criteria. Sick patients with active bleeding, mesenteric ischemia, liver failure and MELD score of ≥ 30, or patients with extensive burns were excluded. Also patients requiring more than 500 mg daily of hydrocortisone or equivalent glucocorticoid medication as a standing dose were excluded. On the contrary, only patients with the worst CV SOFA score = 4 (i.e.: ≤ 3) were included.

Treatments

LJPC-501 was manufactured by solid phase peptide synthesis and is isolated as an acetate salt. LJPC-501 was supplied as a clear aqueous solution in single-use clear glass vials containing 5 mg angiotensin II and 50 mg mannitol as excipient in a volume of 2 ml (2.5 mg/ml angiotensin II and 25 mg/ml mannitol). LJPC-501 for this study came from 5 manufacturing lots.

LJPC-501 was diluted in normal saline prior to delivery by IV infusion. The Pharmacy Manual (in the Trial Master File) contains detailed directions to the unblinded pharmacist for storage and preparation of LJPC-501 for administration. Placebo treatment was normal saline (0.9% sodium chloride solution). Normal saline for administration as placebo and for dilution of LJPC-501 was provided by each study site.

Patients were fluid-resuscitated and standard-of-care vasopressor doses were optimized prior to initiating study drug. During the first 3 hours of study drug treatment, up to 750 ml of IV fluids were allowed, but discouraged as these patients were already volume resuscitated.

All patients began treatment (Hour 0) with a starting dose of 20 ng/kg/min LJPC-501 or volume-matched placebo by continuous infusion. The dose could be titrated as often as every 5 minutes based on current MAP, determined as the average of 3 MAP values at least 1 minute apart prior to change in infusion rate (Table E-04).

The target MAP and range of study drug doses allowed during each treatment phase were as follows:

Hour 0 through Hour 3: 1.25 to 200 ng/kg/min to achieve MAP ≥ 75 mmHg at Hour 3 (without changes in vasopressor doses and without allowing MAP ≥ 85 mmHg)

Hour 3 through Hour 48: 1.25 to 40 ng/kg/min to maintain MAP at 65 to 70 mmHg (with rules for changes in concomitant vasopressin and catecholamine doses)

Hour 48 to Discontinuation: Study drug titrated down by ≤ 10 ng/kg/min every 15 minutes until 0 ng/kg/min

Reinitiation after 48 h in patients with no MAP response: Study drug could be reinitiated within 3 hours of discontinuation if the cardiovascular SOFA score = 4 after study drug discontinuation. For those patients with no response up to 48 hours, the recommended dose up to day 7 was 1.25 to 40 ng/kg/min, with final taper off study drug on or before Day 7 (up to 168 hours of total treatment time).

Table 6 Study drug titrations in ATHOS-3 study

Mean arterial pressure (mmHg)	Initial dose (ng/kg/min)	Titration interval (min)	Dose titration (ng/kg/min)	Max. dose (ng/kg/min)	Min. dose (ng/kg/min)
Hours 0–3 (target MAP, ≥ 75 mmHg)					
≤ 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‡
Hours 3–48 (target MAP, 65–70 mmHg)					
≤ 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**
Hour 48 to Day 7 (target MAP, 65–70 mmHg)					
≤ 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**

max. = maximum. min. = minimum. MAP = mean arterial pressure. na = not applicable (patients not eligible for study participation). SOC = standard-of-care. * Dosing schema may be modified by consensus of data and safety monitoring board to as low as 60 ng/kg/min and as high as 120 ng/kg/min, if deemed necessary for safety purposes. † Once a dose of 10 ng/kg/min is reached, study drug dose may be further reduced by halving each titration until the minimum dose is achieved. ‡ Dosing may be modified to as low as 1.25 ng/kg/min for patients considered hyper-responders (ie, MAP remains ≥ 85 mmHg despite discontinuation of vasopressin and all catecholamines). § If the sum of the norepinephrine and epinephrine doses is ≥ 0.03 but < 0.1 µg/kg/min, the study drug dose should be maintained. ¶ If vasopressin is being used, the patient should be weaned off vasopressin first, then titrate SOC vasopressors until the sum of the norepinephrine and epinephrine dose is as low as 0.03 µg/kg/min. ** Dosing may be modified to as low as 1.25 ng/kg/min for patients considered hyper-responders (ie, MAP remains ≥ 70 mmHg despite discontinuation of vasopressin and reduction of sum norepinephrine and epinephrine dose to as low as 0.03 µg/kg/min).

Source: Chawla et al. Crit Care Resusc. 2017;19:43-49.

Selection of LJPC-501 doses during the study:

The starting angiotensin II dose was 20 ng/kg/min during the first 3 hours. The dose could be titrated as often as every 5 minutes based on current MAP, determined as the average of 3 MAP values at least 1 minute apart prior to change in infusion rate. The maximal maintenance dose was 40 ng/kg/min after 3 hours.

These dose regimens were based on literature reports of the use of angiotensin II in hypotensive shock and a consideration of the responses of 10 patients with distributive shock who received angiotensin II acetate (Bachem AG, 5 to 40 ng/kg/min) over a 6-hour period while catecholamine doses were decreased in a controlled manner in a pilot study (Chawla 2014) (described under previous section, dose-response studies). Like other vasopressors for the treatment of shock, study drug was administered as a continuous IV infusion with the infusion rate adjusted based on a target MAP and the individual patient's response.

Objectives

The goal of the study was to compare LJPC-501 treatment versus placebo treatment for efficacy, safety, and tolerability in patients with CRH.

The primary objective was to compare the effect of angiotensin II versus placebo on a surrogate endpoint (increase in MAP) in patients with catecholamine-resistant hypotension (CRH).

Change in SOFA scores was a secondary objective and mortality was an exploratory objective.

Outcomes / endpoints

Measures related to efficacy included MAP, heart rate, doses of vasopressors, survival, and variables included in SOFA scoring (partial pressure of arterial oxygen, fractional inspired oxygen, platelet count, serum bilirubin concentration, serum creatinine concentration, and eye, verbal, and motor responses). Central venous pressure, cardiac output (if possible), and urine output were also monitored.

Primary Efficacy Variable(s)

The **primary efficacy variable** was **MAP at Hour 3** (taken as the average of 3 measurements of MAP at 2:45, 3:00, and 3:15 hours after the initiation of study drug administration at Hour 0).

The primary efficacy endpoint was the proportion of patients in each treatment group with an average MAP ≥ 75 mmHg or with a ≥ 10 mmHg increase in MAP above Baseline MAP at Hour 3, without an increase in standard-of-care vasopressor doses prior to Hour 3. Baseline MAP was defined as the average of 3 recorded MAP values (each measured in triplicate approximately one minute apart) documented within 30 minutes prior to initiation of study drug on Day 1, i.e., at -30 minutes, -15 minutes and 0 minutes (or just prior to study drug initiation).

The secondary efficacy variables were:

- Cardiovascular SOFA scores at Screening and Hour 48. The CV SOFA score was defined from the amount of vasopressor being administered and MAP if a patient is not receiving vasopressors. The original CV SOFA was defined on a limited number of vasopressors in use at the time of definition (norepinephrine, epinephrine, and dopamine). Because current clinical practice uses multiple vasopressors, norepinephrine dose equivalents were used in this study to account for all vasopressors (eg, phenylephrine and vasopressin). It is based on the following: No hypotension: score 0; MAP < 70 mmHg: score +1; On vasopressors, dopamine < 5 microg/kg/min or dobutamine (any dose): score +2; Dopamine > 5 microg/kg/min or epinephrine or norepinephrine < 0.1 microg/kg/min: score +3; Dopamine > 15 microg/kg/min or epinephrine or norepinephrine > 0.1 microg/kg/min: score +4.
- Total SOFA scores at Screening and Hour 48. **Total SOFA score** is based on six different scores from 6 organ systems (i.e., respiratory-*PaO2/FiO2*, 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. There is no direct conversion from SOFA score to mortality. Based on observational studies, if the SOFA score is < 8, mortality is <10%. If the total SOFA score is between 8-11, mortality is around 20-30%; for a score between 12-14, mortality is 40-60%; and for scores >15, mortality is >80%. It is difficult to establish the between-treatment minimum difference in total SOFA score that could be of relevance, but could be approximately one point difference [Jones et al, *Crit Care Med*. 2009;37:1649–54].

Exploratory efficacy variables were:

- Mortality rate at Day 7 and Day 28
- MAP at Hour 1 and Hour 2
- Heart rate between Hour 0 and Hour 48
- Sum vasopressor (norepinephrine-equivalent) dose between Hour 3 and Hour 48

Sample size

The sample size for this study was based on a hypothesized response rate in the primary efficacy endpoint of 40% in the placebo arm and a 60% response rate in the active (LJPC-501) arm. 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 active drug over placebo with a sample size of 150 evaluable subjects per treatment arm. The sample size is based on the number of subjects who receive study drug (evaluable patients). Additional subjects were enrolled based on the anticipation that approximately 5% of patients would be randomized but would not receive study drug.

Randomisation

After informed consent was obtained and study eligibility was established, patients were allocated to treatment groups with stratification by screening MAP (< 65 mmHg or ≥ 65 mmHg) and baseline APACHE II score (≤ 30, 31-40, and ≥ 41) using centralized randomization by an interactive web response system (IWRS). Block randomization within strata was used to assign patients in a 1:1 ratio to LJPC-501 and placebo treatment groups. Additional patients were enrolled to replace patients who withdrew from the study after randomization but before receiving study drug.

Blinding (masking)

The study was blinded using placebo saline infusion to minimize biases in the assessment of efficacy or safety. Serum samples were collected at Screening and at Hour 3 of study drug administration for measurement of angiotensin I and angiotensin II, stored, and shipped to a central location. Serum levels of angiotensin I (endogenous angiotensin II precursor) and angiotensin II (endogenous angiotensin II plus LJPC-501) were not measured until all patients had completed the study. An unblinded study pharmacist at each study site had access to the treatment randomization for each patient enrolled at that site and recorded the study drug lot number on pharmacy source documents which remained separate from clinical source documents. No other study personnel were to be unblinded.

Statistical methods

A statistical analysis plan (SAP) was prepared as part of the Special Protocol Assessment (SAP Version 2.0) and was amended once prior to database lock. SAP Version 3.0 (Amendment 1, 22 December 2016) is provided in Appendix 16.1.9. The database was locked on 23 February 2017.

SAS Version 9.3 or higher (SAS Institute Inc; Cary, NC) was used for all statistical analyses. Graphic displays were produced using SAS, S-Plus (TIBCO Software Inc, Palo Alto, CA), or R (R Foundation for Statistical Computing, Vienna, Austria).

Statistical Analysis Sets: The statistical analysis sets, in addition to “all enrolled patients,” were planned for efficacy and safety analyses as defined in the SAP and in Table below.

Table 7 Statistical Analysis Sets

Analysis Set	Definition
Safety	All patients who received any study drug. Patients analyzed by treatment received.
Modified Intent-to-Treat (mITT)	All patients who were randomized and treated with study drug in any quantity. Patients analyzed as randomized. The primary efficacy analysis set.
Intent-to-Treat (ITT)	All patients who were randomized (regardless of study drug treatment). Patients analyzed as randomized. Analyses based on ITT analysis set were used to test sensitivity of mITT analyses.
Per-Protocol (PP)	All mITT patients who did not have a major protocol deviation. Patients analyzed as treated. Patients excluded from the PP analysis set were identified prior to unblinding. Analyses based on PP analysis set were used to support mITT analyses.

General Statistical Methods: Data are summarized by treatment arm and by time point or study period. Continuous variables are summarized using descriptive statistics, including the number of observations, mean, SD, minimum, median, and maximum values. Measures of change are described with 95% confidence intervals (CIs). Categorical values are summarized using the number of observations and percentages.

Patient disposition, demographic characteristics, and baseline characteristics were summarized descriptively. Statistical comparisons of differences between treatment arms were made using Wilcoxon rank-sum tests for continuous or ordinal variables, Chi-Square tests for discrete variables, and Fisher's Exact tests for binary variables.

Efficacy Analyses

All efficacy analyses compared LJPC-501 and placebo treatment arms using the mITT and PP analysis sets. Certain sensitivity analyses used the ITT analysis population as indicated below. Hour 0 is defined as the time of initiation of study drug infusion.

Primary Efficacy Analysis: The primary efficacy endpoint was analyzed using logistic regression. Predefined covariates were Baseline MAP, APACHE II score, vasopressin use over the 6 hours prior to randomization (yes or no), and quantity of catecholamine use (average norepinephrine equivalents in µg/kg/min) over the 6 hours prior to randomization. The adjusted logistic regression model compared LJPC-501 to placebo in achievement of MAP ≥ 75 mmHg or ≥ 10 mmHg increase in MAP at Hour 3 without an increase in vasopressor doses from baseline. A 2-tailed alpha of 0.05 was used in testing the hypothesis of treatment difference. Reason for non-response (death, treatment failure, or MAP did not meet criteria) was summarized by treatment arm.

Sensitivity Analyses for the Primary Endpoint

The following sensitivity analyses were planned and performed for MAP response at Hour 3:

- Site effect and site by treatment interaction using alpha of 0.15 and calculation of odds ratio and 95% CI.
- Comparison across treatment arms by randomization strata using the Cochran-Mantel-Haenszel test (and repeated using clinical database data to identify strata if different from strata used for randomization). Similar analyses were performed using the ITT and PP analysis populations.

- Comparison across treatment arms by unadjusted chi-square test.
- A stepwise multivariate logistic regression with covariates defined by the subgroups of interest and treatment, age, gender, and stratification variables as fixed factors.

Categories representing < 10% of the population were specified to be dropped; however, after unblinding the data, exposure to ACE inhibitors and exposure to ARBs were included. ACE and ARB exposures were considered as potential key predictors and both included 5% to 10% of the population. Significance level for inclusion is 1.15 and level for staying in the model is 0.05, and only significant covariates were included in the final model. Odds ratio for treatment effect and 95% CI after adjustment for other prognostic factors was reported. Treatment by variable interactions were also explored.

Secondary Efficacy Analysis: Secondary efficacy assessments were:

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

Exploratory Efficacy Analyses

Subgroups of Interest: Treatment effects were compared using predefined subgroups based on age, gender, race, body mass index, baseline MAP, baseline serum albumin, baseline APACHE II score, geographic region, recent exposure to ACE inhibitors, recent exposure to ARBs, history of acute respiratory distress syndrome (ARDS; separately by medical history and Screening chest x-ray finding), history of sepsis, baseline norepinephrine-equivalent dose, baseline endogenous angiotensin I and II levels, and the angiotensin I to angiotensin II ratio.

Subgroups defined by initial response at 30 minutes after start of study treatment were also evaluated for sensitivity to therapy using a landmark approach. Sensitivity to therapy was defined by study drug dose 30 minutes after starting treatment (≤ 5 ng/kg/min, 6-20 ng/kg/min, or > 20 ng/kg/min). For multivariate analyses, the sensitivity measure at 30 minutes divided the population into those with study drug dose < 20 ng/kg/min and those with ≥ 20 ng/kg/min.

Mortality at Day 7 and Day 28: Survival from the time of study drug initiation to time of death from any cause was analyzed by the Kaplan-Meier formula. Estimates and CIs were calculated by the product limit method and Greenwood's formula for the variance and included the difference between treatment arms. Difference between treatment arms was analyzed by a 2-sided log-rank test for mortality to Day 7 and to Day 28. Sensitivity analyses for mortality to both time points included a stratified log-rank test using randomization strata and univariate and multivariate analyses using the subgroups of interest listed above. A sensitivity analysis of mortality was performed in the ITT population using time of randomization to time of death.

MAP Response at Hour 1 and Hour 2: The primary efficacy analysis was repeated for MAP response at Hour 1 and Hour 2 using the average of 3 measurements of MAP (15 minutes before, at the time, and 15 minutes after the time point). Treatment failures (ie, patients with an increase from the baseline norepinephrine-equivalent dose) were classified as non-responders if the increase in norepinephrine-equivalent dose was prior to the respective time point.

Change in non-CV SOFA Component Scores: Change in non-CV component scores were compared across treatment arms using the van Elteren stratified Wilcoxon rank test with strata defined by the randomization strata and using a general linear model with strata defined by the randomization strata.

Change in vasopressor dosing between Hour 3 and Hour 48: The changes in total norepinephrine-equivalent dose between Hour 0, Hour 3, and Hour 48 were analyzed by treatment arm using a 2-sample t test.

Time on Vasopressor, Time on Ventilator, and Time in Intensive Care Unit: Time on vasopressors (Hour 0 to the time all non-study drug 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. Patients who died were censored on the day of death if it was the same as the last day of vasopressor or ventilator treatment, ICU discharge, or hospital discharge.

Handling of Missing Data: For the mITT and PP analysis populations, missing primary or secondary endpoints due to death were imputed as failure for the primary efficacy endpoint. For the secondary endpoints, missing SOFA assessments due to death were assigned a CV SOFA score of 4 and a Total SOFA score of 24, the highest scores for the respective endpoints.

Missing primary and secondary endpoints were also imputed for reasons other than death in the mITT population, but these imputations were not planned for the PP analysis population. As there were only 2 observations with missing CV SOFA scores, similar adjustments that were performed for the mITT population were done for the PP analysis population. In the mITT population, the last observed MAP value was carried forward as a primary imputation method.

Multiple imputation was to be used as a sensitivity analysis for the primary endpoint in the mITT analysis population using baseline MAP group, APACHE II score, vasopressin use over the 6 hours prior to randomization (yes or no), the quantity of catecholamine use over the 6 hours prior to randomization, age, and gender as predictors. As there was no missing MAP value for the primary analysis, the multiple imputation procedure was not performed.

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

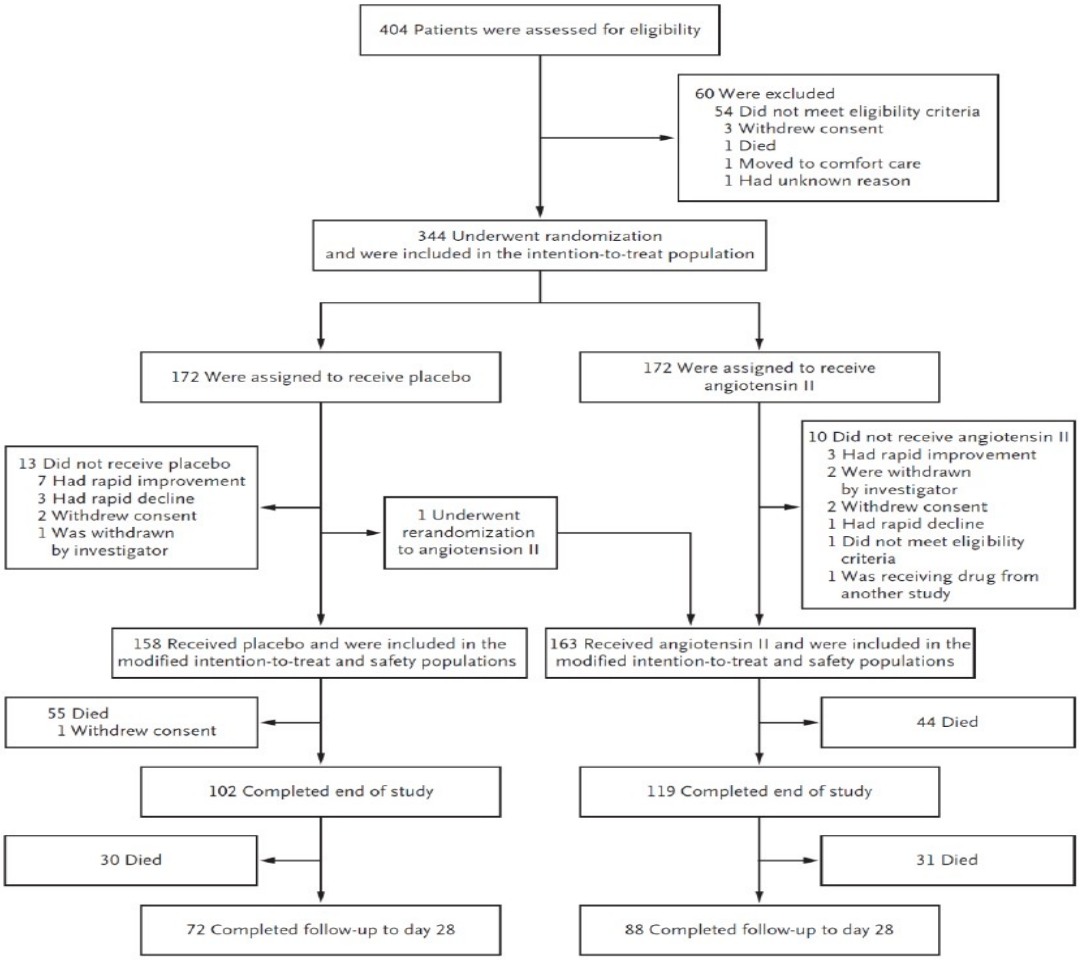
Interim Analyses: An interim analysis was conducted after data for 150 evaluable patients through Day 28 were collected. The interim dataset was frozen on 26 September 2016, and efficacy and safety data were analyzed according to SAP Version 2.0 and the Interim Analysis Plan. Interim blinded data using data pooled across the 2 treatment arms were reviewed by the open-session participants including La Jolla representatives. Unblinded data analyses including tables, figures, and listings were provided by an independent statistician to the DSMB for review of efficacy and safety according to the DSMB Charter. The DMSB met on 18 October 2016 and recommended that the study continue without modifications to the protocol or to the conduct of the study.

Changes to Planned Analyses: SAP Version 2.0 (dated 31 January 2015) was accepted as part of the Special Protocol Assessment and was amended once. Amendment 1 (SAP Version 3.0 dated 22 December 2016) to the SAP was undertaken to harmonize the SAP with the protocol, to provide greater clarity on the statistical analyses of exploratory and safety endpoints that were not specified in the prior SAP.

Results

Participant flow

A total of 344 patients were randomised (ITT population), 172 to the placebo group and 172 to LJPC-501 treatment, and 321 patients started study drug (mITT population), 158 in the placebo group and 163 in the LJPC-501 group (Figure 8). Therefore, a total of 14 patients randomized to placebo and 9 randomized to angiotensin II were excluded from the mITT population.



Source: Khanna 2017; LJ501-CRH01 CSR, Table 14.1.1.1.1, Table 14.1.1.1.2, Table 14.1.1.5.2, and information from outside the clinical database (screened not randomised, randomised not treated).
Note: Patient disposition from screening through Day 28 is shown. Efficacy and safety analyses are based on the mITT population. The patient identified as undergoing rerandomisation was initially assigned to the placebo group and had to be withdrawn from the study before the first dose was administered because he underwent an operative procedure. This patient subsequently underwent rerandomisation to the LJPC-501 group. In accordance with the preapproved statistical analysis plan, this patient was included in the LJPC-501 group for the mITT and safety analyses and in the placebo group for the ITT analyses. The end of study was Day 7 or 3 days after the last administration of LJPC-501 or placebo, whichever occurred later. Of the 119 patients in the LJPC-501 group who completed the end of study, 3 died by Day 7 but after the end-of-study assessment. The 72 patients in the placebo group who completed follow-up to Day 28 includes 2 patients who were discharged before the end-of-study visit but later completed follow-up to Day 28; these 2 patients have been included in the completed end of study category.
Abbreviations: ITT=intent-to-treat, mITT=modified intent-to-treat.

Figure 6 Patient Disposition and Analysis Populations.

ITT population

A total of 404 patients were screened after obtaining informed consent. Of these, 344 were randomized, 172 to the placebo group and 172 to LJPC-501 treatment (All Enrolled Patients or ITT Population). Twenty-three patients (6.7%) were randomized but did not receive study drug. The patients, randomization date, and reason for not initiating study drug are presented in Table 10. The primary reason for not initiating study drug was rapid improvement in health including hemodynamic parameters from the time of randomization to time of planned study drug administration (3 patients in the placebo group and 6 patients in the LJPC-501 group).

Table 8 Patients Randomized but not Treated (ITT Population)

Patient	Randomization Date	Reason Patient Not Treated
001-012	13 Sep 2016	Patient not treated due to a series of values precluding treatment at several different time points
004-006	28 Mar 2016	Withdrew consent as patient was quickly deteriorating, and requested withdrawal of all care
015-003	23 Nov 2015	Patient's EF dropped so patient was not treated due to safety concerns / PI discretion
015-007	16 Mar 2016	Non-study team physician overseeing patient's care objected to study participation
015-018	3 Aug 2016	Patient was randomized in error. Screen failure due to MELD score > 30 in the setting of liver failure
015-020	6 Oct 2016	High concern of bowel ischemia based on CT results obtained after randomization
018-004	11 Apr 2016	Screen failure: taken to the OR for an exploratory lap; MAPs too erratic; study drug could not be started within the 48-hour screening period
018-010	29 Jun 2016	Patient's daughter withdrew consent right before treatment
021-014	1 Aug 2016	Subject's family withdrew consent and all care prior to initiation of study drug
021-027	27 Oct 2016	Patient was enrolled in another clinical trial.
026-001	5 Oct 2015	Patient rapidly improved and no longer requiring high doses of vasopressors
026-005	1 Mar 2016	Patient rapidly improved and no longer required high doses of vasopressors
042-002	23 Apr 2016	Patient was randomized, pharmacy sent drug for a different drug trial
042-004	15 Sep 2016	The wife decided to pull all life support just prior to the site starting the study drug
047-001	20 Oct 2016	Patient not dosed due to decreasing MAPs after randomization
050-003	28 Sep 2016	Patient's vasopressor requirement reduced by the time for study drug
066-004	23 Nov 2016	Patient was improving
067-008	23 Sep 2016	Patient improved rapidly
074-001	3-Nov 2016	Patient was improving
079-003	30 Aug 2016	Patient's vasopressor requirements began to drop before dosing began
119-002	28 Jun 2016	Patient became too unstable
119-003	15 Nov 2016	Patient was improving
126-001	14 Sep 2016	Patient rapidly improved before initiation of study treatment.

Abbreviations: CT = computerized tomography; EF = ejection fraction; ITT = intent-to-treat; MAP = mean arterial pressure; MELD = Model for End-stage Liver Disease; PI = principal investigator

mITT population

Table 11 summarises patient disposition in the mITT population following randomisation and following initiation of study drug treatment. Early discontinuation of study treatment, before the end of the protocol-defined treatment period of 48 hours, was most often due to death (18.4%) in the placebo group and to MAP recovery (19.6%) in the LJPC-501 group. MAP recovery was defined as improvement in blood pressure sufficient to allow discontinuation of study drug as determined by the investigator. In the placebo group, 63.3% of patients completed the study (completed end-of-study assessments at Day 7 or 3 days after last administration of study drug). In the LJPC-501 group, 73.0% completed the study. Among those who did not complete the study, death was the primary reason in both treatment groups (33.5% of placebo-treated and 24.5% of LJPC-501-treated patients).

Table 9 Patient Disposition (mITT Population)

	Placebo n (%)	LJPC-501 n (%)	Total n (%)
Number of patients	158	163	321
Treatment initiated (mITT/Safety population)	158 (100%)	163 (100%)	321 (100%)
Included in Per Protocol population	149 (94.3%)	150 (92.0%)	299 (93.1%)
Treatment discontinued prior to Hour 48	57 (36.1%)	60 (36.8%)	117 (36.4%)
Primary reason for treatment discontinuation prior to Hour 48:			
Death	29 (18.4%)	21 (12.9%)	50 (15.6%)
MAP recovery	16 (10.1%)	32 (19.6%)	48 (15.0%)
Adverse event	6 (3.8%)	3 (1.8%)	9 (2.8%)
Accidental [a]	2 (1.3%)	3 (1.8%)	5 (1.69%)
Investigator decision	2 (1.3%)	1 (0.6%)	3 (0.9%)
Withdrew consent	2 (1.3%)	0	2 (0.6%)
Completed study	100 (63.3%)	119 (73.0%)	219 (68.2%)
Discontinued study	58 (36.7%)	44 (27.0%)	102 (31.8%)
Primary reason for discontinuation from study:			
Death	53 (33.5%)	40 (24.5%)	93 (29.0%)
Investigator decision	0	1 (0.6%)	1 (0.3%)
Withdrawal by patient	2 (1.3%)	0	2 (0.6%)
Adverse event	1 (0.6%)	2 (1.2%)	3 (0.9%)
Other	2 (1.3%)	1 (0.6%)	3 (0.9%)
Day 28 follow-up conducted	72 (45.6%)	88 (54.0%)	160 (49.8%)

Source: LJ501-CRH01 CSR, Table 10, Table 14.1.1.1.2, Listing 16.2.1.2
Abbreviations: MAP=mean arterial pressure; mITT=modified intent-to-treat.
[a] For example, study drug drip turned off accidentally by health care professional.

PP population

The Per Protocol population was balanced with 149 patients in the placebo group and 150 patients in the LJPC-501 group. A total of 5.7% of patients in the placebo arm and 8.0% of patients in the LJPC-501 arm had 1 or more major protocol deviations. The rate and type of major protocol deviations was balanced across arms. Most were related to inclusion and/or exclusion criteria (LJPC-501: 6.7% of patients; placebo: 5.1% of patients).

Recruitment

The study was initiated at 128 sites in 10 countries; 75 sites enrolled at least 1 subject, and 74 sites treated at least 1 patient with study drug (Table 12). First patient was enrolled on 06 May 2015 and last patient was completed on 09 February 2017.

Table 10 Number of Patients Enrolled by Country Country Number of Study Sites Number of Patients

Country	Number of Study Sites	Number of Patients
United States	35	216
Australia	16	47
Canada	7	36
United Kingdom	8	21
New Zealand	2	9
Finland	3	7
France	2	6
Belgium	1	1
Germany	1	1

Source: Table 14.1.1.3.1

Conduct of the study

There were no amendments to the original protocol dated 05 December 2014. Protocol clarification memoranda that were communicated with all study sites are kept in the Trial Master File. These provided further details on down-titration of study drug at Hour 3:15 and Hour 48; use of norepinephrine-equivalent dose to calculate cardiovascular SOFA score; definition of “another interventional clinical trial” (exclusion criteria); time periods for collection of AEs, AESIs (vasopressor toxicities), and SAEs (initiation of study drug through Day 28); definition of dedicated port, and sedation and the Glasgow Coma Scale. Also provided were results demonstrating that no in vitro chemical interactions occur between LJPC-501 and other vasopressors allowed during the study.

The DSMB met 4 times to review unblinded safety data and each time recommended that enrollment continue without modifications to study conduct. These meetings were held on 11 December 2015, 05 April 2016, 21 July 2016, and 18 October 2016. Enrollment proceeded beyond 315 patients to ensure that there would be at least 300 evaluable patients, since there were more than 15 patients who were randomized but did not receive study drug when 315 patients had been enrolled.

Baseline data

Patient demographics and disease characteristics are summarized for the primary analysis population (mITT) inTable 13 and Table 14, respectively. Overall, 80.0% of the population were white, 60.7% were male, and 48.0% were at least 65 years old.

Table 11 Demographic Characteristics (mITT Population).

Characteristic	Placebo (N = 158)	LJPC-501 (N = 163)	All Patients (N = 321)
Age, n (%)			
< 65 years	77 (48.7%)	90 (55.2%)	167 (52.0%)
≥ 65 years	81 (51.3%)	73 (44.8%)	154 (48.0%)
< 75 years	116 (73.4%)	122 (74.8%)	238 (74.1%)
≥ 75 years	42 (26.6%)	41 (25.2%)	83 (25.9%)
Mean (SD), years	62.5 (15.16)	62.1 (15.59)	62.3 (15.36)
Median (range), years	65 (22 – 89)	63 (22 – 89)	64 (22 – 89)
Gender, n (%)			
Male	103 (65.2%)	92 (56.4%)	195 (60.7%)
Female	55 (34.8%)	71 (43.6%)	126 (39.3%)
Ethnicity, n (%)			
Hispanic or Latino	7 (4.4%)	10 (6.1%)	17 (5.3%)
Not Hispanic or Latino	151 (95.6%)	153 (93.9%)	304 (94.7%)
Race, n (%)			
White	122 (77.2%)	135 (82.8%)	257 (80.1%)
Black or African American	19 (12.0%)	14 (8.6%)	33 (10.3%)
Asian	8 (5.1%)	5 (3.1%)	13 (4.0%)
Native Hawaiian/Other Pacific Islander	1 (0.6%)	0	1 (0.3%)
American Indian/Alaska Native	0	1 (0.6%)	1 (0.3%)
Other	8 (5.1%)	8 (4.9%)	16 (5.0%)
Geographic region, n (%)			
US/Canada	120 (75.9%)	116 (71.2%)	236 (73.5%)
Europe	14 (8.9%)	19 (11.7%)	33 (10.3%)
Australia/New Zealand	24 (15.2%)	28 (17.2%)	52 (16.2%)
Body mass index at baseline, kg/m^2	(N = 155)	(N = 161)	(N = 316)
< 30	84 (54.2%)	92 (57.1%)	176 (55.7%)
≥ 30	71 (45.8%)	69 (42.9%)	140 (44.3%)

Source: Table 14.1.2.2.2
Note: There were no statistically significant differences between treatment arms for any subgroups based on demographic characteristics. For continuous variables, the Wilcoxon rank sum test was use. For binary variables the Fisher's exact test was used, and for other categorical variables the chi-square test was used.
Abbreviation: mITT = modified intent-to-treat

Disease Characteristics at Screening/Baseline:

Disease characteristics at baseline are shown in Table E-09. There were no statistically significant differences between treatment arms for any subgroups based on baseline disease characteristics.

Sepsis was reported to be the primary or likely reason for shock in approximately 90% of the mITT population. Vasoplegia was the next most common etiology, identified in 5.9% of patients.

Table 12 Disease Characteristics at Baseline (mITT Population).

Median (range)	29.0 (12 – 51)	27.0 (9 – 54)	28.0 (9 – 54)
Baseline albumin (g/dL)	(N = 156)	(N = 154)	(N = 310)
< 2.5 g/dL	89 (57.1%)	103 (66.9%)	192 (61.9%)
≥ 2.5 g/dL	67 (42.9%)	51 (33.1%)	118 (38.1%)
Mean (SD)	2.4 (0.56)	2.3 (0.66)	2.3 (0.61)
Median (range)	2.4 (1.1 – 3.8)	2.2 (1.0 – 4.7)	2.3 (1.0 – 4.7)
$ScvO_2$ (%)	(N = 117)	(N = 120)	(N = 237)
Mean (SD)	77.2 (8.60)	77.6 (8.92)	77.4 (8.75)
Median (range)	77.0 (35.0 – 96.5)	76.9 (44.9 – 99.0)	77.0 (35.0 – 99.0)
Central venous pressure (mmHg)	(N = 123)	(N = 126)	(N = 249)
Mean (SD)	12.8 (4.67)	13.7 (5.05)	13.3 (4.88)
Median (range)	12.0 (1 – 28)	13.0 (5 – 35)	12.0 (1 – 35)
Cardiac index ($L/min/m^2$)	(N = 73)	(N = 69)	(N = 142)
Mean (SD)	3.4 (1.01)	3.3 (0.93)	3.4 (0.97)
Median (range)	3.2 (2.4 – 6.6)	3.0 (2.1 – 6.4)	3.1 (2.1 – 6.6)
Baseline MELD score			
Mean (SD)	21.9 (7.28)	20.4 (7.46)	21.1 (7.40)
Median (range)	23.0 (4 – 41)	21.0 (6 – 36)	22.0 (4 – 41)
< 30	138 (87.3%)	145 (89.0%)	283 (88.2%)
≥ 30	20 (12.7%)	18 (11.0%)	38 (11.8%)
Exposure to ACE inhibitors	15 (9.5%)	15 (9.2%)	30 (9.3%)
Exposure to ARBs	11 (7.0%)	11 (6.7%)	22 (6.9%)
Chest x-ray finding of ARDs	51 (32.3%)	40 (24.7%)	91 (28.4%)
Medical history of sepsis	132 (83.5%)	127 (77.9%)	259 (80.7%)
Cause of distributive shock			
Sepsis	132 (83.5%)	127 (77.9%)	259 (80.7%)
Other/potentially sepsis	11 (7.0%)	20 (12.3%)	31 (9.7%)
Vasoplegia	9 (5.7%)	10 (6.1%)	19 (5.9%)
Pancreatitis	2 (1.3%)	0	2 (0.6%)
Other	4 (2.5%)	6 (3.7%)	10 (3.1%)
Vasopressin use during 6 h prior to randomization	111 (70.3%)	113 (69.3%)	224 (69.8%)
Average NED dose during 6 h prior to randomization (µg/kg/min)			
Mean (SD)	0.53 (0.423)	0.49 (0.340)	0.51 (0.383)
Median (range)	0.41 (0.10 – 3.02)	0.40 (0.09 – 2.97)	0.40 (0.09 – 3.02)
Number of vasopressors at Baseline			
Mean (SD)	2.0 (0.74)	1.9 (0.80)	2.0 (0.77)
Median (range)	2 (1-4)	2 (1-4)	2 (1-4)
Baseline NED dose (µg/kg/min)			
Mean (SD)	0.48 (0.445)	0.45 (0.353)	0.46 (0.400)
Median (range)	0.34 (0.05 – 3.80)	0.33 (0.08 – 2.58)	0.34 (0.05 – 3.80)
< 0.2 µg/kg/min	15 (9.5%)	20 (12.3%)	35 (10.9%)
≥ 0.2 – < 0.35 µg/kg/min	68 (43.0%)	63 (38.7%)	131 (40.8%)
≥ 0.35 – < 0.50 µg /kg/min	27 (17.1%)	34 (20.9%)	61 (19.0%)
≥ 0.50 µg /kg/min	48 (30.4%)	46 (28.2%)	94 (29.3%)

Source: Table 14.1.2.2.2, Table 14.2.4.1.3.1
Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin II receptor type 1 blocker; ARDS = acute respiratory distress syndrome; MELD = Model for end-stage Liver Disease; NE = norepinephrine equivalent dose; $ScvO_2$ = central venous oxygen saturation.

Screening and Baseline mean and median MAP values were similar overall, within both groups, and across groups. There were statistical differences in some characteristics between the US and Europe or Australia/New Zealand, but representation of these regions was relatively low in the overall population.

Prior vasopressor medications

Given that the inclusion criteria were based on catecholamine administration and response, all patients received at least 1 vasoactive drug prior to initiation of study drug. All except one patient had prior norepinephrine and 72.0% had received prior vasopressin, 35.8% prior phenylephrine, and 24.6% prior epinephrine.

Geographic differences in the use of vasopressor medications: There were also regional differences in the use of vasopressors. In Europe, average NED was the highest (0.72 microg/kg/min), while in US/Canada was the lowest (0.49 microg/kg/min). The opposite trend was evident for vasopressin use, which was the lowest in Europe (21%) and the highest in US/Canada (81%). This means that in Europe, catecholamine doses to qualify for further vasopressor therapy are much higher than in the US and that vasopressin in infrequently used, probably because it is not available in many countries.
Nevertheless, Screening and Baseline MAP values were similar across regions (mean and median MAP between 65.2 and 67.5 mmHg at Screening and Baseline across all regions).

Actual angiotensin and placebo doses administered during the study.

Mean and median dose infusion rates over the duration of treatment were higher in the placebo arm than the LJPC-501 arm ($p < 0.0001$) although the range of infusion rates was broad in both groups (Table 15). In the placebo arm, the median of the patient mean infusion rate over all treatment was 41.75 ng/kg/min (range 3.13–151.54 ng/kg/min) compared with 14.30 ng/kg/min (range 1.33–123.70 ng/kg/min) for LJPC-501. The majority of patients had a dose decrease of LJPC-501 after a starting dose of 20 ng/kg/min. The median of per-patient mean LJPC-501 doses was 9.17 ng/kg/min during Hour 0-1 and 10.0 ng/kg/min during Hour 1-2 and Hour 2-3.

Table 13 Study Drug Dose Titrations (mITT population)

Treatment Period Statistic	Placebo (N = 158)	LJPC-501 (N = 163)	Total (N = 321)
Overall treatment (ng/kg/min)	(N = 158)	(N = 163)	(N = 321)
Mean dose titration level			
Mean (SD)	39.57 (20.577)	20.85 (21.348)	30.07 (22.941)
Median (range)	41.75 (3.13 - 151.54)	14.30 (1.33 - 123.70)	31.94 (1.33 - 151.54)
p value	< 0.0001		
Hours 0 – 1 (ng/kg/min)	(N = 158)	(N = 163)	(N = 321)
Mean dose titration level			
Mean (SD)	50.76 (36.584)	15.82 (16.123)	33.02 (33.081)
Median (range)	35 (12.82-171.00)	9.17 (1.67-92.33)	32.50 (1.67-171.00)
p value	< 0.0001		
Minimum dose titration level			
Mean (SD)	19.78 (3.545)	8.82 (7.429)	14.21 (8.015)
Median (range)	20 (1.25 - 40)	5 (0 - 20)	20 (0 - 40)
p value	< 0.0001		
Maximum dose titration level			
Mean (SD)	75.30 (54.335)	28.34 (19.848)	51.45 (46.914)
Median (range)	50 (15.32 - 200)	20 (5 - 130)	40 (5 - 200)
p value	< 0.0001		
Hours 1 – 2 (ng/kg/min)	(N = 156)	(N = 163)	(N = 319)
Mean dose titration level			
Mean (SD)	90.54 (52.763)	23.88 (32.257)	56.48 (54.781)
Median (range)	75 (2.5 - 200)	10 (0 – 182.5)	45 (0 - 200)
p value	< 0.0001		
Minimum dose titration level			
Mean (SD)	77.08 (54.824)	18.51 (25.023)	47.15 (51.418)
Median (range)	60 (0 - 200)	5 (0 - 140)	40 (0 - 200)
p value	< 0.0001		
Maximum dose titration level			
Mean (SD)	103.14 (52.249)	29.21 (39.002)	65.37 (58.954)
Median (range)	90 (2.5 - 200)	10 (0 - 200)	50 (0 - 200)
p value	< 0.0001		
Hours 2 – 3 (ng/kg/min)	(N = 156)	(N = 163)	(N = 319)
Mean dose titration level			
Mean (SD)	113.32 (53.439)	32.37 (45.612)	71.96 (63.986)
Median (range)	115 (0.33 - 200)	10 (0 - 200)	55 (0 - 200)
p value	< 0.0001		
Minimum dose titration level			
Mean (SD)	99.14 (53.626)	27.41 (39.391)	62.49 (59.009)
Median (range)	100 (0 - 200)	10 (0 - 200)	50 (0 - 200)
p value	< 0.0001		
Maximum dose titration level			
Mean (SD)	126.28 (54.855)	36.87 (50.233)	80.59 (68.967)
Median (range)	130 (2.5 - 200)	12.50 (0 - 200)	60 (0 - 200)
p value	< 0.0001		

Source: Table 14.3.1.1
Abbreviation: mITT = modified intent-to-treat

After Hour 3, the maximum infusion rate of study drug was reduced from 200 ng/kg/min to 40 ng/kg/min, and the reductions in mean doses in both treatment groups reflect down-titration from Hour 3 to Hour 4. From Hour 4 to Hour 48, mean doses remained relatively stable in both groups and patients in the placebo group continued to receive more study drug than patients in the LJPC-501 treatment group. The difference was statistically significant at all hourly time points from Hour 1 to Hour 48 in the mITT and Per Protocol populations.

Sensitivity to LJPC-501 Dose and Relationship to Response

The starting dose of study drug was 20 ng/kg/min. Per protocol, the dose was to be titrated based on the observed MAP. By 30 minutes, 109 of the 163 patients (67%) in the LJPC-501 group were receiving doses below 20 ng/kg/min including **79** (48.4%) with doses of 5 ng/kg/min or less and **39 patients (23.9%) with doses of 2.5 ng/kg/min or less** (Table 14.3.1.1 of the CSR).

Within the LJPC-501 treatment group, the subgroup of patients whose dose was unchanged or increased after the first half hour of treatment had a significantly lower MAP response rate at Hour 3 than those patients who had study drug down-titrated (OR = 0.11; 95% CI: 0.05-0.23; p < 0.0001). The risk of mortality within the LJPC-501 treatment group was significantly greater in the subgroup of patients with less sensitivity to LJPC-501, both at Day 7 (HR = 2.57; 95% CI: 1.45–4.55; p = 0.0008) and at Day 28 (HR = 1.62; 95%CI: 1.02-2.58; p = 0.0402).

Concomitant Medications

All patients received concomitant medications. As with prior medications, most common were drugs targeting the cardiovascular system (100% of patients). Also common were those affecting blood and blood forming organs, the alimentary tract and metabolism, and the nervous system; 99% of patients in both groups received systemic anti-infectives between initiation of study drug and end of study (Table 14.3.7.2.2 of ATHOS CSR).

Corticosteroid use: A total of 65.2% of patients in the placebo group and 69.9% in the LJPC-501 group received 1 or more glucocorticoids after beginning study drug treatment. The higher percent of use corresponded to hydrocortisone, administered to 41.1% of patients, with a significant imbalance between treatment groups (48.5% of patients in the angiotensin II group and only 33.5% in patients on the placebo group).

Numbers analysed

Analysis populations are summarized in Table 16. All enrolled patients were included in the Intent-to-treat population as randomized. All patients who received study drug were included in the mITT and Safety populations which were identical; 92.4% of patients randomized to placebo and 94.2% of patients randomized to LJPC-501 received study drug. Approximately 87% of patients in both arms were included in the PP population.

Table 14 Analysis Populations in ATHOS-3 trial.

	Number (Percentage) of Enrolled Patients		
Population	**Placebo**	**LJPC-501**	**All Patients**
All Enrolled, n (%)	172 (100%)	172 (100%)	344 (100%)
Intent-to-treat (ITT), n (%)	172 (100%)	172 (100%)	344 (100%)
Modified Intent-to-treat (mITT), n (%)	158 (92.4%)	163 (94.2%)	321 (93.3%)
Per-Protocol (PP) Population, n (%)	149 (86.6%)	150 (87.2%)	299 (86.9%)
Safety, n (%)	158 (92.4%)	163 (94.2%)	321 (93.3%)

Source: Table 14.1.1.1.1, Table 14.1.1.1.2

Outcomes and estimation

Primary efficacy outcome (% of patients with MAP response at 3 hours).

The target MAP at Hour 3 was obtained in 69.9% (95% CI: 62.3%-76.9%) of patients receiving LJPC-501 and in 23.4% (95% CI: 17.1%-30.8%) of patients receiving placebo. In the primary analysis model using logistic regression adjusting for 4 variables chosen to reflect baseline disease severity, treatment with LJPC-501 was highly statistically significant with an odds ratio (OR; LJPC-501 to placebo) of 7.95 (95% CI: 4.76–13.3, p = 2.54 × 10-15).

The LJPC-501 treatment effect was robust and odds ratios for the treatment effect were ≥ 7.6 in unadjusted analyses or sensitivity analyses that adjusted for stratification (Table 17).

Table 15 Mean Arterial Pressure at Hour 3: Primary Efficacy Analysis (Logistic Regression) and Sensitivity Analyses (mITT Population)

Analysis	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Number responding (n)	37	114	151
Percent responding	23.4%	69.9%	47.0%
95%[a]	17.1% - 30.8%	62.3% - 76.9%	41.5% - 52.7%
Primary analysis[b] **Independent variable[b]:**	**Odds Ratio (95% CI)**		**p value**
Treatment, LJPC-501	7.95 (4.76 - 13.3)		2.54E-15
Baseline MAP, < 65 mmHg	0.49 (0.28 - 0.86)		0.0122
Baseline APACHE II score	1.00 (0.97 - 1.03)		0.9218
Vasopressin during 6 h prior to randomization	0.93 (0.53 - 1.62)		0.7938
Average NED in 6 h prior to randomization	0.60 (0.29 - 1.26)		0.1803
Sensitivity analyses **Stratification**			
Randomization stratification[c]	7.88 (4.74 - 13.1)		7.18E-17
Clinical database stratification[c]	7.79 (4.66 - 13.0)		7.73E-17
Unadjusted logistic regression[d]	7.61 (4.63 - 12.5)		1.33E-15
Unadjusted[e]			3.45E-17

Source: Table 14.2.1.1.1
Abbreviations: APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; MAP = mean arterial pressure; mITT = modified intent-to-treat; NED = norepinephrine-equivalent dose.

[a] Exact binomial 95%
[b] Chi-square test from logistic regression model including LJPC-501 treatment (compared to placebo) adjusted by baseline MAP (<65 mmHg / ≥ 65 mmHg), baseline APACHE II score, vasopressin use 6 hours prior to randomization (yes / no), and mean norepinephrine-equivalent dose over the 6 hours prior to randomization.
[c] Cochran-Mantel-Haenszel test of LJPC-501 compared to placebo stratified by baseline MAP and baseline APACHE II score.
[d] Chi-square test from logistic regression model including LJPC-501 treatment compared to placebo.
[e] Fisher's exact test of LJPC-501 treatment compared to placebo

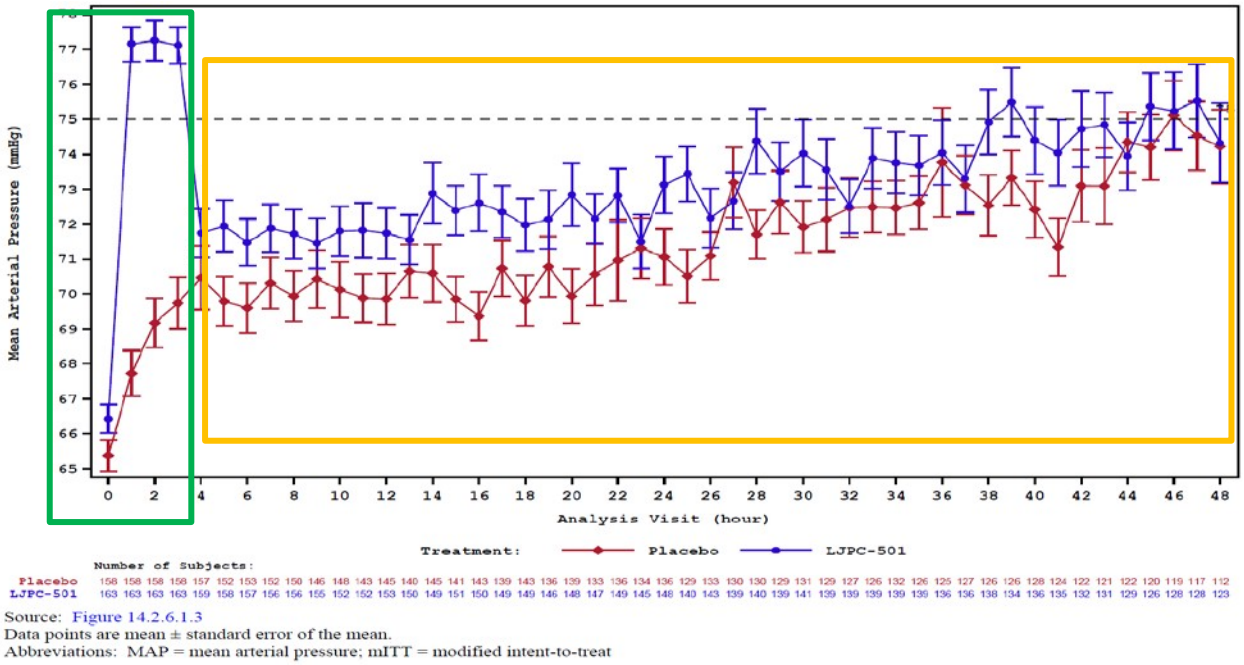
In the placebo arm, 121 patients did not respond including 109 who did not achieve MAP ≥ 75 mmHg or an increase from baseline of ≥ 10 mmHg. An additional 12 patients achieved the target but had an increase in other standard-of-care vasopressors within the first 3 hours. In the LJPC-501 arm, 49 patients did not respond with 42 not achieving a MAP ≥ 75 mmHg or an increase from baseline of ≥ 10 mmHg. An additional 7 patients achieved the target but had an increase in other standard-of-care vasopressors within the first 3 hours. In the placebo arm 35 patients had an increase in norepinephrine-equivalent dose and still did not meet the target MAP at Hour 3 compared to 8 patients on the LJPC-501 arm. As specified in the protocol, other vasopressors were not to be increased during Hour 0 to Hour 3 unless for safety reasons. Overall, the norepinephrine-equivalent dose was increased in 47 of 158 (29.7%) patients in the placebo arm and 15 of 163 (9.2%) patients in the LJPC-501 arm.

Primary Efficacy Analysis in the Per Protocol and ITT population

The results in the PP and ITT population were similar to those in the mITT population (Tables 28 and 30 of the ATHOS CSR).

MAP course by hour (from baseline to Hour 48)

Change in MAP hourly is depicted graphically for the mITT population in Figure E04. The change in mean MAP from baseline was significantly higher in the LJPC-501 arm than the placebo arm during Hour 0 to 3 ($p < 0.001$) (time point for primary analysis; highlighted in green in Figure below) but not during Hour > 3 to 48 (highlighted in orange in Figure below). After Hour 3, the maximum allowed study drug dose was 40 ng/kg/min, the target MAP was 65 to 70 mmHg, and other vasopressor doses could be adjusted and potentially discontinued in a defined order. MAP by study period (Hour 0 to 3, Hour > 3 to 48, and change from Baseline or Hour 3) is compared between placebo and LJPC-501 treatment arms of the mITT population in Table 14.2.1.4.1 and the PP population in Table 14.2.1.4.2 of the ATHOS CSR.



Source: Figure 14.2.6.1.3
Data points are mean ± standard error of the mean.
Abbreviations: MAP = mean arterial pressure; mITT = modified intent-to-treat

Figure 7 MAP by Hour: Baseline to Hour 48 (mITT Population)

Secondary Endpoint: Sequential Organ Failure Scores at 48 Hours

Cardiovascular SOFA Score: All patients had a CV SOFA score of 4 at the time at Screening, based on vasopressor doses. The change in CV SOFA score from Screening to Hour 48 was −1.28 in the placebo group compared with −1.75 in the LJPC-501 group ($p = 0.0129$). At Hour 48, 28.5% of patients in the placebo group compared with 40.5% of patients in the LJPC-501 group were no longer receiving vasopressors (CV SOFA of ≤ 1).

Total SOFA Score

Total SOFA score is a sum of 6 individual SOFA scores, based on a battery of indicators of organ function. The mean (SD) change in Total SOFA score from Screening to Hour 48 was an increase (worsening) of 1.04 (5.336) in the placebo group (baseline: 12.72) compared with an increase (worsening) of 1.05 (5.500) in the LJPC-501 group (baseline: 11.77) (p = 0.4901).

Exploratory efficacy outcome (mortality to day 7 and 28)

There was a non-significant trend of improved survival in the LJPC-501 group. At Day 7 the mortality was 29% (47 of 163) in the LJPC-501 group compared to 35% (55 of 158) at Day 7 in the placebo group of the mITT population (Table 41 of the ATHOS-3 CSR). At Day 28 the mortality was 46% (75 of 163) in the LJPC-501 group and 54% (85 of 158) in the placebo group the mITT population. Analysis of mortality to Day 28 is summarized in**Table 18**. The relative risk of mortality in the mITT population to Day 28 was 0.78 (95% CI: 0.57–1.07; unstratified logrank test). Similar results were found in the ITT population to Day 28 was 0.80 (95% CI: 0.59 - 1.08; unstratified logrank test).

Table 16 Mortality to Day 28 in ATHOS-3 trial

LJPC:Placebo	Randomization Stratification	Clinical Database Stratification	Unstratified
mITT Population (Placebo, N = 158; LJPC-501, N = 163)			
Relative risk (95% CI)	0.780 (0.571 - 1.065)	0.813 (0.595 - 1.111)	0.784 (0.574 - 1.069)
Log-rank p value	0.1173	0.1924	0.1229
ITT Population (Placebo, N = 172; LJPC-501, N = 172			
Relative risk (95% CI)	0.780 (0.573 - 1.061)	0.810 (0.596 - 1.101)	0.796 (0.586 - 1.082)
Log-rank p value	0.1121	0.1778	0.1439

Source: Table 14.2.3.2.1 and 14.2.3.2.3

Results of Other Exploratory Analyses:

Other exploratory efficacy endpoints included change in vasopressor doses over time, individual noncardiovascular SOFA scores, and health resource utilisation outcomes (time to discontinuation of vasopressors, time to discontinuation of mechanical ventilation, time to ICU discharge, and time to hospital discharge).

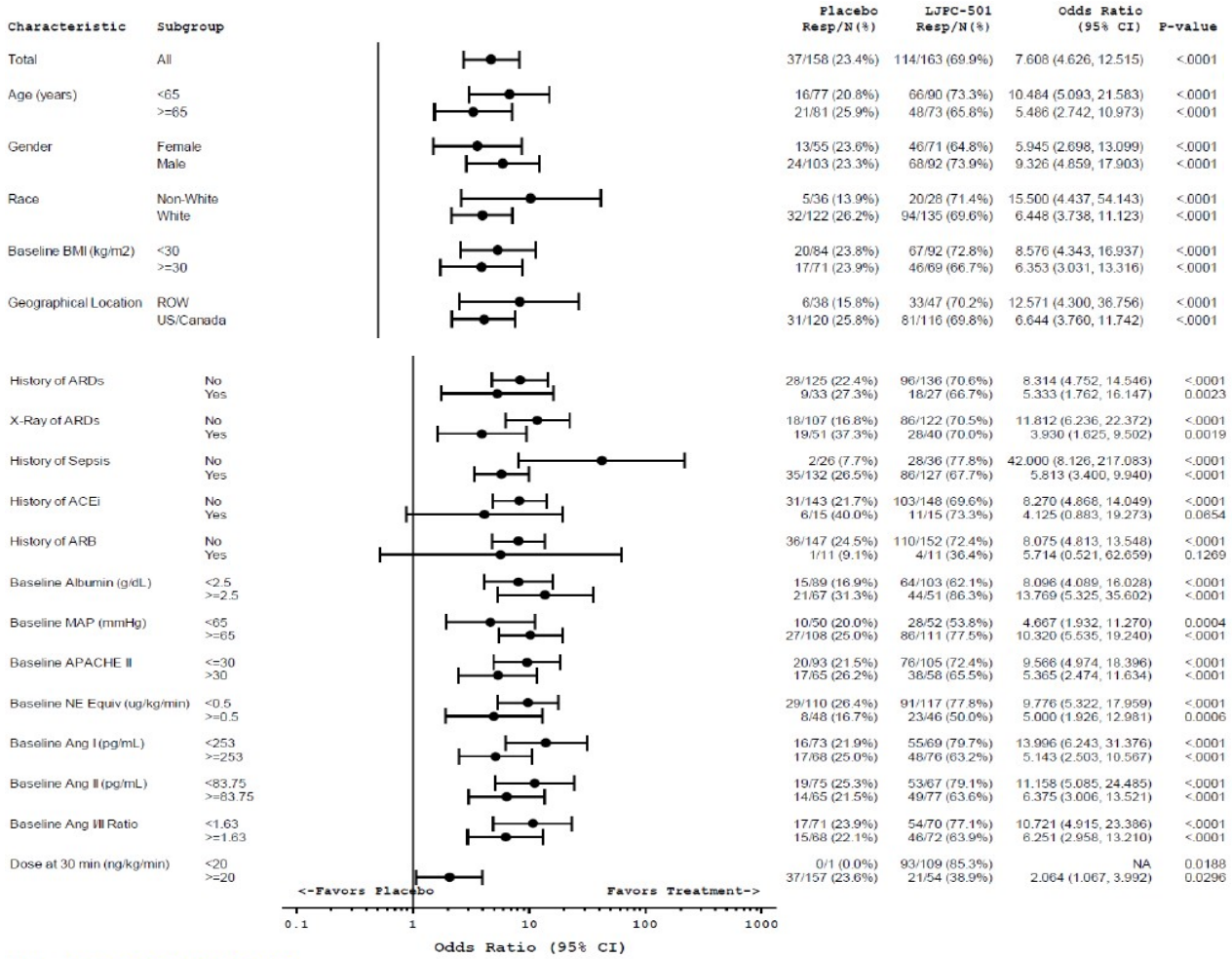
Change in Vasopressor Doses over Time: The mean change in vasopressor dose (other than angiotensin II) from baseline dose level to the Hour 0 to 3 study period was an increase of 0.01 µg/kg/min in the placebo group compared with a reduction of 0.03 µg/kg/min in the LJPC-501 group (p = 1.09 × 10-6). The mean change in other vasopressor dose from baseline dose level during the Hour 3 to 48 study period was a greater decrease in the LJPC-501 group compared to the placebo group. The mean change was −0.04 µg/kg/min in the placebo group and −0.11 µg/kg/min in the LJPC-501 group. The LJPC-501 group had a greater decrease in the mean change in doses of other vasopressors from Baseline dose level at all hourly time points (Figure E-06 of the Clinical Assessment Report).

Other exploratory endpoints: there were not statistically significant differences between treatment groups in individual non cardiovascular SOFA scores or in health resource utilization outcomes (i.e.: time on vasopressors, time on ventilation, stay in ICU, time in hospital) (sections 11.4.1.3.6 and 11.4.1.3.7 of the ATHOS-3 CSR).

Ancillary analyses

Subgroup analyses of MAP response at 3 hours:

Treatment effects within subgroups based on demographic, baseline, and study drug titration level at 30 minutes are displayed by forest plot in Figure 10. All odds ratio point estimates were >1 for LJPC-501 to placebo and only two 95%CIs included 1 (history of ACE inhibitor therapy and history of ARB therapy). All other treatment effects were significant for LJPC-501 over placebo.



Source: Figure 14.2.6.2.1, Table 14.2.9.1.1
Note: Odds ratio and 95% CIs with Chi-square test p values. The cutoff values for subgroups by angiotensin I and II levels and I/II ratio are median values.
Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor type 1 blocker; ARDS = acute respiratory distress syndrome; BMI = body mass index; MAP = mean arterial pressure; NE = norepinephrine.

Figure 8 Univariate Analysis of Mean Arterial Pressure at Hour 3 (mITT Population)

Treatment-subgroup interactions were investigated by including a treatment by subgroup factor in a model that already included treatment and subgroup. Only chest x-ray finding of ARDS was statistically significant (p = 0.0478) with higher odds ratio (OR) of 11.8 (LJPC-501 to placebo) in subjects with no chest x-ray findings compared with an odds ratio of 3.9 in subjects with chest x-ray findings. The interaction was driven by the higher response rate in the placebo arm in patients with chest x-ray findings (37.3%) than in patients with no chest x-ray findings (16.8%).

Post-hoc subgroup analysis of MAP response according to baseline NED: The Applicant believes that treatment with LJPC-501 is most beneficial in patients whose vasopressor doses are lower, ie, earlier in the progression of disease, such that the outcome is still modifiable; however, there remains potential benefit in treating patients with higher NEDs as well. Given that only 21 patients were on NED ≥ 1 microg/kg/min at baseline, and that the trend on MAP response favoured placebo in this small subgroup, a statement has been included in the SmPC that the effect of the product when added to maximum doses of other vasopressors is unknown.

Table 17 Primary Efficacy Analysis: MAP Response at Hour 3 by NED Baseline

	Response Rate, n/N (%) (95%CI)		LJPC-501:Placebo [a]	
NED Group	Placebo	LJPC-501	OR (95% CI)	p value
< 0.5 µg/kg/min	29/110 (26.4%)	91/117 (77.8%)	9.78 (5.32-18.00	< 0.0001
≥ 0.5 to < 1.0 µg/kg/min	6/40 (15.0%)	19/33 (57.6%)	7.69 (2.54-23.31)	0.0003
≥ 1.0 µg/kg/min	2/8 (25.0%)	4/13 (30.8%)	1.33 (0.18-9.72)	0.7766

Source: LJ501-CRH01 Day 120 Table 80.2.1, Table 80.11.1; LJ501-CRH01 CSR Table 14.2.9.1.1
[a] Unadjusted; Chi-square test from logistic regression model including LJPC-501 treatment compared to Placebo

Multivariate Analysis of MAP at Hour 3 by Logistic Regression:

The subgroups in the univariate analysis were entered as covariates in a multivariate logistic regression model. The treatment effect maintained statistical significance and a larger effect size in the multivariate model with the LJPC-501 treatment odds ratio of 12.4 (95% CI: 6.72-22.8; p < 0.0001). Other predictors of more likely achieving the target Hour 3 MAP response were no prior exposure to an ARB, chest x-ray findings of ARDS, albumin > 2.5 g/dL, and NE-equivalent dose < 0.5 µg/kg/min. The chest x-ray finding of ARDS was related to a difference in response rates within the placebo treatment arm (37.3% among patients with ARDS by chest x-ray versus 16.8% without) but no difference between these subgroups within the LJPC-501 arm (70.0% and 70.5%, respectively) [page 100, LJ501-CRH01 CSR].

Analysis in ITT and Per Protocol Populations

The treatment effect in achieving the target MAP endpoint was consistent in 3 analysis populations (mITT, ITT, and Per Protocol) and sensitivity analyses (Table 20).

Table 18 Primary Endpoint Across Analysis Populations and Sensitivity Analyses.

	mITT Population		Per Protocol Population		ITT Population	
Analysis	**Placebo (N=158)**	**LJPC-501 (N=163)**	**Placebo (N=149)**	**LJPC-501 (N=150)**	**Placebo (N=172)**	**LJPC-501 (N=172)**
Number responding (n)	37	114	35	104	41	116
Percent responding	23.4%	69.9%	23.5%	69.3%	23.8%	67.4%
95% CI [a]	17.1%-30.8%	62.3%-76.9%	16.9%-31.1%	61.3%-76.6%	17.7%-30.9%	59.9%-74.4%
Primary analysis [b] Independent variable:	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Treatment, LJPC-501	7.95 (4.76-13.3)	2.54×10^{-15}	7.85 (4.61-13.4)	$3.49\ 10^{-14}$	6.96 (4.27-11.3)	7.13×10^{-15}
Baseline MAP, < 65 mmHg	0.49 (0.28-0.86)	0.0122	0.49 (0.28-0.87)	0.0150	0.50 (0.30-0.86)	0.0114
Baseline APACHE II score	1.00 (0.97-1.03)	0.9218	1.00 (0.96-1.03)	0.7953	0.99 (0.96-1.02)	0.6552
Vasopressin Hour −6 to Hour 0	0.93 (0.53-1.62)	0.7938	0.89 (0.51-1.58)	0.6978	1.06 (0.63-1.80)	0.8243
Average NED Hour −6 to Hour 0	0.60 (0.29-1.26)	0.1803	0.60 (0.29-1.28)	0.1862	0.60 (0.30-1.22)	0.1573
Sensitivity analyses Stratification						
Randomisation stratification [c]	7.88 (4.74-13.1)	7.18×10^{-17}	7.75 (4.57-13.2)	1.55×10^{-15}	6.85 (4.23-11.1)	5.04×10^{-16}
Clinical database stratification [c]	7.79 (4.66-13.0)	7.73×10^{-17}	7.58 (4.45-12.9)	1.57×10^{-15}	6.69 (4.12-10.9)	6.27×10^{-16}
Unadjusted logistic regression [d]	7.61 (4.63-12.5)	1.33×10^{-15}	7.36 (4.41-12.3)	2.58×10^{-14}	6.62 (4.12-10.6)	5.56×10^{-15}
Unadjusted [e]		3.45×10^{-17}		1.05×10^{-15}		3.75×10^{-16}

Source: LJ501-CRH01 CSR, Table 14.2.1.1.1, Table 14.2.1.1.2, Table 14.2.1.1.3

Abbreviations: APACHE II=Acute Physiology and Chronic Health Evaluation II; CI=confidence interval; ITT=intent-to-treat; MAP=mean arterial pressure; mITT=modified intent-to-treat; NED=norepinephrine-equivalent (sum vasopressor) dose; OR=odds ratio.

[a] Exact binomial 95% CI

[b] Chi-square test from logistic regression model including LJPC-501 treatment (compared to placebo) adjusted by Baseline MAP (< 65 mmHg / ≥ 65 mmHg), Baseline APACHE II score, vasopressin use 6 hours prior to randomisation (yes / no), and average sum vasopressor (norepinephrine-equivalent) dose over the 6 hours prior to randomisation.

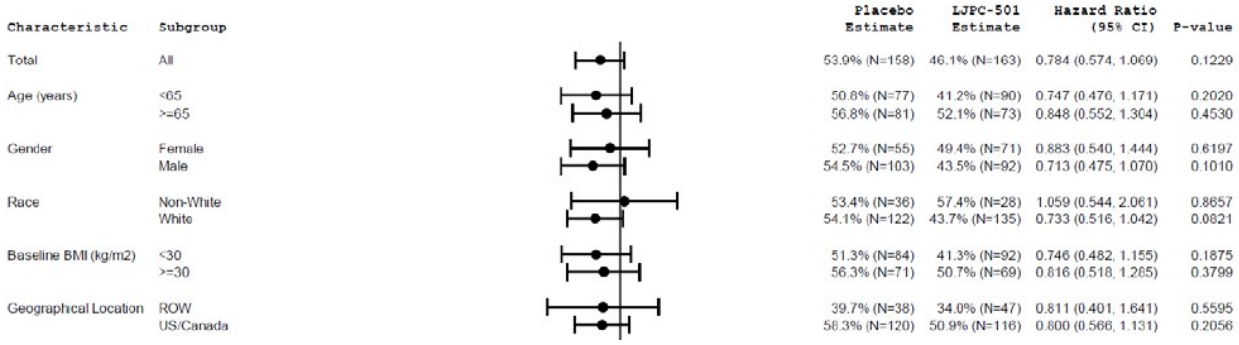
[c] Cochran-Mantel-Haenszel test of LJPC-501 compared to placebo stratified by baseline MAP and baseline APACHE II score.

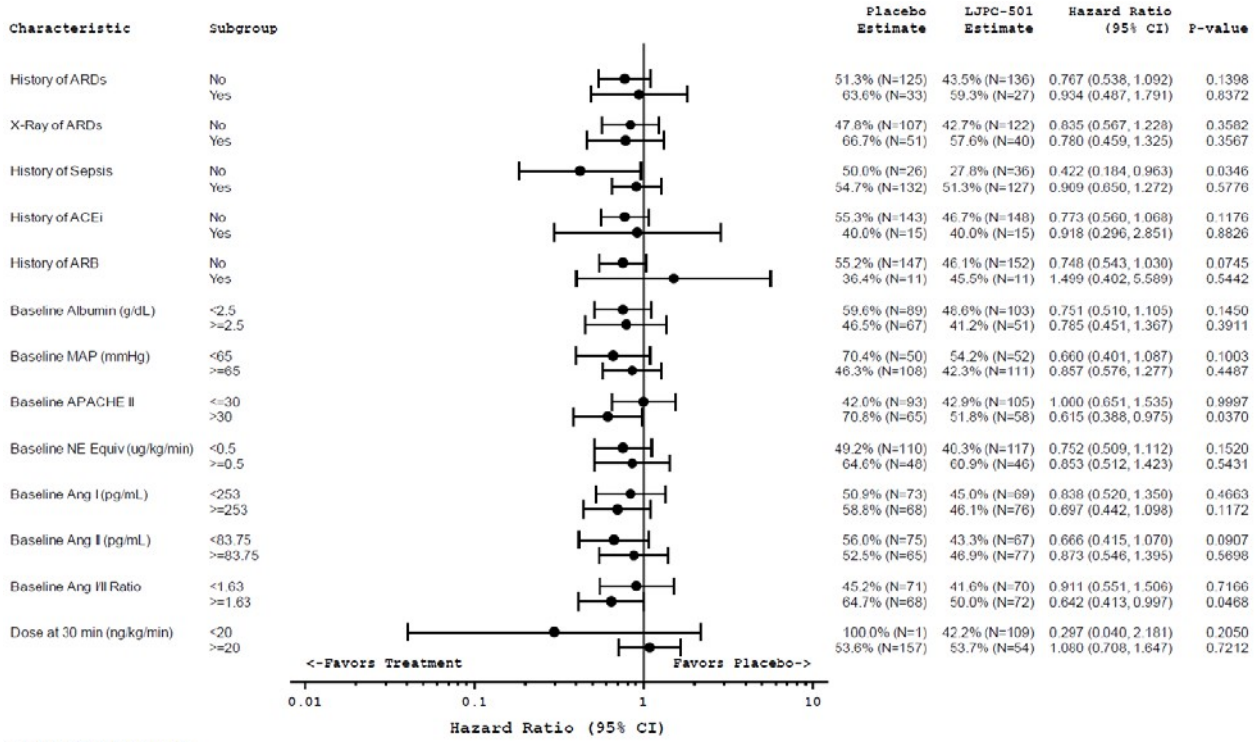
[d] Chi-square test from logistic regression model including LJPC-501 treatment compared to placebo.

[e] Fisher's exact test of LJPC-501 treatment compared to placebo.

Univariate Analyses of Mortality to Day 28

Univariate analyses of mortality to Day 28 comparing LJPC-501 to placebo in the mITT population are provided in Figure 11. Notably, the subset of patients with baseline MAP < 65 mmHg had a 70.4% mortality in the placebo group compared with 54.2% in the LJPC-501 group (HR = 0.66, 95% CI: 0.40-1.09). In the mITT population, point estimates for most subgroups favored LJPC-501 with 2 subgroup CIs not including 1. For patients with high APACHE II scores (> 30) at Screening, the risk of mortality at Day 28 was higher in the placebo arm (70.8%) than the LJPC-501 treatment arm (51.8%) with a hazard ratio (LJPC-501 to placebo) of 0.62 (95% CI, 0.39–0.98). Similarly, for patients with high angiotensin I to angiotensin II ratio (≥ 1.63, the median value across treatment arms), the HR of LJPC-501 to placebo was 0.64 (95% CI: 0.41-1.00). There were no treatment-subgroup interactions of note for mortality at Day 28 in the pre-specified subgroups.





Source: Figure 14.2.6.4.8
Note: Odds ratio and 95% CIs with Chi-square test p values. The cutoff values for subgroups by angiotensin I and II levels and I/II ratio are median values.
Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor type 1 blocker; ARDS = acute respiratory distress syndrome; BMI = body mass index; MAP = mean arterial pressure; mITT = modified intent-to-treat; NE = norepinephrine.

Figure 9 Univariate Analysis of Mortality at Day 28 (mITT Population).

Post-hoc subgroup analysis of mortality according to baseline NED: Mortality tended to be lower in the experimental group regardless of baseline NED.

Table 19 Day 28 Mortality by NED at Baseline (Univariate analysis, mITT Population)

NED Group	Mortality Rate (95%CI)		LJPC-501:Placebo	
	Placebo	LJPC-501	OR (95% CI)	p value
< 0.5 µg/kg/min	49% (40%-59%)	40% (32%-50%)	0.75 (0.51-1.11)	0.1520 [a]
≥ 0.5 to < 1.0 µg/kg/min	60% (45%-75%)	55% (39%-72%)	0.840 (0.455-1.547)	0.5746 [b]
≥ 1.0 µg/kg/min	88% (58%-99%)	77% (53%-94%)	0.468 (0.174-1.260)	0.1246 [b]

Source: LJ501-CRH01 CSR Table 14.2.9.5.1; LJ501-CRH01 Day 120 Table 80.4.1, Table 80.13.1
[a] Chi-square test
[b] Log-rank test

Multivariate Analysis of Mortality to Day 28

Eight covariates met the criteria for inclusion in the final models for mortality to Day 7 and to Day 28 (treatment arm angiotensin; age ≥ 65 years; sex male; baseline MAP < 65 mmHg; Baseline APACHE score >30; US or Canada geographic region; chest X-ray finding of ARDS; and baseline NE-equivalent dose ≥ 0.5 µg/kg/min).

Patients with Baseline MAP < 65 mmHg, APACHE II score > 30, enrollment in the US and Canada versus rest of world, chest x-ray finding of ARDS, and baseline NE-equivalent dose ≥ 0.5 µg/kg/min had significantly higher risk of mortality at Day 28 (Table 22). On the contrary, randomization to LJPC-501 was not a factor associated with a lower mortality risk. The hazard ratio for LJPC-501 versus placebo in the final multivariate model was 0.89 (95% CI, 0.64–1.24; p = 0.4865). Multivariate analyses in the ITT population and the PP population (Table 14.2.9.6.2 of the CSR) were consistent with the results in the mITT population.

Table 20 Mortality at Day 28: Multivariate Analyses (mITT and ITT Populations).

Final Model Covariate	Hazard Ratio (95% CI)	p value
mITT Population (N = 321)		
Treatment arm, LJPC-501	0.89 (0.64 - 1.24)	0.4865
Age, ≥ 65 years	1.44 (1.04 - 2.01)	0.0305
Sex, male	0.90 (0.65 - 1.26)	0.5518
Baseline MAP, < 65 mmHg	1.61 (1.15 - 2.26)	0.0057
Baseline APACHE II score, > 30	1.67 (1.19 - 2.33)	0.0027
Geographic region, US or Canada	1.80 (1.18 - 2.76)	0.0066
Chest x-ray finding of ARDS, Yes	1.58 (1.10 - 2.25)	0.0122
Baseline NE-equivalent dose, ≥ 0.5 µg/kg/min	1.77 (1.25 - 2.51)	0.0013
ITT Population (N = 344)		
Treatment arm, LJPC-501	0.87 (0.63 - 1.21)	0.4224
Age, ≥ 65 years	1.44 (1.04 - 2.01)	0.0301
Sex, male	0.90 (0.65 - 1.26)	0.5445
Baseline MAP, < 65 mmHg	1.61 (1.15 - 2.26)	0.0058
Baseline APACHE II score, > 30	1.67 (1.20 - 2.33)	0.0026
Geographic region, US or Canada	1.80 (1.18 - 2.75)	0.0069
Chest x-ray finding of ARDS, Yes	1.57 (1.10 - 2.25)	0.0124
Baseline NED, ≥ 0.5 µg/kg/min	1.77 (1.25 - 2.51)	0.0013

Source: Table 14.2.9.6.1, and Table 14.2.9.6.3
Abbreviations: ACE = angiotensin converting enzyme; APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II; ARDS = acute respiratory distress syndrome; ITT= intent-to-treat; MAP = mean arterial pressure; mITT = modified intent-to-treat; NED = norepinephrine equivalent dose;

Post Hoc subgroup analysis of patients with AKI (Organ Failure) on Dialysis at Baseline

In order to link MAP recovery to organ function, the subgroup of patients in study LJ501-CRH01 who had AKI (acute renal failure) and were receiving RRT at Baseline was analysed post hoc for treatment effects (Summary of clinical efficacy to treat hypotension).

The subgroup analysis included 105 patients from the mITT population of study LJ501-CRH01 who were receiving RRT at Baseline and had no history of end-stage renal disease (60 of 158 patients in the placebo group, 45 of 163 patients in the LJPC-501 group). Twelve patients with chronic end-stage renal disease (6 of whom were receiving RRT at Baseline, 3 in each treatment group) were excluded from this subgroup analysis (LJ501-CRH01 CSR). Twenty-three patients without chronic kidney disease who started RRT after Baseline were not included in the subgroup analysis (placebo 10 patients, LJPC-501 13 patients; LJ501-CRH01 CSR).

MAP Response at Hour 3: The treatment effect of LJPC-501 versus placebo on MAP response rates at Hour 3 was significant in this high-risk subgroup and robust across sensitivity analyses; 24 (53.3%) patients in the LJPC-501 group met the MAP target at Hour 3, as compared with 13 (21.7%) patients in the placebo group (odds ratio for LJPC-501 versus placebo of 4.31, 95% CI: 1.77-10.5).

Mean CV SOFA score improved from Screening to Hour 3 and Hour 48 in patients with AKI on RRT at Baseline. The mean change from Screening to Hour 48 was significantly better in the LJPC-501 group than in the placebo group (mean change from baseline: angiotensin –0.82 vs. placebo –1.31; Dif.: -0.49; p = 0.04). This was at expenses of the differences in MAP response (CV SOFA score = 0.

Total SOFA score: There was no significant difference in post-baseline Total SOFA scores between the treatment groups in the subgroup of patients with AKI on RRT (Table 34; Summary of clinical efficacy).

Mortality: In the AKI subgroup, Day 28 mortality rates were 70% (95% CI: 59%-81%) in the placebo group and 47% (95% CI: 33%-62%) in the LJPC-501 group (LJ501-CRH01 Supplemental Table 3.4.1). Within this high-risk subgroup, 53.2% of LJPC-501-treated patients versus 29.6% of placebo-treated patients survived to Day 28 (hazard ratio = 0.52; 95% CI: 0.30-0.87; p = 0.01). Multivariate analyses of Day 28 mortality were also performed for the AKI subgroup. In the final model (LJ501-CRH01), the treatment difference for mortality at Day 28 was no longer statistically significant (LJPC-501:placebo, hazard ratio = 0.62; 95% CI: 0.36-1.08; p = 0.0930) (Table 23). Baseline NED ≥ 5 µg/kg/min was the only covariate associated with greater risk of death by Day 28.

Table 21 Multivariate Analysis of Mortality at Day 28 in Patients with AKI on RRT at Baseline (Final Model, mITT Population)

Model Covariate	Hazard Ratio (95% CI)	p value
Unadjusted		
Treatment, LJPC-501	0.52 (0.30 - 0.87)	0.0118
Final Model		
Treatment, LJPC-501	0.62 (0.36 - 1.08)	0.0930
Age, ≥ 65 years	1.39 (0.84 - 2.30)	0.2002
Sex, male	1.25 (0.75 - 2.09)	0.3937
Baseline NED ≥ 5 µg/kg/min	1.81 (1.08 - 3.04)	0.0243

Source: LJ501-CRH01 Supplemental Table 3.4.1, Table 3.4.2
Abbreviations: AKI=acute kidney injury; mITT=modified intent-to-treat; NED=norepinephrine-equivalent dose; RRT=renal replacement therapy.

Assessments of Organ Function: In the AKI subgroup, a significant advantage was found for LJPC-501 treatment on time to discontinuation of RRT. Patients treated with LJPC-501 recovered renal function earlier than patients receiving placebo and standard-of-care therapy. Among the 60 patients with AKI receiving placebo, 9 (15%) had discontinued RRT by Day 7, compared with 17 (38%) of the 45 patients with AKI receiving LJPC-501.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 Summary of Efficacy for trial LJ501-CRH01 (ATHOS-3).

Title: **LJPC-501 (ANGIOTENSIN II) LJ501-CRH01 A PHASE 3, PLACEBO-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY OF LJPC-501 IN PATIENTS WITH CATECHOLAMINE-RESISTANT HYPOTENSION (CRH)**			
Study identifier	LJ501-CRH01 (ATHOS-3)		
Design	PLACEBO-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Primary outcome assessed at 3 hours; Secondary outcomes assessed at 48 hours (end of treatment); End of study visit at day 7; follow-up at day 28. not applicable. not applicable.
Hypothesis	Superiority		
Treatments groups	Angiotensin II (LJ501)		Starting dose: 20 ng/kg/min and then titrated depending on blood pressure until a maximum (up-titration) of 40 ng/kg/min and minimum (down-titration) of 2.5 ng/kg/min for 48-hour duration (n = 163).
	Placebo		Same treatment scheme than experimental group (n = 158).
Endpoints and definitions	Primary endpoint	MAP response to hour 3	Proportion of patients in each treatment group with an average MAP ≥ 75 mmHg or with a ≥ 10 mmHg increase in MAP above Baseline MAP at Hour 3, without an increase in standard-of-care vasopressor doses prior to Hour 3.
	Secondary endpoint	CV SOFA score at 28 hours	Mean change in cardiovascular SOFA scores at Hour 48 compared to the score at Screening. It is based on the following: No hypotension: score 0; MAP < 70 mmHg: score +1; On vasopressors, dopamine < 5 microg/kg/min or dobutamine (any dose): score +2; Dopamine > 5 microg/kg/min or epinephrine or norepinephrine < 0.1 microg/kg/min: score +3; Dopamine > 15 microg/kg/min or epinephrine or norepinephrine > 0.1 microg/kg/min: score +4. All patients had the worst CV SOFA (= 4) at baseline as per inclusion criteria.
	Secondary endpoint	Total SOFA score at 48 hours	Mean change in total SOFA scores at Hour 48 compared to the score at Screening. The total score is the sum of six different 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.
	Exploratory endpoint	Mortality	Mortality rates at day 7 (end-of-study visit) and day 28 (follow-up).
Database lock	23 February 2017		
Results and Analysis			
1) MAP response at hour 3			
Analysis description	**Primary Analysis**		
Analysis population and time point description	mITT 3 hours		
Descriptive statistics and estimate variability	**Treatment group**	**Angiotensin II (LJPC-501)**	**Placebo**
	Number of subjects analyzed (n)	163	158
	Number responding (n)	114	37
	Percent responding (%)	69.9%	23.4%
	95% CI	62.3% to 76.9%	17.1% to 30.8%
Effect estimate per	MAP response at	Angiotensin II vs. Placebo	

comparison	hour 3	Odds ratio	7.95
		95% CI	4.76 to 13.3
		P-value (Chi-square test from logistic regression model)*	2.54E-15
2) CV SOFA at hour 48			
Analysis description	**Secondary Analysis**		
Analysis population and time point description	mITT 48 hours		
Descriptive statistics and estimate variability	**Treatment group**	**Angiotensin II (LJPC-501)**	**Placebo**
	Number of subjects analyzed (n)	163	158
	Mean score at screening (SD)	4 (0)	4 (0)
	Mean score at hour 48 (SD)	2.25 (1.77)	2.72 (1.65)
Effect estimate per comparison	Mean change in CV SOFA score from screening to hour 48	Angiotensin II vs. Placebo	
		Angiotensin II Mean change (SD)	-1.75 (1.77)
		Placebo Mean change (SD)	-1.28 (1.65)
		P-value (van Elteren Wilcoxon)	0.0129
3) Total SOFA at hour 48			
Analysis description	**Secondary Analysis**		
Analysis population and time point description	mITT 48 hours		
Descriptive statistics and estimate variability	**Treatment group**	**Angiotensin II (LJPC-501)**	**Placebo**
	Number of subjects analyzed (n)	163	158
	Mean score at screening (SD)	11.77 (2.84)	12.72 (3.31)
	Mean score at hour 48 (SD)	12.69 (6.033)	13.76 (6.70)
Effect estimate per comparison	Mean change in Total SOFA score from screening to hour 48	Angiotensin II vs. Placebo	
		Angiotensin II Mean change (SD)	+1.05 (5.50)
		Placebo Mean change (SD)	+1.04 (5.336)
		P-value (van Elteren Wilcoxon)	0.9755
3) All-cause mortality to day 28			
Analysis description	**Exploratory Analysis**		
Analysis population and time point description	mITT Day 28		
Descriptive statistics and estimate variability	**Treatment group**	**Angiotensin II (LJPC-501)**	**Placebo**
	Number of subjects analyzed (n)	163	158
	Deaths (n)	75	85
	Percent of deaths (%)	46%	54%
	95% CI	39% to 54%	46% to 62%
Effect estimate per comparison	Mortality to day 28	Angiotensin II vs. Placebo	
		Hazard ratio	0.784
		95% CI	0.574 to 1.069
		P-value (unstratified logrank test)	Not appropriate for a exploratory analysis

CI = confidence interval; CV = cardiovascular; FiO_2: fraction of inspired oxygen; MAP = mean arterial pressure; mITT = modified intention to treat population; PaO_2: partial pressure or arterial oxygen SD = standard deviation; SOFA: sequential organ failure assessment.
* Logistic regression model included LJPC-501 treatment (compared to placebo) adjusted by baseline MAP (<65 mmHg / ≥ 65 mmHg), baseline APACHE II score, vasopressin use 6 hours prior to randomization (yes/no), and mean norepinephrine-equivalent dose (NED) over the 6 hours prior to randomization

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

There is an ongoing open-label, multi-center, expanded access, US study. The interim analysis is briefly mentioned because some mortality data are available.

Study LJ501-EAP01. Expanded access to LJPC-501 in the US.

First patient enrolled: 27 October 2017

Cut off for Interim Report: 01 March 2018

Release date of report: 17 March 2018

Planned sample size: 300 patients

This is an ongoing open-label, multi-center expanded access treatment protocol of LJPC–501 conducted in the US. Adult patients with septic or other distributive shock who remain hypotensive despite fluids and vasopressor therapy, and who are hospitalized in an intensive care unit setting are eligible to participate. Up to 300 patients from sites in the US are planned to be enrolled in the study. The FDA allows sponsors to provide investigational drugs to patients with immediate life-threatening conditions upon request by treating physicians if there are no available therapies for the condition. Based on the results of the ATHOS-3 study, and the lack of available therapies for patients in this critically ill patient population, this expanded access protocol was designed to both provide treatment to patients in need and to help collect additional safety data for the use of LJPC-501.

Objectives: The primary objective of the study is to provide access to LJPC-501 for distributive shock patients who remain hypotensive despite receiving fluid and vasopressor therapy while the new drug application (NDA) was under review by US FDA. The secondary objective of the study is to assess the safety of LJPC-501.

Selection of Study Population: Adult patients with distributive or vasodilatory shock who remained hypotensive despite fluid and vasopressor therapy who met the eligibility inclusion criteria and none of the eligibility exclusion criteria were considered for enrollment. Prior to enrolling a patient in the study, sites contacted the EAP call center to confirm eligibility.

Treatment Administered: All eligible patients approved for treatment were to receive LJPC-501 via a central venous line for up to 7 days (168 hours). The recommended starting dose of LJPC-501 was 5 nanograms (ng)/kg/min via continuous intravenous infusion. Following initiation of study drug, sites were instructed to monitor blood pressure response and titrate LJPC-501 by increments of up to 10 ng/kg/min, as needed, to achieve or maintain target blood pressure. Study drug was not to exceed 40 ng/kg/min. Timing of increase or decrease of LJPC-501 was dependent on the MAP response. Doses as low as 1.25 ng/kg/min could be used. Down-titration of other vasopressors was done per institutional standard of care. Treatment with LJPC-501 was allowed for up to 7 days, per PI discretion.

Results (interim analysis, 17 March 2018)

Disposition of Patients: A total of 56 patients were screened as of 01 March 2018, the data cutoff date for this interim clinical report. Of these, 54 patients signed informed consent and were enrolled. One patient discontinued without receiving LJPC-501: patient 188-005 discontinued after the vasopressor need decreased prior to study drug initiation.

The primary reasons for treatment discontinuation were completion of treatment (i.e., MAP recovery) in 34 (64.2%) patients, adverse event/death in 12 (22.6%) patients, and other reasons in 7 (13.2%) patients (the majority of 'other' reasons were decisions to withdraw all treatment/transition to palliative care). The primary reasons for study discontinuation were death (58.5%) and completion of Day 28 visit (39.6%).

Extent of Exposure: Study drug was titrated to effect, starting at an initial dose of 5 ng/kg/min. The mean (SD) duration of exposure of 62.9 (51.6) hours. Duration of exposure was less than 24 hours in 12 patients (22.6%), between 24-48 hours in 13 patients (24.5%), between 48-72 hours in 13 patients (24.5%) and >72 hours in 15 patients (28.3%). The maximum duration of exposure was 241.25 hours (10 days; Patient 205-001).

Deaths: Overall, 31 of 53 (58.5%) patients have died (Table 14.4.1) including 21 (39.6%) patients who died on or before Day 7 (for further details, see also Table 9 in the clinical safety section of current AR).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

ATHOS-3

This marketing authorisation application is based on a single pivotal study (LJ501-CRH01; ATHOS-3) to determine the safety and efficacy of angiotensin II in patients with distributive shock (mainly septic shock) refractory to catecholamines and other vasopressors. The study design and choice of control group was agreed upon after discussion with the FDA, and the study was conducted in the US as part of the Special Protocol Assessment. The applicant did not seek advice in the EU before conducting the pivotal study ATHOS-3. Two scientific advices (SA) were given by the CHMP after the results of the ATHOS-3 study were available in 2017 and 2018 respectively. Some limitations of the study design and uncertainties in study results were noted in the CHMP 2017 SA. Particularly, as the primary endpoint was based on the increase in MAP, the study was underpowered for morbidity/mortality endpoints, which were considered exploratory. Therefore, in the 2018 follow-up SA, a post-authorisation placebo-controlled study in patients with shock and advanced kidney injury (AKI), powered to show an effect on resolution of organ failure and survival, was proposed to alleviate these concerns. The data presented falls within the scope of the European guideline 'Points to Consider on application with one pivotal study' (CPMP/EWP/2330/99), which indicated that the strength of evidence must be particularly robust with respect to clinical and statistical significance.

Choice of control group in ATHOS-3 study: since eligible patients received standard-of-care fluid resuscitation prior to study drug treatment and continued to receive standard-of-care catecholamine and/or other vasopressor treatment during study drug treatment, placebo can considered to be an acceptable choice of control in a parallel treatment group.

The main **inclusion criteria** were high-output shock with hypotension resistant to catecholamines. High output shock was characterized by a central venous oxygen saturation > 70% (measured by oximetry catheter or central venous blood gas) and central venous pressure > 8 mmHg or a cardiac index > 2.3 L/min/m2. The definition was agreed. It was also agreed that the indication pursued (distributive or vasodilatory shock) inherently reflects the term "high-output shock" used in the ATHOS study protocol and publication. Hypotension was defined as a MAP < 65 mmHg and resistance to catecholamines with or without other vasopressors, defined as requiring a sum vasopressor dose (norepinephrine-equivalent dose, NED) > 0.2 µg/kg/min, since doses above 0.1 µg/kg/min in high-dose vasopressor-dependent shock were associated with mortality in excess of 50% across several studies. The definition of resistance to catecholamines was quite liberal, given that NED > 0.5 microg/kg/min are not unusual in these patients. The positive consequence is that the broad definition allowed to investigate the effect of angiotensin II on MAP response on top of different NED ranges. On the contrary, the no need for a maximum catecholamine dose at baseline (i.e.: inclusion of patients not on maximum catecholamines doses), coupled with the recommendation of not increasing NED in the placebo group up to 3 hours (measurement of primary endpoint), were considered as features of a proof-of concept study under highly controlled conditions favoring the demonstration of a treatment effect. The study protocol had many exclusion criteria. Sick patients with active bleeding, mesenteric ischemia, liver failure and MELD score of ≥ 30, or patients with extensive burns were excluded. Also patients requiring more than 500 mg daily of hydrocortisone or equivalent glucocorticoid medication as a standing dose were excluded. On the contrary, only patients with the worst CV SOFA score = 4 (i.e.: ≤ 3) were included.

Study treatments: Angiotensin II was given at a starting dose of 20 ng/kg/min. The dose could be titrated as often as every 5 minutes based on current MAP, determined as the average of 3 MAP values at least 1 minute apart prior to change in infusion rate. The maximal maintenance dose was 40 ng/kg/min after 3 hours. The choice of the starting dose tested in ATHOS- (20 ng/mg/kg) was considered overestimated in an attempt to get a fast and significant MAP response at 3 hours versus placebo, which was the primary endpoint and study time point. A lower angiotensin II starting dose could have been more appropriate. In fact, the authors of the ATHOS pilot study concluded that "initial dosing ranges are most likely between 2 and 10 ng/kg/min". During the ATHOS-3 study, the angiotensin-II 20 ng/kg/min starting dose had to be down titrated during the first 30 min in about two thirds of patients, which also supports the assumption that many treatments in the experimental group received higher starting doses than needed. In the response to the D120 CHMP LoQ, the applicant provided additional safety data suggesting that a starting dose of 20 ng/kg/min (tested in the ATHOS-3 study) is not likely to cause harm in drug-sensitive patients, but a smaller subset of less sensitive patients might have an extended time with low MAP if drug needed to be up-titrated from 5 ng/kg/min to the maximum recommended dose of 80 ng/kg/min. Therefore, the proposed 20 ng/kg/min starting dose was considered acceptable by the CHMP.

Study objectives: The primary objective was to compare the effect of angiotensin II versus placebo on a surrogate endpoint (increase in MAP) in patients with catecholamine-resistant hypotension (CRH). Change in SOFA scores was a secondary objective and mortality was an exploratory objective.

Primary outcome: The primary efficacy endpoint was a surrogate endpoint defined as the proportion of patients in each treatment group with an average MAP ≥ 75 mmHg or with a ≥ 10 mmHg increase in MAP above Baseline MAP at Hour 3, without an increase in standard-of-care vasopressor doses prior to Hour 3. Baseline MAP was defined as the average of 3 recorded MAP values (each measured in triplicate approximately one minute apart) documented within 30 minutes prior to initiation of study drug on Day 1, i.e., at -30 minutes, -15 minutes and 0 minutes (or just prior to study drug initiation). MAP at Hour 3 was taken as the average of 3 measurements of MAP at 2:45, 3:00, and 3:15 hours after the initiation of study drug administration at Hour 0. The primary outcome definition is acceptable to assess the drug effect in terms of raising blood pressure (i.e.: surrogate PD endpoint), but is not in line with the primary endpoint recommended in confirmatory studies in sepsis (i.e.: the vast majority of the population recruited into the pivotal study), which is all-cause mortality [Clinical investigation of medicinal products for the treatment of sepsis. CHMP/EWP/4713/03].

Secondary and exploratory outcomes: SOFA score outcomes (cardiovascular and total) were used as secondary outcomes, while mortality was investigated as an exploratory endpoint.

Primary efficacy analysis: The primary efficacy analysis focused on the comparison between treatment groups in the rate of MAP responders at hour 3. More specifically, the "estimand" was the difference in the proportion of patients between each treatment groups (angiotensin II or placebo) with an average MAP ≥ 75 mmHg or with a ≥ 10 mmHg increase in MAP above Baseline MAP at Hour 3, without an increase in standard-of-care vasopressor doses prior to Hour 3, analyzed in the mITT population using adjusted logistic regression with predefined covariates being Baseline MAP, APACHE II score, vasopressin use over the 6 hours prior to randomization (yes or no), and quantity of catecholamine use (average norepinephrine equivalents in µg/kg/min) over the 6 hours prior to randomization. A 2-tailed alpha of 0.05 was used in testing the hypothesis of treatment difference.

Statistical plan and analysis: Sample size calculation (n= 150 evaluable subjects per treatment arm) was appropriate for a study based on the surrogate endpoint of MAP response, but underpowered for mortality-morbidity. Randomisation strategy was appropriate. The study was double-blind. However, it was unblinded for a pharmacist at each center who was responsible for study drug preparation and labelling. The DSMB reviewed SAEs and deaths during an interim analysis, in order to stop treatment only for safety reasons. However, the statistician and DSMB also reviewed unblinded efficacy data at the interim analysis after 150 patients had been treated. The applicant has explained that the planned interim analysis was an unblinded review of safety data by the Data Safety Monitoring Board (DSMB) and was not intended as an interim efficacy analysis. The study was intended to enrol and treat > 315 patients to ensure at least 300 evaluable patients completed the study. There were no plans to modify the sample size based on the interim review of data, and the sample size was not modified after the interim analysis was completed. The applicant provided baseline characteristics and drug effect in post-interim versus interim analysis populations. Baseline differences were related to more patients post-interim analysis that were enrolled in Australia/New Zealand and Europe (expected due to the sequence of opening clinical sites). These patients had lower baseline MAP, lower mean $ScvO_2$, and higher mean MELD score than those recruited before the interim analysis. Results for the primary efficacy endpoint consistently demonstrated a significant treatment advantage with LJPC-501, with no difference for interim and post-interim populations.

The application with one single pivotal study was based on a hypothesized response rate in the primary efficacy endpoint of 40% in the placebo arm and 60% rate in the active (LJPC-501) arm. There is a gap between this expected response rate and the one actually observed especially in the placebo group (40% expected versus 23% observed, same magnitude than what was planned between Giapreza and placebo arms). This has been translated into an observed odds-ratio of 8 which is 3.5 higher than the 2.25 odds-ratio expected on the 300 subjects planned for the trial. There is no doubt that the pivotal trial was well-executed and the applicant conducted this trial with care, which ended up with compelling results (a very low p-value of $2.5\ 10^{-15}$ which is somewhat atypical). This is in line with the point-to-consider with one pivotal study (CPMP/EWP/2330/99). Nevertheless, some points in the guideline are still pending such as: a) the plausibility of the hypothesis tested is questionable although the CHMP agreed not to pursue this issue further; b) some clinical outcomes across sub-populations showed significant discrepancies at geographical level; for instance: responder rates odd-ratios were OR=6.6, OR=9.5 et OR=28.2 respectively in US/Canada, AUS/NZL and EU where there was a lack of response in the EU placebo arm: 7% responder rate versus more than 20% in other regions, the difference in mortality rates at 28 days between US and other countries involved in the trial (HR=1.80 with 95% CI [1.18 - 2.76], p=0.0066).

Efficacy data and additional analyses

The single pivotal study LJ501-CRH01 (ATHOS-3) was conducted to determine the safety and efficacy of angiotensin II. First patient was enrolled on 06 May 2015 and last patient was completed on 09 February 2017. The study was initiated at 128 sites in 10 countries. The study recruited 321 patients with hypotension and shock.

Demographic characteristics: Overall, 80.0% of the population was white, 60.7% were male, and 48.0% were at least 65 years old. Overall, demographic and disease characteristics were balanced between treatment groups. The vast majority of patients (90%) had septic shock as the cause of hypotension. The following more frequent underlying cause was vasoplegia. Data from subgroups do not suggest that angiotensin II only works in septic shock. In fact, the MAP response is much higher in non-septic shock subgroup and the trend towards decreased mortality in the overall population seems to be obtained at expenses of non-septic shocks. The majority of patients recruited into the ATHOS-3 study (80%) had septic shock (259/321), while 20% had distributive shock without sepsis (62/321). Drug effect was significantly higher in the subgroup of patients without sepsis compared with septic patients in terms of MAP response (OR: 42.0 vs. 5.81) and death (OR: 0.91 vs. 0.42). It should also be noted that since ATHOS-3 was not a sepsis trial, the ascertainment of sepsis was conducted through medical history and was not consistent across all sites. Sepsis was determined to be the primary or likely reason for shock in 90.4% of the mITT population after retrospective medical review of each patient by the Applicant, even though only 80.7% of patients were reported to have septic shock by medical history. Patients could have been entered into the study with undiagnosed septic shock, as this diagnosis was not an inclusion criterion. In summary, exploratory analyses suggest that the effect size is of a greater magnitude in non-septic distributive shock than in septic distributive shock. However, patients with septic shock also had a 5-fold increase in probability of achieving a MAP response than patients with septic shock on placebo.

There were statistical differences in some characteristics between the US and Europe or Australia/New Zealand, but representation of these later regions was relatively low in the overall population.

Prior vasopressor use: Vasopressin was used before randomization in 70% of patients, and 90% of patients had a baseline norepinephrine equivalent dose (NED) of vasopressors ≥0.2 microg/kg/min and 29% had a NED ≥0.5 microg/kg/min, which can be considered a high dose. Data from subgroups suggest that angiotensin II increases the MAP response regardless of the baseline NED, which is consistent with its different mechanism of action. Mortality was equally non-significant regardless of baseline NED of vasopressors (see ancillary analyses). There were also regional differences in the use of vasopressors. In Europe, average NED was the highest (0.72 microg/kg/min), while in US/Canada was the lowest (0.49 microg/kg/min). The opposite trend was evident for vasopressin use, which was the lowest in Europe (21%) and the highest in US/Canada (81%). This means that in Europe, catecholamine doses to qualify for further vasopressor therapy are much higher than in the US and that vasopressin in infrequently used, probably because it is not available in many countries. Nevertheless, screening and baseline MAP values were similar across regions (mean and median MAP between 65.2 and 67.5 mmHg at screening and Baseline across all regions). Only 21 patients were on NED ≥ 1 microg/kg/min at baseline (and the trend on MAP response favoured placebo in this small subgroup). Therefore, a statement has been included in the SmPC that "*the effect of Giapreza when added to maximum doses of other vasopressors is unknown*". Given the uncertainty in MAP response in patients on maximum doses of other vasopressors, the applicant was asked to define the conditions of administration (especially time to initiate LJPC-501 relative to other vasoactive treatments) and the target population (including definition of the refractory shock) which could benefit from the LJPC-501 treatment while minimising the risk of adverse event. On the one hand, the applicant accepted the inclusion of "refractory hypotension" in the wording of the indication, as proposed by the CHMP. On the other hand, the company proposed to include *"...**one or more** catecholamines and other available vasopressor therapies*" instead of *"...catecholamines and other available vasopressor therapies*" in order to prevent from the use of the product as third line treatment only. In the Rapporteur's view, this addition was not useful for the prescribers. The CHMP considered that the indication already includes a cross-reference to section 5.1, in which more detailed information about concomitant therapies is given. Concomitant treatment with catecholamines was already described in section 5.1 in terms of active ingredients ("*At the time of study drug administration, 97% of subjects were receiving norepinephrine, 67% vasopressin, 15% phenylephrine, 13% epinephrine, and 2% dopamine*"), in terms of number of vasopressors ("*83% of subjects had received two or more vasopressors and 47% three or more vasopressors prior to study drug administration*"), and in terms of NED ("*of the 321 patients, 71% were receiving a baseline NED < 0.5 microg/kg/min, 23% were receiving baseline NED ≥ 0.5 to < 1 microg/kg/min and 6% were receiving high NED ≥ 1.0 microg/kg/min*"). This was considered a more useful and complete approach as compared to simple statement in section 4.1 that the patient could have received one or more catecholamines. In addition, the indication also includes "other available vasopressor therapies" to acknowledge that other vasopressor therapies (i.e.: vasopressin analogues) may not be available in some European countries. Therefore, the indication can be interpreted as a second line therapy, in addition to catecholamines, or third line therapy in addition to catecholamines and other available vasopressor therapies, which is consistent with the data generated by the company, and further clarification about "*one or more catecholamines*" was not needed according to the CHMP. Some morbidity and mortality data are available with Giapreza, but they are exploratory and subject to a high degree of uncertainty (i.e.: very few data on top of high doses of vasopressors; very few data in the EU population, relatively small sample sizes with wide confidence intervals). A reference to the lack of robust data on morbidity-mortality was included in section 5.1 of the final SmPC: "*The effect of Giapreza on morbidity and mortality has not been determined in appropriate studies*". In the response to the second D180 LoI, the applicant also proposed changes in section 4.2 to reinterpret the indication, thus allowing for use even as first line treatment (i.e.: "*Therapy with GIAPREZA in adults with refractory hypotension is **preferably** started after treatment with catecholamine(s) and other available vasopressor therapies are unable to stabilise blood pressure)*. This was not considered acceptable by the CHMP. The indication already included a cross reference to section 5.1, which means that the prescribing

physician can consult the population and conditions (e.g.: concomitant medications, etc.) under which the product was investigated. The information in section 4.2 should be limited to ensure a safe dosing by providing clear instructions on how to administer the medicinal product.

Angiotensin and placebo doses administered during the study: Mean and median dose infusion rates over the duration of treatment were higher in the placebo arm than the LJPC-501 arm ($p < 0.0001$), which can be explained by a lack of efficacy with placebo in reaching MAP targets and subsequent up-titrations. In the placebo arm, the median of the patient mean infusion rate over all treatment was 41.75 ng/kg/min (range 3.13–151.54 ng/kg/min) compared with only 14.30 ng/kg/min (range 1.33–123.70 ng/kg/min) for LJPC-501. The majority of patients had a dose decrease of LJPC-501 after a starting dose of 20 ng/kg/min, thus indicating a short onset of action in reaching MAP targets. The median of per-patient mean LJPC-501 doses was 9.17 ng/kg/min during Hour 0-1 and 10.0 ng/kg/min during Hour 1-2 and Hour 2-3. A sensitivity to LJPC-501 dose by 30 minutes was conducted, instead of the planned "hyper-responder analysis". At 30 minutes, most patients (67%) required doses below the 20 ng/kg/min starting dose, half of patients required 5 ng/kg/min or less and 24% of patients required 2.5 ng/kg/min or less. Therefore, it seems that the recommended LJPC-501 starting dose (20 ng/kg/min) was a forced dose. In fact, in the expanded access study provided as supportive, the recommended starting dose is 5 ng/kg/min instead of 20 ng/kg/min. The applicant was requested to discuss about the benefits and risks of recommending a 20 ng/kg/min starting dose instead of a 5 ng/kg/min starting dose recommended in the ongoing at the time of the evaluation expanded access study. A description of the adverse effects reported during the first 30 mins (i.e.: all SAEs, CV SAEs like hypertension, heart failure, infarction, maximum MAP, cardiovascular) in patients sensitive vs. non-sensitive to angiotensin-II was provided by the applicant in order to check that starting with 20 mg/kg/min had not detrimental effects on safety in patients sensitive to LJPC-501. The safety data provided suggest that a starting dose of 20 ng/kg/min (tested in the ATHOS-3 study) is not likely to cause harm in drug-sensitive patients, but a smaller subset of less sensitive patients might have an extended time with low MAP if drug needed to be up-titrated from 5 ng/kg/min to the maximum recommended dose of 80 ng/kg/min. Therefore, the proposed 20 ng/kg/min starting dose was considered acceptable to the CHMP.

Actual corticosteroid use: One of the exclusion criteria was the use of hydrocortisone > 500 mg/day or equivalent glucocorticoid medication. However, a total of 65.2% of patients in the placebo group and 69.9% in the LJPC-501 group received 1 or more glucocorticoids after beginning study drug treatment (dose not specified). The higher percent of use corresponded to hydrocortisone, with a significant imbalance between treatment groups (48.5% of patients in the angiotensin II group and only 33.5% in patients on the placebo group were administered hydrocortisone; non-specified dose). Glucocorticoid therapy can be considered among the rescue therapies available in refractory shock [Jentzer JC, et al. Chest. 2018], and therefore its frequent concomitant use in patients recruited into the ATHOS-3 study is not surprising. In this respect, some clarifications regarding the actual glucocorticoid dose administered were provided by the applicant. The imbalance in hydrocortisone use between treatment groups had no significant impact in the study results with respect to efficacy or safety.

Volume infused for fluid resuscitation: According to protocol, patients were fluid-resuscitated and standard-of-care vasopressor doses were optimized prior to initiating study drug. Actual volumes of fluid administered to meet inclusion criterion #4 (≥ 25 mL/kg in the previous 24 hours) were not recorded. During the first 3 hours of study drug treatment, up to 750 mL of IV fluids were allowed, but discouraged as these patients were already volume resuscitated. The mean CVP was 13.3 mmHg, which can be considered above the target CVP values of 8–12 mmHg [Rivers et al. N Engl J Med. 2001;345:1368–77]. Therefore, these data support that volume resuscitation was appropriate and even slightly above the target.

Primary outcome (MAP response at 3 hours): The target MAP at Hour 3 was obtained in 69.9% (95% CI: 62.3%-76.9%) of patients receiving LJPC-501 and in 23.4% (95% CI: 17.1%-30.8%) of patients receiving placebo. Therefore, angiotensin II was clearly superior to placebo in increasing blood pressure to MAP target > 75 mmHg. The treatment effect maintained statistical significance and a larger effect size in the multivariate model with the LJPC-501 treatment odds ratio of 12.4 (95% CI: 6.72-22.8; p < 0.0001). Other predictors of more likely achieving the target Hour 3 MAP response were no prior exposure to an ARB, chest x-ray findings of ARDS, albumin > 2.5 g/dL, and NE-equivalent dose < 0.5 µg/kg/min. The multivariate analyses of MAP response supports the results obtained in the primary univariate analysis. However, as specified in the protocol, other vasopressors were not to be increased during Hour 0 to Hour 3 unless for safety reasons. This protocol feature, which is more reflective of a proof-of concept study than of a confirmatory study, allowed for an artificial comparison in which most patients in the placebo group did not receive the best standard of care during the first 3 hours (the rule was not to up-titrate concomitant vasopressors in the control group), while the vasopressor angiotensin dose could be up-titrated in the experimental group on demand. Interestingly, even with the said protocol restriction, there was an increase in NED in the placebo group during the first 3 hours that can be explained by the "safety reason" exception included as a result of the expected life-threatening lack of efficacy of placebo in at least a proportion of these patients. The study reached the objective to confirm what is known since decades, which is that angiotensin II raises blood pressure, and also gave information about the approximate dose needed to achieve the effect with the formulation of angiotensin II intended for market authorisation, which is approximately 5 ng/kg/min in many patients and then can be adjusted depending on patients' response. It was questioned during the initial assessment of the data whether the protocol feature of delaying 3-hours the up-titration of catecholamines in the placebo group had some influence in the trend towards a decreased mortality with angiotensin. Mortality rates were higher in patients in the placebo arm who received increases in SOC vasopressors during the first 3 hours (as measured by NED) regardless of changes in MAP at Hour 3. Patients in the placebo arm with an increase in NED during the first 3 hours of treatment tended to be older and have lower Baseline MAP within both “response” and “no response” subgroups. The data suggest that the delay of titration of standard-of-care vasopressors did not have a significant effect on 28-day mortality for patients in the placebo arm. The very high and early (first hour) response in the LJPC-501 group on the primary afficacy endpoint (MAP) compared to the placebo group could have given a clear indication on the administrated treatment. The applicant clarified that reasonable actions were taken to ensure as much as possible the blinding of the randomisation (blinded and unblinded personal at clinical sites), along with the masking of treatments and the key endpoints for which measures are considered as objective.

The mean duration of exposure was statistically longer by 7 hours in the LPJC-501 arm (47h ± 27h) compared to the placebo arm (40h ± 14h). The main feature coming out from the provided analyses is the higher death rate when the treatment is prolonged beyond 51 hours compared to a shorter exposure (<51h). From 14 days follow-up till 28 days, the risk of death increases for at least 60% when the exposure is higher than 51 hours (OR=1.69, 95%CI = [0.98-2.91], p=0.05 at 28-days, with less than 51h exposure as reference). However, duration of exposure is not at random. The subgroup of patients with longer exposure may correspond to those in which MAP response is not achieved or not maintained after trying to withdraw vasopressors. Therefore, from these data it cannot be concluded that maintaining treatment longer is the responsible of patients' death, but the data suggests that prolonged vasoconstriction, regardless of the vasopressor used, can be deleterious for the patients. In this respect, given that the treatment duration is not sufficiently established and in order to avoid adverse events derived from a prolonged vasoconstriction, it was included in the SmPC posology that "*In order to prevent adverse events derived from a prolonged vasoconstriction, treatment with Giapreza should be withdrawn as soon as underlying shock is sufficiently improved".*

Cardiovascular (CV) SOFA score was chosen by the sponsor as key secondary endpoint. Between group differences in CV sofa at 48 hours were 0.47 points, which was statistically significant but of uncertain clinical relevance, as the minimum difference of clinical relevance for CV SOFA score is not defined in the literature. In addition, CV SOFA score is measuring the same thing than the primary endpoint, as achieving a SOFA score = 0 (33% of patients in the experimental group vs. 23% in the placebo group), is driving the between-group difference in CV SOFA and equals to have a response with MAP > 70 mmHg, the latter being the main component of the primary efficacy endpoint. Furthermore, the improvement in mean CV SOFA score at 48 hours by 0.47 points may be simply an artifact of the study design, which listed catecholamines but not angiotensin on the CV SCOFA score calculation (sparing part of the protocol after 3 hours). Simply replacing a vasopressor by another (i.e.: epinephrine by angiotensin) is not considered itself as clinically beneficial, as there is no evidence that angiotensin is a safer vasoconstrictor than catecholamines.

Sepsis-related organ failure assessment score, also known as **sequential organ failure assessment score** (**SOFA score**), was used as secondary endpoint. The total SOFA score ranges from 0 to 24. There is no direct conversion from SOFA score to mortality. Based on observational studies, if the SOFA score is < 8, mortality is <10%. If the total SOFA score is between 8-11, mortality is around 20-30%; for a score between 12-14, mortality is 40-60%; and for scores >15, mortality is >80%. In ATHOS-3 study, total SOFA score at baseline was approximately 11.77 points in the angiotensin group and 12.72 points in the placebo group, which was translated into a mortality rate of 46% in the angiotensin group and 54% in the placebo group at day 28. According to the CHMP calculation, the baseline imbalance in total SOFA score was statistically significant (angiotensin II SOFA score 11.77 points vs. placebo 12.72 points; Difference: -0.95; 95%CI: -1.63 to -0.27), suggesting that sicker patients were randomized to placebo. The applicant argued that a higher total SOFA score tended to be associated with poorer survival (HR = 1.38; 95% CI:0.97-1.96), but the trend was not statistically significant (p = 0.0760), and therefore the final model did not include total SOFA score. There were more patients with SOFA score >12 at baseline (poorer prognosis) in the placebo group than in the experimental group (80 vs. 65), and a higher total SOFA score was significantly associated to a higher mortality risk within the placebo group (HR: 1.84; 95%CI: 1.19 to 2.84; p=0.0053). In addition, the analysis of the relative risk of death in patients with SOFA >12 (59%; 85 or 145) versus SOFA ≤12 (43%; 74 of 171) in the overall population (regardless of treatment group) was also statistically significant (RR: 1.35; 95%CI: 1.09 to 1.69; CHMP calculation). Therefore, the trend towards a lower mortality rate in the experimental group could be partly due to an imbalance in baseline characteristics regarding organ failure (more patients with organ failure in the placebo group). Multivariate analyses including baseline SOFA as covariate (post-hoc analysis, as per CHMP request) yields a HR 0.92 (0.66 - 1.27) for the comparison between angiotensin-II and placebo in mortality. This point estimate was considered more realistic than the HR reported in the publication of the ATHOS-3 study results (HR, 0.78; 95% CI, 0.57 to 1.07; P = 0.12) (Khanna et al. N Engl J Med 2017;377:419-30.), which was not adjusted by baseline SOFA score. A confirmatory phase III study in a high-risk population was considered needed to ascertain the true effect of angiotensin-II on morbidity and further reassurance regarding mortality.

The CHMP agreed that a post-authorisation efficacy study (PAES) should be conducted as the initial efficacy assessment is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions.

A draft protocol for this post-authorization efficacy study (PAES) to be included in Annex II (LJ501-CRH06) was provided and agreed with the CHMP. The title of the study is: **A phase 4, randomised, double-blind, placebo-controlled, multicentre study of LJPC-501 in adult patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy**. The study will enrol at least 400 patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy (AKI/RRT). At least 50% of patients will be enrolled in Europe, so that at least 100 patients in Europe will be treated with LJPC-501. Given that patients recruited in Europe had a lower mortality rate than in other regions (30% in Europe vs. >50%), the expected mortality rate in the proposed study (60%) may have been overestimated. This study will confirm the potential clinical benefit imparted via improved haemodynamics. The primary endpoint will be the change in NED from Baseline to Hour 2 (#1 hierarchical). The study drug must generate an increase in blood pressure response in order for the clinician to safely decrease the NED. The secondary endpoints will include mortality (Non-inferior survival to Day 28, #2 hierarchical; and Superior survival to Day 28, #4 hierarchical), time to RRT discontinuation, RRT-free days (#3 hierarchical) as well as measurements of tissue perfusion utilising capillary refill time. The study will enrol at least 400 patients who will be randomized 1:1 to LJPC-501 or placebo. The sample size of 400 provides over 90% power to detect a treatment difference in Change in NED from Baseline to Hour 2 between LJPC-501 and placebo under the following assumptions: a) Mean change in NED from baseline to Hour 2 of −0.04 and 0.00 µg/kg/min for LJPC-501 and placebo, respectively; b) Common Standard Deviation of 0.10; c) 2-sided alpha of 0.05.

Mortality to day 28: At Day 28 the mortality was 46% in the LJPC-501 group and 54% in the placebo group in the mITT population (8% absolute risk difference). Regarding causes of death, the majority of patients died from sepsis, while cardiac or vascular death rates were only 7.9% and 12.7% in the angiotensin and placebo groups, respectively (a 4.7% absolute risk difference). In univariate analysis, the HR for all-cause mortality was 0.78 (95% CI: 0.57–1.07; unstratified logrank test). The mortality rates in the ITT (45% vs. 52%) and HR (0.80) to day 28 were very similar than the above corresponding numbers in the mITT population. The non-significant trend of improved survival in the LJPC-501 group occurred early with a mortality rate of 29% at day 7 in the angiotensin II group and 35% at Day 7 in the placebo group. The study was not powered/designed to show differences in mortality or morbidity, and therefore, the results of this, mainly proof-of-concept study, are within expected for a mortality exploratory outcome (i.e.: inconclusive). In multivariate analyses, patients with baseline MAP < 65 mmHg, APACHE II score > 30, enrolment in the US and Canada versus rest of world, chest x-ray finding of ARDS, and baseline NE-equivalent dose ≥ 0.5 µg/kg/min had significantly higher risk of mortality at Day 28. On the contrary, randomization to LJPC-501 was not a factor associated with a lower mortality risk, and the hazard ratio for LJPC-501 versus placebo in the final multivariate model was 0.89 (95% CI, 0.64–1.24; p = 0.4865). It is positive that survival tends to be in favour of the experimental group. However, the more conservative conclusion that we could take from this exploratory analysis is that, looking at the upper 95%CI of the HR in the final multivariate model for death provided (HR: 0.89; 95% CI, 0.64–1.24), a relative increase in mortality with angiotensin II ≥ 25% could be, in principle, ruled out. The level of uncertainty is marginally higher if baseline SOFA score is included as covariate (post-hoc analysis after CHMP request on D120). In this case, a relative increase in mortality ≥27% can be reasonably ruled out (HR 0.92; 95%CI: 0.66 to 1.27), which is somewhat reassuring.

Subgroup analyses of MAP response and deaths:

The sponsor analyzed 18 different pre-specified subgroup analyses, which were generally consistent with those obtained in the overall population (i.e.: consistent effect of angiotensin II versus placebo in achieving MAP response and favourable trend in survival). The group of sicker patients (i.e.: baseline MAP < 65 mmHg, Baseline APACHE-II > 30, baseline NED > 5 microg/kg/min) had less MAP response to angiotensin vs. placebo than the other subgroups, but on the contrary, a more favourable trend in survival. The applicant was requested to explore the individual correlation between both outcomes (i.e.: having a MAP response and survival; not having a MAP response and mortality) for all study patients and separately for angiotensin and placebo patients**.** With treatment groups combined, there were 62 deaths among 151 responders (41.0% mortality by Day 28) and 98 deaths among 170 nonresponders (57.6% mortality). By treatment group and MAP response, the best subgroup in mortality was comprised by the 114 responders to angiotensin-II (35% mortality), followed by 121 non-responders to placebo (52% mortality), 37 responders to placebo (59% mortality) and 49 non-responders to angiotensin (71% mortality). Therefore, MAP response was a predictor of survival in the angiotensin-II group but not in the placebo group. Overall, the data suggest that angiotensin-II may rescue some additional patients compared to placebo, and that the lack of response to angiotensin-II is a marker of poor prognosis. The potential benefit in mortality will have to be ascertained in the planned post-authorisation clinical trial included in Annex II.

The raising blood pressure effect was consistent regardless of baseline NED (above or below 0.5 microg/kg/min), and there is no need to restrict the indication to those sicker patients with a NED ≥0.5 microg/kg/min. However, it is indeed usually considered that a high NA dose is around 1 microg/kg/min (Brown SM, et al. Chest. 2013; 143:664-71). The applicant was asked to discuss what could be expected in term of benefit with a higher dose of NA. Given that only 21 patients were on NED ≥ 1 microg/kg/min at baseline, and that the trend on MAP response favoured placebo in this small subgroup, a statement has been included in the SmPC that "*the effect of Giapreza when added to maximum doses of other vasopressors is unknown*". The applicant believes that treatment with LJPC-501 is most beneficial in patients whose vasopressor doses are lower, i.e., earlier in the progression of disease, such that the outcome is still modifiable; however, there remains potential benefit in treating patients with higher NEDs as well. The trend towards lower mortality in this small subgroup suggests that this could be the case. This suggestion will be further tested in a prospective clinical trial. Given the uncertainty in MAP response in patients on maximum doses of other vasopressors, the applicant was asked to discuss and define the conditions of administration (especially time to initiate LJPC-501 relative to other vasoactive treatments) and the target population (including definition of the refractory shock) which could benefit from the LJPC-501 treatment while minimising the risk of adverse event. The CHMP requested as well the inclusion of "refractory hypotension" in the wording of the indication and this was accepted. Data from subgroups also suggest that angiotensin II increases the MAP response regardless of the baseline angiotensin levels. Therefore, the indication should not be restricted to "replacement therapy" in patients with low angiotensin II levels at baseline. The vast majority of patients (90%) had septic shock as the cause of hypotension. The following more frequent underlying cause was vasoplegia. Data from subgroups do not suggest that angiotensin II only works in septic distributive shock. In fact, the MAP response is much higher in the non-septic distributive shock subgroup than in the septic shock subgroup. In addition, the trend towards decreased mortality in the overall population seems to be obtained at expenses of the small subgroup of patients with non-septic distributive shocks (n=30). Exploratory analyses suggest that the effect size is of a greater magnitude in non-septic distributive shock than in septic distributive shock. However, patients with septic shock also had a 5-fold increase in probability of achieving a MAP response than patients with septic shock on placebo. The geographic region subgroups provided are limited to dichotomisation between North-America (4.8% of the global population) vs. rest of the world ("ROW"; 95.2% of the global population). There may be differences in

patients profiles and there are proven differences in clinical practice between regions that can influence the efficacy of angiotensin II. For example, higher catecholamine doses and less vasopressin is used in Europe compared to North-America according to the data provided. In addition, in multivariate analyses of mortality, enrolment in North-America was an independent risk factor for death. The applicant was invited to provide separately the subgroup analysis of efficacy (MAP response and mortality) for the European region, as well as to provide demographic characteristics and prior treatments (volume replacement, vasopressor use) in the European population of the pivotal study, in order to assess the external validity of the study to the European practice. In this respect, the company provided demographics and baseline characteristics by geographic region. Baseline characteristics of BMI, albumin, CVP, MELD score, APACHE II score, and total SOFA score differed across regions. Baseline norepinephrine dose and NED were higher and vasopressin use was lower in Europe. Baseline steroids were utilized more in the US and Canada. Despite these differences in baseline characteristics and treatment methods, the effect of LJPC-501 in achieving MAP response was consistent across all regions. When evaluating the data in aggregate, the European sub-population was relatively less sick than the overall population. Treatment comparisons for mortality were not statistically significant in any of the regions. The applicant did not collect data regarding volume resuscitation prior to study drug initiation. However, the inclusion criteria stipulated that the subject must be adequately fluid resuscitated in the opinion of the treating investigator and that the subject have clinical features of high-output shock (defined as: $ScvO_2$ > 70% and CVP > 8 mmHg or CI > 2.3 L/min/1.73 m^2). The variability in the baseline characteristics of the European population versus the US/Canada population may be due more to ICU admission differences between these regions, rather than a difference in the actual disease characteristics of the patients or a difference in the efficacy of LJPC-501.

Finally, ancillary univariate and multivariate analyses were provided comparing treatment effects in White and non-White subgroups, which showed that MAP response and mortality at Day 7 or Day 28 did not vary significantly by race.

AKI/RRT post-hoc subgroup analyses: The investigators have recently published a "post-hoc" subgroup analysis in a subgroup of patients with acute kidney injury (AKI) treated with renal replacement therapy (RRT) at initiation of angiotensin II or placebo (n= 45 and n= 60, respectively) [Tumlin et al, Crit Care Med. 2018;46:949-957]. This subgroup is reported in the Summary of Clinical Efficacy but not included in the ATHOS-3 CSR. Angiotensin was superior to placebo in the main outcome of MAP response in this post hoc subgroup, either in the Summary of Clinical Efficacy or in the said publication. The fact that angiotensin raises blood pressure is well understood. However, the publication is not entirely consistent with the information provided in the Summary of Clinical Efficacy regarding mortality, and claims a "robust" survival benefit attributable to angiotensin II in the AKI/RRT post-hoc analysis of this post hoc subgroup. This conclusion is not supported by the data available. In addition, the company has used an exploratory analysis of subgroups of a secondary endpoint to power the planned pivotal study. These analyses are fraught with risk, as baseline characteristics are not distributed at random. In this respect, the applicant provided an updated protocol. The study will provide reassurance that there is no detrimental effect on mortality at day 28.

Assessments of Organ Function: In the AKI/RRT subgroup, among the 60 patients with AKI receiving placebo, 9 (15%) had discontinued RRT by Day 7, compared with 17 (38%) of the 45 patients with AKI receiving LJPC-501. However, this post-hoc analysis did not consider that, in the same period, in patients with no AKI/RRT at baseline, more patients in the angiotensin group (n=13) started RRT versus only 10 on placebo (LJ501-CRH01 CSR). The small sample size in this subgroup also prevents for firm conclusions regarding the potential benefit of angiotensin II in preventing/reversing renal failure.

Other exploratory endpoints: there were not statistically significant differences between treatment groups in individual non-cardiovascular SOFA scores or in health resource utilization outcomes (i.e.: time on vasopressors, time on ventilation, stay in ICU, time in hospital). Therefore, the extent of the benefit mainly relies on the effect of increasing MAP.

Angiotensin II use in special populations: No dedicated studies have been conducted in the elderly. Main efficacy (MAP response, mortality) and safety data in ATHOS-3 trial should be provided by age ranges. No dedicated studies have been conducted in renal or hepatic impairment. The applicant provided subgroup analyses also for patients with renal failure (on AKI/RRT at baseline) and patients with hepatic impairment in the ATHOS-3 study. The information in patients >75 years is limited to 44 patients. Data available suggest that the effect on MAP response and mortality was not influenced by age, and that no a special dose-adjustment is needed in the elderly, but a statement indicating that the experience in patients > 75 years old is limited has been included in the SmPC. There were 38 patients with MELD ≥ 30 (11.8% of the mITT population) and only 9 (23.7%) survived to Day 28. The treatment effect on MAP at Hour 3 in this subgroup was not statistically significant (OR = 1.49; 95% CI: 0.40-5.49, p = 0.5520), but a higher rate of MAP responders was found in the experimental group compared with placebo (44.4% vs. 35.5%). Mortality rates at Day 28 in this subgroup with MELD ≥ 30 were 66.7% with LJPC-501 versus 85.0% with placebo (HR = 0.57; 95% CI: 0.27-1.21; p = 0.1405). Clinical outcomes in the 105 patients with AKI receiving RRT at baseline and suggest that this high risk population could be a population with a particularly relevant benefit from the treatment with LJPC-501. It is agreed that no dose adjustments are needed in patients with renal or hepatic impairment.

With respect to paediatric data, a PIP (EMEA-001912-PIP02-16-M01) has been agreed by the PDCO in 2018 (EMA Decision(s) P/0130/2018). Some measures were deferred up to March 2024. The indication targeted by the PIP is the treatment of hypotension associated with distributive or vasodilatory shock, and the population concerned by the paediatric development is the overall paediatric population, from birth to less than 18 years of age. Two clinical studies will be conducted in children (n≥100) and pediatric patients less than 2 years old (n≥40).

Supportive studies: The dossier includes an interim analysis, dated on 17 March 2018, with 53 patients included in an ongoing prospective cohort expanded access protocol with similar inclusion criteria than the ATHOS-3 study (Adult patients with distributive or vasodilatory shock who remained hypotensive despite fluid and vasopressor therapy). However, starting dose in this expanded access study is 5 ng/kg/min, while in the ATHOS-3 study the starting dose was 20 ng/kg/min. This expanded access study is relevant because it provides mortality data. Overall, 31 of 53 (59%) patients have died up to day 28, including 21 (40%) patients who died on or before Day 7. No effectiveness or demographic data are available, and between study comparisons are fraught with risk. Notwithstanding, mortality reported with angiotensin II in the expanded access protocol (59%) seems similar or even higher than that reported with placebo in the ATHOS-3 trial (54%), and much higher than the mortality rates reported with angiotensin II in the overall population ATHOS-3 trial (46%) and in the high-risk subgroup with AKI/RRT at baseline (47%). These data highlights the need for controlled data on mortality/morbidity versus best standard of care, to assess whether an increase in MAP versus placebo shown in the ATHOS-3 trial would translate into a reduced morbidity-mortality.

2.5.4. Conclusions on the clinical efficacy

Angiotensin II raises blood pressure in patients with hypotension due to distributive shock (mainly septic shock) who remain hypotensive despite volume resuscitation and administration of catecholamines, with or without other vasopressors. The effect is consistent across a wide number of subgroups and ancillary analyses. However, the evidence is primarily based on the results of a single pivotal study that mainly enrolled patients from North-America, of whom only about 6% received a high vasopressor dose at baseline (NED > 1 microg/kg/min), which is poorly representative of European practice. In the responses to the CHMP list of outstanding issues, the applicant proposed a new wording of the indication and posology to define the conditions of administration and the target population which could benefit from the LJPC-501 treatment while minimising the risk of adverse event. After some discussions and modifications, the wording was considered acceptable.

In addition, mortality was assessed as exploratory endpoint. There were no significant differences between groups in survival, which was within expected, as the study was not powered to detect such differences. The scarce data available (i.e.: lack of improvement in SOFA score) are not in support of a correlation between MAP response and prevention/reversal of organ failure. Whether the angiotensin II blood pressure raising effect is associated with a benefit in morbidity-mortality is pending to be established. It was included in section 5.1 of the SmPC that "the effect of Giapreza on morbidity and mortality has not yet been determined in appropriate studies". A post-authorization efficacy study (PAES) in a subpopulation at high risk (e.g.: patients with renal failure on AKI/RRT, with or without concomitant liver failure, MELD score ≥ 30, ARDS, SOFA score at baseline >15, baseline MAP < 65 mmHg, APACHE II score > 30, baseline NE-equivalent dose ≥ 0.5 µg/kg/min) was considered needed to further investigate the potential benefit of the product in preventing organ damage and prolonging survival, as well as the impact of treatment in the Clinical Global Impressions-Improvement scale (CGI-I), to quantify and track patient progress and treatment response over time. The protocol of the PAES was agreed upon by CHMP during the procedure. The PAES was requested as the initial efficacy assessment is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions.

Therefore, the CHMP considers the following measures necessary to address issues related to efficacy:

Post-authorisation efficacy study (PAES): In order to further investigate the efficacy and safety of Giapreza in the treatment of refractory hypotension in adults with septic or other distributive shock, the MAH should conduct and submit the results of a randomized, double-blind placebo-controlled multicentre study in adult patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy to provide: (1) data on the effect of the product on morbidity events and organ perfusion with and adequate representation of European patients, (2) reassurance that there is no detrimental effect on mortality at day 28, (3) additional safety data about ischemic and thromboembolic events associated with the use of the product and (4) the record of clinical global impression of the response to treatment .

2.6. Clinical safety

The primary data to support the safety of LJPC-501 derive from the Phase 3 study LJ501-CRH01 which included 321 patients who were representative of severely ill patients with vasodilatory shock who remain hypotensive despite receiving fluid and vasopressor therapy, with this condition being referred to as CRH in the LJ501-CRH01 trial. Two other company-sponsored trials were submitted: a) Expanded Access Study LJ501-EAP01: open-label, multicentre, expanded access treatment protocol conducted in the US (LJ501-EAP01 CSR). An interim analysis including 53 adult patients with refractory hypotension in shock has been submitted; b) A phase 1/2 Study LJPC-501-CS-5001 single-arm, open-label, non-randomised, multicentre safety and tolerability study of LJPC-501 (angiotensin II) in 6 patients with HRS designed to determine a maximum tolerated dose of LJPC-501 in that population. Finally, there are also safety data available from literature that are considered as supportive (Table 25).

Table 23 Clinical Studies Investigating LJPC-501 and Literature Reports Supporting the Safety of Angiotensin II in Research Subjects and Patients Treated for Shock

Study/Reference	Study (angiotensin II form)	Study Population
Clinical studies		
LJ501-CRH01/ Khanna 2017	Prospective Phase 3 randomized, placebo-controlled, double-blind, multicenter safety and efficacy study (LJPC-501) (Ile^5-angiotensin II)	321 adults with CRH received study drug (158 placebo-treated, 163 LJPC-501-treated)
LJPC-501-CS-5001	Phase 1/2 single group, dose escalation, open-label safety and tolerability study (LJPC-501) (Ile^5-angiotensin II)	6 adults with Type 1 HRS received LJPC-501
LJ501-EAP01	Expanded Access for LJPC-501 (Ile^5-angiotensin II)	53 adults with CRH received LJPC-501
Published studies: 70 patients with vasodilatory shock		
Chawla 2014	IV angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study (Ile^5-angiotensin II)	10 received angiotensin II in combination with norepinephrine, other vasopressors 10 received placebo in combination with norepinephrine, other vasopressors
Singh 1966	Comparative study of angiotensin and nor-adrenaline in hypotensive states (shock) (Val^5-angiotensin II amide)	25 received angiotensin II 25 received norepinephrine (noradrenaline)
Published studies: 72 healthy, normotensive subjects		
Brod 1969	Comparison of haemodynamic effects of equipressor doses of IV angiotensin and noradrenaline in man (Val^5-angiotensin II amide)	15 received angiotensin II /norepinephrine (noradrenaline) in crossover
Broughton Pipkin 1981	Angina-like pain: an unexpected side-effect following the simultaneous administration of angiotensin II and prostaglandin E_2 in normal adults (Val^5-angiotensin II amide)	2 received angiotensin II

Study/Reference	Study (angiotensin II form)	Study Population
Published studies: 72 healthy, normotensive subjects (continued)		
Hausdorf 1987	Non-invasive assessment of end-systolic pressure-length and stress-shortening relationships in normal individuals: significance of different loading conditions induced by methoxamine and angiotensin II (unknown)	30 received angiotensin II 10 received methoxamine
Lim 2007	Angiotensin II type 1 receptor *1166A/C* polymorphism in association with blood pressure response to exogenous angiotensin II (Ile^5-angiotensin II)	13 received angiotensin II
Sluiter 1987	The natriuretic effects of the dihydropyridine calcium antagonist felodipine: a placebo-controlled study involving IV angiotensin II in normotensive volunteers (Val^5-angiotensin II amide)	12 received angiotensin II /felodipine in crossover
Systematic review of safety: 31 281 subjects		
Busse 2017	Clinical experience with IV angiotensin II administration: a systematic review of safety (Val^5-angiotensin II amide, Ile^5-angiotensin II, or not reported)	31 281 subjects (healthy volunteers and patients, adults and children)

Abbreviations: CRH=catecholamine-resistant hypotension; HRS=hepatorenal syndrome; Ile^5-angiotensin II=angiotensin II with isoleucine at amino acid #5 (Clinalfa formulation, Bachem AG); IV=intravenous; Val^5-angiotensin II amide=angiotensin II with valine at amino acid #5 and amide substitution on amino acid #1 (Hypertensin, Ciba-Geigy)

Phase 3 Study LJ501-CRH01

LJ501-CRH01 was a Phase 3, placebo-controlled, randomised, double-blind, parallel group, international multicentre study of LJPC-501 in 321 patients with catecholamine resistant hypotension (CRH). A placebo-controlled design was appropriate, given that patients continued to receive standard-of-care therapy in both groups of the study.

The Safety population used in summarising all safety data was defined independently. In practice, this population was identical to the primary efficacy analysis set, the modified intent-to-treat population (mITT). For all safety analyses, patients were analysed as treated, which in all cases was the same as treatment randomisation. Safety assessments and collection windows are summarised in Table 26, below:

Table 24 Safety Assessment in the Phase 3 Study LJ501-CRH01

Assessment	Time Point or Period
Study drug administration	Hour 0 to 3, Hour 3 to 48, and Hour 48 until last study drug
Treatment-emergent adverse events (TEAEs)	Hour 0 through End of Study (Day 7 or 3 days after last study drug)
Serious adverse events (SAEs)	Hour 0 through Day 28
Deaths	Hour 0 through Day 28
AEs of special interest (predefined vasopressor toxicity events)	Hour 0 through Day 28
12-lead electrocardiograms	Screening/Baseline and Hour 48
Limited physical examination	Screening and Day 7/End of Study
Haematology[a] and clinical chemistry[b]	Screening, Day 1 at 3 hours, and Day 2 at 48 hours
Systolic and diastolic blood pressure, respiration rate, and temperature	Screening, just prior to initiation of study drug on Day 1, Day 1 at 3 hours, Day 1 at 24 hours, Day 2 at 48 hours, and once daily on Days 3 to 7

[a] **Haematology parameters**: red blood cells, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width, reticulocytes, platelets, white blood cells, differential (lymphocytes, neutrophils, eosinophils, basophils, monocytes)

[b] **Clinical chemistry parameters**: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyltransferase, creatinine, blood urea nitrogen, uric acid, phosphate, glucose, albumin, total protein, calcium, bicarbonate, chloride, sodium, potassium, magnesium, lactic acid.

Other haemodynamic measurements were collected as efficacy assessments, including MAP, heart rate, central venous pressure, and cardiac output. Organ function was assessed using the Sequential Organ Failure Assessment (SOFA) scoring for the respiratory system (PaO2/FiO2), nervous system (Glasgow Coma Scale), cardiovascular (CV) system (MAP or vasopressors required), liver (bilirubin), coagulation (platelets) and renal (creatinine or urine output). Laboratory assessments were carried out for haematology, urinalysis, clinical chemistry, biomarkers (angiotensin I and II) and a pregnancy test at investigators' discretion.

Expanded Access Study LJ501-EAP01

Study LJ501-EAP01 was an open-label, multicentre, expanded access treatment protocol conducted in the US (LJ501-EAP01 CSR). Adult patients with septic or other distributive shock who remained hypotensive despite fluids and vasopressor therapy and who were hospitalized in an intensive care unit setting were eligible to participate and receive LJPC-501. Up to 300 patients from sites in the US were allowed to be enrolled in the study.

Phase 1/2 Study LJPC-501-CS-5001

Study LJPC-501-CS-5001 was a Phase 1/2, single-arm, open-label, non-randomised, multicentre safety and tolerability study of LJPC-501 (angiotensin II) in 6 patients with HRS designed to determine a maximum tolerated dose of LJPC-501 in that population. The planned duration of treatment was 5 days, with 7 days of follow up, but treatment could have been extended up to 14 days if the patient was showing signs of improvement. In addition to standard safety assessments, serum creatinine, ascites, urine output, and sodium excretion were monitored.

Studies from the Literature

Literature data supporting the safety of LJPC-501 was derived from 7 studies (see Table 1, above). The studies were selected for this application from a systematic review (Busse 2017) of studies using IV angiotensin II because safety event data were collected prospectively, either as stated in methods, or a table of AEs was presented in the publication. These included 2 randomised, controlled studies of angiotensin II versus placebo or norepinephrine in 70 patients with vasodilatory shock. Also included were 5 studies in 72 healthy, normotensive volunteers which prospectively collected safety events. Verbatim adverse event terms from the 2 studies in patients with vasodilatory shock (Chawla 2014, Singh 1966) were converted to MedDRA preferred terms.

- **Published Randomised, Controlled Studies of Angiotensin II in Patients with Vasodilatory Shock**

  Two studies of angiotensin II in patients with vasodilatory shock were identified that collected adverse event data:

- *Chawla 2014:* A study in 20 patients with high output shock compared Ile5-angiotensin II (Bachem) (n=10) to placebo (n=10) when added to ongoing norepinephrine and other vasopressors. Study drugs were titrated to effect with a goal of maintaining MAP at approximately 65 mmHg while reducing the norepinephrine dose over a 6-hour period. This study was sponsored by George Washington University (NCT01393782).
- *Singh 1966:* A study in 50 patients with vasodilatory shock of various aetiologies (mostly related to infections) compared Val5-angiotensin II amide (n=25) to norepinephrine (n=25) for efficacy and safety. Both drugs were titrated to effect, ie, blood pressure support.

- **Published Studies of Angiotensin II in Healthy Volunteer Subjects**

Five studies were identified in which 72 healthy, normotensive subjects received IV infusions of angiotensin II. Blood pressure was monitored, and AE data were collected. The study titles and sample sizes are listed in Table 1; further details on study designs are provided in Table 58 in Section 8.3. Three studies administered incremental dose series of angiotensin II (Lim 2007, Sluiter 1987, Broughton Pipkin 1981) before and after other drugs and 2 administered dose titrations to a predetermined pressor response (Hausdorf 1987, Brod 1969).

Patient exposure

Phase 3 Study LJ501-CRH01 in Patients with CRH: Median duration of exposure was 48 hours in both treatment groups. The mean (SD) duration of exposure in the placebo group of 40.4 (14.24) hours was significantly shorter than 47.0 (27.11) hours in the LJPC-501 group (p=0.0072). Twenty-five patients continued LJPC-501 after Hour 48, defined for analysis purposes as at least 51 hours after initiating study drug administration. The maximum duration of study drug infusion was 60 hours in the placebo group and 168 hours (1 patient) in the LJPC-501 group; 13 patients received at least 72 hours of LJPC-501 compared with no patients in the placebo group, 1 patient (060-004) was still on LJPC-501 at 168 hours.

Table 25 Duration of Exposure to Study Drug (LJ501-CRH01 mITT/Safety)

	Placebo (N=158)	LJPC-501 (N=163)	p value
Number exposed	158	163	
Duration of exposure, hours			
Mean (SD)	40.4 (14.24)	47.0 (27.11)	0.0072
Median	48.0	48.0	
Range	0.7 - 60.1	3.5 - 168.0	
Duration of exposure, n (%)			
> 0 to < 3 hours	3 (1.9%)	0	
3 to < 45 hours	51 (32.3%)	61 (37.4%)	
45 to < 51 hours	99 (62.7%)	77 (47.2%)	
51 to < 72 hours	5 (3.2%)	12 (7.4%)	
≥ 72 hours	0	13 (8.0%)	

Source: LJ501-CRH01 CSR Table 14.3.1.1

Expanded Access Study LJ501-EAP01

The mean (SD) duration of exposure was 62.9 (51.6) hours among 53 patients who received LJPC-501 in study LJ501-EAP01 (LJ501-EAP01 Interim CSR, Table 14.2.1. The maximum duration of exposure was 241.25 hours, and 15 (28.3%) patients received study drug for 72 hours or longer.

Phase 1/2 Study LJPC-501-CS-5001

The range of LJPC-501 treatment durations across the 6 patients in the study was 2,040 to 10,854 minutes (34.0 to 180.9 hours) with a median duration of 70.4 hours. Mean (SD) duration of LJPC-501 infusion was 90.1 (57.19) hours. Mean (SD) cumulative exposure to LJPC-501 was 216.0 (277.13) µg/kg. When the dose rate was averaged over the duration of infusion for each patient, the mean infusion rate was 39.86 ng/kg/min with a range of 1.3 to 119.7 ng/kg/min.

Studies from the Literature

For the 7 studies that reported prospective safety data, the reported infusion rate normalized by body weight ranged from 0.5 to 3780 ng/kg/min (Table 1). Some studies administered bolus injections of a few micrograms. Others reported doses unadjusted by body weight. Most subjects from these published studies received Val5-angiotensin II amide (manufactured as Hypertensin).

Adverse events

Analysis of Adverse Events in the Phase 3 Study LJ501-CRH01

Treatment-emergent adverse events (TEAEs) were collected from the time of first dose to end of study (Day 7 - 10). All serious adverse events (SAEs) including deaths were collected from time of first dose through to Day 28 (follow-up). An overview of TEAEs is displayed in Table 28. Fewer LJPC-501-treated patients than placebo-treated patients experienced at least one reported TEAE (87.1% versus 91.8%), Grade 3/4 TEAE (65.6% versus 69.6%), SAE (60.7% versus 67.1%), or fatal event (46.6% versus 53.8%). Similarly, fewer LJPC-501-treated patients discontinued treatment due to an AE than placebo-treated patients, 14.1% versus 21.5%, respectively. Overall, 20.9% of LJPC-501-treated patients and 12.0% of placebo-treated experienced at least 1 TEAE that the investigator considered at least possibly related to study drug.

Table 26 Overview of Treatment-emergent Adverse Events (LJ501-CRH01, Safety Population)

Adverse Event Category	Placebo (N=158)		LJPC-501 (N=163)	
	No. of Events	No. (%) of Patients	No. of Events	No. (%) of Patients
All TEAEs				
All	562	145 (91.8%)	669	142 (87.1%)
Related to study drug	24	19 (12.0%)	64	34 (20.9%)
Grade 3/4 TEAEs				
All	189	110 (69.6%)	206	107 (65.6%)
Related to study drug	7	7 (4.4%)	19	15 (9.2%)
Non-serious TEAES				
All	395	110 (69.6%)	498	110 (67.5%)
Related to study drug	16	12 (7.6%)	49	27 (16.6%)
Treatment-emergent SAEs				
All	167	106 (67.1%)	171	99 (60.7%)
Related to study drug	8	7 (4.4%)	15	9 (5.5%)
TEAEs resulting in discontinuation of study drug				
All	34	34 (21.5%)	24	23 (14.1%)
Related to study drug	3	3 (1.9%)	3	3 (1.8%)
Fatal outcome TEAEs				
All	85	85 (53.8%)	76	76 (46.6%)
Related to study drug	0	0	1	1 (0.6%)

Source: LJ501-CRH01 CSR Table 14.3.2.1
Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Note: For each category, patients are counted once even if they experienced multiple events. Related to study drug is by investigator assessment that the event was possibly, probably, or definitely related to study drug.
The overall mortality in the mITT population to Day 28 in the LJPC-501 group was 22% lower than that in the placebo group with a hazard ratio of 0.784 (95% CI: 0.574-1.069; p = 0.1229 unstratified log-rank test), see Module 2.7.3 Section 3.4.

Common Adverse Events

Common TEAEs (≥ 5% of patients, regardless of severity) and Grade 3/4 TEAEs (≥ 2% of patients) are summarized in Table 13. By system organ class (SOC), in both treatment groups, TEAEs in the Cardiac Disorders SOC were most commonly reported; 41.8% of patients in the placebo group and 35.0% in the LJPC-501 group experienced at least 1 cardiac TEAE (Table 29). Next most common in the LJPC-501 group were TEAEs in the Metabolism and Nutrition Disorders SOC (32.5%) and Infections and Infestations SOC (30.1%) compared with 27.2% and 19.0%, respectively, in the placebo group.

The most common individual AE was multi-organ failure, which occurred at a similar frequency in both treatment groups, 25 (15.3%) patients in the LJPC-501 group versus 24 (15.2%) patients on placebo. The next most common was atrial fibrillation which also occurred at a similar frequency in both treatment groups with 22 (13.5%) patients in the LJPC-501 group versus 21 (13.3%) patients on placebo. Septic shock was more common in the LJPC-501 group with 18 (11.0%) patients versus 10 (6.3%) on placebo. Hypotension was higher in the LJPC-501 group with 17 (10.4%) patients versus 10 (6.3%) on placebo. Delirium occurred in 9 patients (5.5%) in the LJPC-501 group versus one patient (0.6%) on placebo. Grade 3/4 TEAEs showed no notable imbalances between the treatment groups.

Table 27 Treatment-emergent Adverse Events (≥ 5% of Patients in Either Treatment Group) and Grade 3 or 4 Events (≥ 2%) (LJ501-CRH01 Safety Population)

System Organ Class Preferred Term	Number (%) of Patients			
	Any Severity		Grade 3/4	
	Placebo (N=158)	LJPC-501 (N=163)	Placebo (N=158)	LJPC-501 (N=163)
Overall	145 (91.8%)	142 (87.1%)	110 (69.6%)	107 (65.6%)
Cardiac disorders	66 (41.8%)	57 (35.0%)	34 (21.5%)	27 (16.6%)
Atrial fibrillation	21 (13.3%)	22 (13.5%)	3 (1.9%)	3 (1.8%)
Bradycardia	11 (7.0%)	7 (4.3%)	4 (2.5%)	1 (0.6%)
Cardiac arrest	9 (5.7%)	7 (4.3%)	9 (5.7%)	7 (4.3%)
Ventricular tachycardia	8 (5.1%)	5 (3.1%)	3 (1.9%)	4 (2.5%)
Cardio-respiratory arrest	5 (3.2%)	3 (1.8%)	5 (3.2%)	3 (1.8%)
Cardiogenic shock	4 (2.5%)	2 (1.2%)	4 (2.5%)	2 (1.2%)
Metabolism & nutrition disorders	43 (27.2%)	53 (32.5%)	4 (2.5%)	8 (4.9%)
Hypokalaemia	10 (6.3%)	13 (8.0%)	0	0
Hypophosphataemia	11 (7.0%)	6 (3.7%)	0	0
Infections & infestations	30 (19.0%)	49 (30.1%)	19 (12.0%)	30 (18.4%)
Septic shock	10 (6.3%)	18 (11.0%)	10 (6.3%)	16 (9.8%)
Sepsis	5 (3.2%)	3 (1.8%)	4 (2.5%)	3 (1.8%)
Vascular disorders	31 (19.6%)	43 (26.4%)	14 (8.9%)	23 (14.1%)
Hypotension	10 (6.3%)	17 (10.4%)	3 (1.9%)	9 (5.5%)
Hypertension	9 (5.7%)	9 (5.5%)	0	0
Peripheral ischaemia	4 (2.5%)	7 (4.3%)	3 (1.9%)	5 (3.1%)
Distributive shock	4 (2.5%)	1 (0.6%)	4 (2.5%)	1 (0.6%)

System Organ Class Preferred Term	Number (%) of Patients			
	Any Severity		Grade 3/4	
	Placebo (N=158)	LJPC-501 (N=163)	Placebo (N=158)	LJPC-501 (N=163)
Respiratory, thoracic & mediastinal disorders	41 (25.9%)	39 (23.9%)	24 (15.2%)	21 (12.9%)
Pleural effusion	9 (5.7%)	9 (5.5%)	0	1 (0.6%)
Respiratory failure	12 (7.6%)	9 (5.5%)	11 (7.0%)	8 (4.9%)
Acute respiratory failure	5 (3.2%)	5 (3.1%)	5 (3.2%)	4 (2.5%)
Gastrointestinal disorders	32 (20.3%)	38 (23.3%)	9 (5.7%)	4 (2.5%)
Blood & lymphatic system disorders	25 (15.8%)	28 (17.2%)	9 (5.7%)	4 (2.5%)
Anaemia	10 (6.3%)	12 (7.4%)	3 (1.9%)	2 (1.2%)
Thrombocytopenia	11 (7.0%)	16 (9.8%)	4 (2.5%)	1 (0.6%)
Psychiatric disorders	11 (7.0%)	21 (12.9%)	0	0
Agitation	8 (5.1%)	6 (3.7%)	0	0
Delirium	1 (0.6%)	9 (5.5%)	0	0
Nervous system disorders	19 (12.0%)	14 (8.6%)	10 (6.3%)	8 (4.9%)
Hepatobiliary disorders	10 (6.3%)	8 (4.9%)	6 (3.8%)	6 (3.7%)
Skin & subcutaneous tissue disorders	11 (7.0%)	22 (13.5%)	2 (1.3%)	3 (1.8%)
Renal & urinary disorders	18 (11.4%)	16 (9.8%)	6 (3.8%)	4 (2.5%)
Acute kidney injury	10 (6.3%)	8 (4.9%)	2 (1.3%)	2 (1.2%)
General disorders & administration site conditions	39 (24.7%)	45 (27.6%)	27 (17.1%)	27 (16.6%)
Multi-organ failure	24 (15.2%)	25 (15.3%)	24 (15.2%)	25 (15.3%)
Investigations	30 (19.0%)	30 (18.4%)	5 (3.2%)	9 (5.5%)
Injury, poisoning & procedural complications	9 (5.7%)	11 (6.7%)	3 (1.9%)	2 (1.2%)

Source: LJ501-CRH01 CSR Table 14.3.2.2, Table 14.3.2.12
Note: Number of patients experiencing events one or more times, the percentage is of all patients assessed for adverse events.

Adverse Events in the European study subpopulation: Only 33 European patients contributed to the safety population (19 on angiotensin II and 14 on placebo). In the company's opinion, the overall study population is considered to be representative of the European population in terms of safety. However, compared to placebo there were more cardiac disorders (47% vs 14%), mainly atrial fibrillation, and vascular disorders (47% vs 29%), mainly peripheral ischemia, with angiotensin II in the European subpopulation.

Adverse Events by Severity: Approximately a quarter of all patients in both treatment groups experienced TEAEs that were mild to moderate, but over half of patients had at least 1 life-threatening event (50.9% of LJPC-501-treated patients and 58.9% of patients receiving placebo). Overall, 65.6% of patients in the LJPC-501 group versus 69.6% of patients in the placebo group experienced a Grade 3/4 TEAE. Multi-organ failure was the most common event in both groups with 25 (15.3%) patients in the LJPC-501 group versus 24 (15.2%) on placebo. Grade 3/4 septic shock was more common in the LJPC-501 group with 16 (9.8%) patients in the LJPC-501 group versus 10 (6.3%) on placebo, as was Grade 3/4 hypotension with 9 (5.5%) patients in the LJPC-501 group versus 3 (1.9%) on placebo. Grade 3/4 respiratory failure was more common in the placebo group with 8 (4.9%) patients in the LJPC-501 groups versus 11 (7.0%) on placebo.

Adverse Events by Investigator Assessment of Relatedness: Overall, 34 (20.9%) patients in the LJPC-501 group versus 19 (12.0%) patients in the placebo group experienced at least 1 TEAE that the investigator considered at least possibly related to study drug (Table 30). The most common related TEAEs were atrial fibrillation with 10 (6.1%) patients in the LJPC-501 group versus 4 (2.5%) in the placebo group, peripheral ischaemia with 5 (3.1%) patients in the LJPC-501 group versus 3 (1.9%) on placebo, and hypertension with 4 (2.5%) in the LJPC-501 group versus 1 (0.6%) on placebo.

Table 28 Most Frequent (> 1% in Either Treatment Group) Treatment-Emergent Adverse Events Related to Study Drug (Safety Population)

System Organ Class Preferred Term	Number (%) of Patients	
	Placebo (N=158)	LJPC-501 (N=163)
Overall	19 (12.0%)	34 (20.9%)
Cardiac disorders	8 (5.1%)	14 (8.6%)
Atrial fibrillation	4 (2.5%)	10 (6.1%)
Tachycardia	0 (0.0%)	3 (1.8%)
Vascular disorders	4 (2.5%)	11 (6.7%)
Hypertension	1 (0.6%)	4 (2.5%)
Peripheral ischaemia	3 (1.9%)	5 (3.1%)
Poor peripheral circulation	0 (0.0%)	2 (1.2%)
Investigations	3 (1.9%)	7 (4.3%)
Blood lactic acid increased	0 (0.0%)	2 (1.2%)
Cardiac output decreased	0 (0.0%)	2 (1.2%)
Gastrointestinal disorders	3 (1.9%)	6 (3.7%)
Intestinal ischaemia	2 (1.3%)	1 (0.6%)
Metabolism and nutrition disorders	2 (1.3%)	4 (2.5%)
Hypernatraemia	2 (1.3%)	0 (0.0%)
Blood and lymphatic system disorders	0 (0.0%)	2 (1.2%)
Thrombocytopenia	0 (0.0%)	2 (1.2%)
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	2 (1.2%)
Skin and subcutaneous tissue disorders	0 (0.0%)	3 (1.8%)

Source: LJ501-CRH01 CSR Table 14.3.2.9
Note: Number of patients experiencing events one or more times, the percentage is of all patients assessed for adverse events. Related = Possibly, Probably or Definitely

Adverse Events by Study Period

The frequency of TEAEs increased in both treatment groups from Hour 0 to 3 to Hour 3 to 48 and from Hour 3 to 48 to Hour 48 to end of study (Table 18). These study periods represent different time durations as well as different exposures to study drug and individual changes in clinical status. During Hour 0 to 3, 11.0% of LJPC-501-treated patients and 8.9% of placebo-treated experienced TEAEs with no discernible pattern of imbalance in frequency between treatment groups. The most frequent events were in the Cardiac Disorders SOC with 3 (1.8%) patients in LJPC-501 group and 5 (3.2%) patients in the placebo group. During the Hour 3 to Hour 48 treatment period, the frequencies of TEAEs were 62.0% in the LJPC-501 group and 63.9% in the placebo group. The most frequent TEAE was atrial fibrillation which occurred in 18 (11.0%) patients in the LJPC-501 group versus 12 (7.6%) patients in the placebo group. Thrombocytopenia was reported in 10 (6.1%) patients in the LJPC-501 group versus 6 (3.8%) patients in the placebo group. During the Hour 48 to End of Study treatment period, multi-organ failure was the most frequent TEAE, which occurred at a similar frequency between treatment groups: 16 (11.3%) patients in the LJPC-501 group versus 16 (12.4%) in the placebo group. Hypotension occurred with higher frequency in 14 (9.9%) patients in the LJPC-501 group versus 7 (5.4%) patients in the placebo group, as did septic shock with 10 (7.0%) patients in the LJPC-501 group versus 5 (3.9%) in the placebo group.

Adverse Events by Total Exposure to LJPC-501

LJPC-501 is titrated to haemodynamic effect and therefore drug exposure was expected to vary across the patient population. Among patients requiring higher doses of LJPC-501, a greater proportion of patients had MAP < 65 mmHg at Baseline and required a NED ≥ 0.5 µg/kg/min. The mean (SD) NED at Baseline was 0.38 (0.318) µg/kg/min in the lower exposure group (LJPC-501 ≤ 36.36 µg/kg) and 0.53 (0.371) µg/kg/min in the higher exposure group (p=0.0014). Baseline differences within the LJPC-501 group suggest that patients who required higher doses of LJPC-501 had more refractory disease, confounding the interpretation of TEAEs by drug exposure. An analysis of TEAEs by overall exposure to LJPC-501 over the duration of therapy was performed for the 2 subgroups based on median exposure, ie, those receiving ≤ 36.36 µg/kg and those receiving > 36.36 µg/kg. Most TEAEs by preferred term occurred more frequently in the higher exposure group with 76 (93.8%) patients experiencing any TEAE versus 66 (80.5%) in the lower exposure group. Multi-organ failure was more than twice as frequent in the higher LJPC-501 exposure subgroup with 17 (21.0%) patients versus the lower exposure subgroup with 8 (9.8%) patients. The frequency of atrial fibrillation was higher in the higher exposure group, with 12 (14.8%) patients, versus 10 (12.2%) patients in the lower exposure group, as were septic shock with 10 (12.3%) versus 8 (9.8%) patients and hypotension with 9 (11.1%) versus 8 (9.8%) patients. All 5 (6.2%) patients experiencing ventricular tachycardia in the LJPC-501 treatment group were in the higher exposure subgroup. Grade 3/4 TEAEs occurred more frequently in the higher exposure subgroup with 67 (82.7%) patients than in the lower exposure group with 40 (48.8%) patients. The events of multi-organ failure described above were all Grade 3/4 TEAEs. Other notable imbalances between exposure groups for Grade 3/4 TEAEs were septic shock with 9 (11.1%) patients in the higher exposure group versus 7 (8.5%) patients in the lower exposure group; respiratory failure with 6 (7.4%) versus 2 (2.4%); peripheral ischaemia with 4 (4.9%) versus 1 (1.2%); cardiac arrest with 5 (6.2%) versus 2 (2.4%); and ventricular tachycardia with 4 (4.9%) versus no patients in the lower exposure group.

Adverse Events by Baseline Vasopressor Doses: Vasopressor doses above 0.5 µg/kg/min reflect a more refractory disease and are generally associated with mortality rates > 50% (Bassi 2013). In the LJPC-501 treatment group, patients with higher Baseline NEDs (NED ≥ 0.5 µg/kg/min) received higher doses of LJPC-501 during the treatment period with a mean (SD) dose titration of 32.17 (25.980) ng/kg/min compared with 16.41 (17.434) ng/kg/min among patients with Baseline NED < 0.5 µg/kg/min. Treatment durations were similar. Adverse events were more frequently reported for patients receiving higher doses of vasopressors at Baseline in both treatment groups. In the higher vasopressor dose subgroup, TEAEs were less frequent in the LJPC-501 group for 20 (43.5%) versus 24 (50.0%) patients on placebo for the SOC of Cardiac Disorders, however they were more frequent for Infections and Infestations with 19 (41.3%) patients in the LJPC-501 group versus 13 (27.1%) on placebo; for Metabolism and Nutrition Disorders with 15 (32.6%) in the LJPC-501 group versus 13 (27.1%) on placebo; for General Disorders and Administration Site Conditions with 14 (30.4%) in the LJPC-501 group versus 9 (18.8%) on placebo; and Gastrointestinal Disorders with 13 (28.3%) in the LJPC-501 group versus 6 (12.5%) on placebo.

Adverse Events in Patients Not Receiving Vasopressin: Overall frequency of TEAEs between the treatment groups was similar with 44 (84.6%) patients in the LJPC-501 group versus 45 (83.3%) on placebo.

Transient Hypertension

Within the LJPC-501 group, there were 37 patients who were more sensitive to the effects of LJPC-501 and experienced an increase in MAP to above 100 mmHg (range: 101.3 to 142 mmHg) within 15 minutes of initiating study drug. Study drug dose was then down-titrated in all 37 patients and the median time to MAP below 85 mmHg was 25 minutes (range: 7 to 65 minutes).

Amongst the 37 patients in the LJPC-501 group, the mean NED at Baseline was notably lower than that for the full population (mean: 0.33 versus 0.45 µg/kg/min). Even so, 33 (89.2%) these patients had a Baseline MAP ≥ 65 mmHg. These patients experienced a rapid elevation of MAP upon initiation of LJPC-501 (20 ng/kg/min), with a mean time to MAP > 100 mmHg of 5.4 minutes and mean maximum MAP of 111.7 mmHg. Per protocol, these patients had the study drug rapidly down-titrated.

That the mean dose of LJPC-501 was only 10.2 ng/kg/min at MAP > 100 mmHg, demonstrates that investigators initiated down-titration ahead of maximum MAP to correct the hypertensive overshoot in target blood pressure. Correction of this overshoot was rapid. Mean time to MAP < 85 mmHg was 26.4 minutes, demonstrating the ability to promptly reduce MAP in patients who are found to be particularly sensitive to angiotensin II.

This transient hypertension is distinct from hypertension recorded as an AE throughout the study. The frequency of hypertension recorded as an AE through Day 28 was 5.5% in the LJPC-501 group and 5.7% in the placebo group.

Adverse Events of Special Interest

AESIs in the Phase 3 study were defined in the study protocol and the statistical analysis plan and are generally recognised as signs of vasopressor toxicity. These included: a) Myocardial infarction/ischaemia, not simply elevated troponin levels; b) Relevant dysrhythmias including atrial fibrillation; c) Re-entrant atrio-ventricular nodal tachycardia, or ventricular tachycardia; d) Cerebral ischaemia; e) Hypoperfusion such as digital ischaemia, mesenteric ischaemia or shock, liver or renal hypoperfusion; f) Local vasoconstriction or necrosis at or near infusion site; g) QT prolongation.

AESIs were aggregated across SOCs into 2 broad categories, Cardiac and Ischaemic. Overall, 31.3% of LJPC-501 and 34.8% of placebo-treated patients experienced at least 1 AESI, either Ischaemic or Cardiac. Ischaemic events were aggregated from SOCs of Nervous System Disorders, Vascular Disorders, Gastrointestinal Disorders, Hepatobiliary Disorders, and Skin and Subcutaneous Tissue Disorders.

Table 29 Treatment-emergent Adverse Events of Special Interest: Ischaemic Events (Safety Population)

AESI Category Preferred Term	Number (%) of Patients			
	Any Severity		Grade 3/4	
	Placebo (N=158)	LJPC-501 (N=163)	Placebo (N=158)	LJPC-501 (N=163)
Any ischaemic event	13 (8.2%)	15 (9.2%)	8 (5.1%)	13 (8.0%)
Peripheral ischaemia	4 (2.5%)	7 (4.3%)	3 (1.9%)	5 (3.1%)
Ischaemic hepatitis	4 (2.5%)	2 (1.2%)	1 (0.6%)	2 (1.2%)
Poor peripheral circulation	0	2 (1.2%)	0	2 (1.2%)
Intestinal ischaemia	3 (1.9%)	1 (0.6%)	3 (1.9%)	1 (0.6%)
Skin necrosis	1 (0.6%)	1 (0.6%)	0	1 (0.6%)
Brain hypoxia	0	1 (0.6%)	0	1 (0.6%)
Hypoxic-ischaemic encephalopathy	0	1 (0.6%)	0	1 (0.6%)
Ischaemic stroke	0	1 (0.6%)	0	1 (0.6%)
Vasospasm	0	1 (0.6%)	0	0
Cerebral infarction	0	1 (0.6%)	0	0
Cerebral ischaemia	1 (0.6%)	0	1 (0.6%)	0
Peripheral coldness	1 (0.6%)	0	0	0

Source: LJ501-CRH01 CSR Table 14.3.3.7.3, Table 14.3.3.8.3
Note: Sorted in order of descending frequency in the LJPC-501 treatment group. For each Preferred Term, patients are counted once even if they experienced multiple events.

Cardiac AESIs were aggregated from SOCs of Cardiac Disorders and Investigations. Cardiac AESIs occurred at a similar frequency among patients, with 43 (26.4%) patients in the LJPC-501 group versus 44 (27.8%) patients on placebo. Most common was atrial fibrillation in LJPC-501 groups and placebo, occurring in 22 (13.5%) and 21 (13.3%) patients, respectively. QT prolongation (in the Investigations SOC) was reported as an adverse event for 1 (0.6%) patient in the LJPC-501 group and 4 (2.5%) patients on placebo.

Grade 3/4 cardiac AESIs were reported for 14 (8.6%) patients in the LJPC-501 group and 12 (7.6%) patients on placebo. Grade 3/4 ventricular tachycardia was reported for 4 (2.5%) patients in the LJPC-501 group versus 3 (1.9%) patients on placebo; supraventricular tachycardia with no patients in the LJPC-501 group versus 3 (1.9%) patients on placebo group; atrial fibrillation occurred in 3 (1.8%) patients in the LJPC-501 group versus 3 (1.9%) on placebo.

ECG parameters:

Electrocardiogram results were compared at Screening/Baseline and at the Hour 48 time-point (Day 2 between Hour 24 and Hour 48). There was no evidence of QTc prolongation in either treatment group. The mean (SD) change in QTcF was −2.1 (62.2) msec in the placebo group and +0.6 (61.1) msec in the LJPC-501 group (Table 47). ECG abnormalities were reported as TEAEs for 2.5% of LJPC-501-treated and 3.8% of placebo-treated patients (Table 48 of the Summary of Clinical Safety). These were QRS complex prolonged (0 patient in the LJPC-501 group and 1 patient in the placebo group); QT prolonged (1 and 4 patients, respectively); ST segment elevation (2 and 0 patients); ST-T segment abnormal (1 and 0 patient); T wave abnormal (0 and 1 patient). No event of Torsade de pointes was reported.

Table 30 Abnormal QTc Intervals and Changes by Category (LJ501-CRH01 Safety Population)

	Number (%) of Patients			
	Placebo (N=158)		LJPC-501 (N=163)	
Interval in msec	QTcF	QTcB	QTcF	QTcB
Baseline	(N=151)		(N=156)	
≤ 450	108 (71.5%)	48 (31.8%)	101 (64.7%)	53 (34.0%)
> 450 to 480	20 (13.2%)	47 (31.1%)	26 (16.7%)	46 (29.5%)
> 480 to 500	12 (7.9%)	23 (15.2%)	6 (3.8%)	21 (13.5%)
> 500	11 (7.3%)	33 (21.9%)	23 (14.7%)	36 (23.1%)
Hour 48	(N=114)		(N=122)	
≤ 450	76 (66.7%)	58 (50.9%)	86 (70.5%)	54 (44.3%)
> 450 to 480	22 (19.3%)	24 (21.1%)	17 (13.9%)	32 (26.2%)
> 480 to 500	8 (7.0%)	14 (12.3%)	7 (5.7%)	14 (11.5%)
> 500	8 (7.0%)	18 (15.8%)	12 (9.8%)	22 (18.0%)
Change	(N=109)		(N=118)	
≤ 30	84 (77.1%)	89 (81.7%)	85 (72.0%)	92 (78.0%)
> 30 to 60	13 (11.9%)	10 (9.2%)	19 (16.1%)	12 (10.2%)
> 60	12 (11.0%)	10 (9.2%)	14 (11.9%)	14 (11.9%)

Source: LJ501-CRH01 CSR Table 14.3.6.1, Table 14.3.6.2, Table 14.3.6.3

Other cardiovascular events:

Thromboembolic events: in the ATHOS-3 study, there was a higher incidence of arterial and venous thromboembolic events in patients who received LJPC-501 than in the placebo group with 21 (12.9%) patients in the LJPC-501 group versus 8 (5.1%) patients on placebo. DVT being was the most frequently occurring in 7 (4.3%) patients in the LJPC-501 group and none in the placebo group (Table 33):

Table 31 Treatment-emergent Thromboembolic Adverse Events

Thromboembolic Event Types	Placebo (N=158)		LJPC-501 (N=163)	
	Events	Patients (%)	Events	Patients (%)
Any thromboembolic events	8	8 (5.1%)	25	21 (12.9%)
DIC	1	1 (0.6%)	1	1 (0.6%)
Cerebrovascular accident	1	1 (0.6%)	0	0
Cerebral infarction	0	0	1	1 (0.6%)
Cerebral ischaemia	1	1 (0.6%)	0	0
Hemiparesis	0	0	1	1 (0.6%)
Hemiplegia	0	0	1	1 (0.6%)
Ischaemic stroke	0	0	1	1 (0.6%)
Acute myocardial infarction	3	3 (1.9%)	2	2 (1.2%)
Myocardial infarction	1	1 (0.6%)	0	0
Stress cardiomyopathy	0	0	1	1 (0.6%)
Arterial occlusive disease	0	0	2	2 (1.2%)
Deep vein thrombosis	0	0	7	7 (4.3%)
Embolism	0	0	1	1 (0.6%)
Jugular vein thrombosis	0	0	2	2 (1.2%)
Peripheral artery thrombosis	0	0	2	2 (1.2%)
Hepatic vascular thrombosis	0	0	1	1 (0.6%)
Thrombophlebitis superficial	0	0	1	1 (0.6%)
Thrombosis	0	0	1	1 (0.6%)
Device occlusion	1	1 (0.6%)	0	0

Source: LJ501-CRH01 CSR Supplemental Table 17.1
Abbreviation: DIC – disseminated intravascular coagulation.
Note: Number of patients experiencing events on or more times, the percentage is of all patients assessed for AEs.

The incidence of patients receiving a prior or concomitant antithrombotic medication was 142 (87.1%) patients in the LJPC-501 group compared to 114 (72.2%) on placebo. In LJPC-501 group, the incidence of patients with a thromboembolic AE was 8 (16.7%) of patients not receiving an antithrombotic at Baseline compared to 13 (11.3%) of patients receiving an antithrombotic at Baseline. The same trend was observed for patients in the placebo group; the incidence of patients with a thromboembolic adverse event was 4 (5.8%) of patients not receiving an antithrombotic at Baseline compared to 4 (4.5%) of patients receiving an antithrombotic at Baseline.

Other adverse events of potential interest

Fungal infection: In Study LJ501-CRH01, fungal infection was reported in 10 (6.1%) subjects treated with LJPC-501, and in 2 (1.3%) subjects in the control group (LJ501-CRH01 Supplemental Table 17.9). In subjects treated with LJPC-501, 5 case reports referred to Candida colonisation of the skin, or mucous membranes; the remaining reports referred to fungal chest infections, fungaemia, fungal urinary tract infection, and yeast cultured from pleural fluid. The 2 reports in control subjects were *Candida endophthalmitis*, and fungaemia. The location of infectious sites varied and the observed signal was not driven by infection at any 1 site. None of the events were reported to be serious. The clinical impact of fungal infection reported in association with LJPC-501 was minimal.

Delirium: In Study LJ501-CRH01, delirium was reported in 9 (5.5%) subjects treated with LJPC-501, and in 1 (0.6%) subjects in the control group. None of these events were reported to be serious and all were Grade 1 or Grade 2 in severity.

Acidosis: In Study LJ501-CRH01, acidosis (acidosis, lactic acidosis, metabolic acidosis, hyperlacticidaemia) was reported in 9 (5.5%) subjects treated with LJPC-501, and in 1 (0.6%) subjects in the control group. None of these AEs resulted in a fatal outcome. Vasoconstriction due to vasopressor administration may contribute to metabolic acidosis.

Adverse Events in Other Studies

Expanded Access Program LJ501-EAP01

LJPC-501 was given to 53 adult patients as part of an expanded access program. All SAEs were recorded from first administration of LJPC-501. Adverse event collection was focused on the collection of serious adverse events SAEs and adverse events of special interest (AESIs). Overall 42 (79.2%) patients had at least one TEAE (Table 34). Serious AEs were reported in 39 (73.6%) patients including 31 (58.5%) patients experiencing SAEs that resulted in death. TEAEs led to permanent discontinuation of study drug in 11 (20.8%) patients.

Table 32 Summary of Treatment-emergent Adverse Events (LJ501-EAP01 Safety Population)

Adverse Event Category	LJPC-501 (N=53)	
	Events	Number (%) of Patients
All adverse events	75	42 (79.2%)
Related to study drug	17	12 (22.6%)
Serious adverse events	60	39 (73.6%)
Related to study drug	13	9 (17.0%)
Fatal adverse events	33	31 (58.5%)
Related to study drug	1	1 (1.9%)
Resulting treatment discontinuation	13	11 (20.8%)
Related to study drug	5	3 (5.7%)
Adverse event of special interest	17	12 (22.6%)
Related to study drug	8	5 (9.4%)

Source: Study LJ501-EAP01 CSR, Table 14.3.1

ATHOS I exploratory study (Chawla 2014): The most common adverse event thought to be attributable to angiotensin II was hypertension (defined as MAP ≥ 85 mmHg). Other adverse events occurring in the angiotensin II treatment group and not the placebo group were alkalosis (4 patients), atrial fibrillation (2 patients), and wheezing (1 patient). The 30-day mortality rates were 50% (5/10 patients) in the angiotensin II group and 60% (6/10 patients) in the placebo group (p=1.00).

Phase 1/2 Study LJPC-501-CS-5001: All 10 patients experienced at least 1 TEAE. Chest pain, nausea, and vomiting were each experienced by 3 patients, while the majority of TEAEs were experienced by 1 patient each. Five patients experienced 1 or more SAEs, and 4 of these patients died. Chest pain, chronic hepatic failure, and hepatorenal syndrome were reported as SAEs for 2 patients each. Deaths attributed to AEs were: hepatorenal syndrome with onset Day 1 and death on Day 2; hepatorenal syndrome reported on the same day as death (Day 5); chronic hepatic failure reported on Day 7 followed by death on Day 8; and duodenal ulcer haemorrhage beginning on Day 4 followed by death on Day 5.

Singh 1966: Meta-sensitivity was reported for 1 patient receiving angiotensin II and none receiving norepinephrine. All other events occurred with higher frequency in the norepinephrine group than the angiotensin II group. These included tachyphylaxis (15 [60%] norepinephrine-treated versus 8 [32%] angiotensin II-treated patients), thrombophlebitis (14 [56%] versus 1 [4%]), and tissue necrosis (10 [40%] versus 0). In the angiotensin II group, headache was reported in 5 (20%) patients; this was accompanied by flushing of the face in 2 (8%) patients. Mortality rates were 52% in the angiotensin II group (13/25 patients) and 88% in the norepinephrine group (22/25 patients).

Published Studies of Angiotensin II in Healthy Volunteer Subjects: Adverse events reported in the 5 studies in which 72 normotensive subjects received pressor doses of angiotensin II by IV infusion mainly included AEs from the SOC "general disorders & administration site conditions", like chest pressure sensation, headache and flushing with common frequency.

Systematic Review of Safety (Busse, 2017): The systematic review of all 1,124 studies concluded that AEs were infrequent and that most common were headache, chest pressure, and orthostatic symptoms (Busse 2017). The most serious side effects were exacerbation of left ventricular failure in patients with congestive heart failure and exacerbation of asthma.

Serious adverse event / deaths / other significant events

Analysis of Adverse Events in the Phase 3 Study LJ501-CRH01

Overall mortality in study LJ501-CRH01 was 32% at Day 7 and 50% at Day 28. Fatal AEs occurred more often in placebo-treated patients with 85 (53.8%) fatal events in placebo-treated patients and 76 (46.6%) fatal events in LJPC-501-treated patients at Day 28. The relative risk was similar at both time points (approximately 0.78 for LJPC-501 to placebo), but was not statistically significant (see also clinical efficacy).

Multi-organ failure was the most common fatal event in both treatment groups experienced by 23 (14.1%) patients in the LJPC-501 group and 21 (13.3%) patients in the placebo group. Frequencies for most fatal events were similar between the treatment groups, although septic shock accounted for deaths in 15 (9.2%) LJPC-501 patients and 9 (5.7%) patients on placebo. Fatal cardiac arrest, cardiogenic shock, and cardiorespiratory arrest were more common in the placebo group. The Respiratory disorders SOC accounted for more deaths in the placebo group, there were 9 (5.5%) deaths in the LJPC-501 group versus 13 (8.2%) deaths on placebo.

Table 33 FatalTreatment-emergent Adverse Events (LJ501-CRH01 Safety Population, Occuring in≥ 1% in Either Treatment Group)

System Organ Class Preferred Term	Placebo (N=158)	LJPC-501 (N=163)
Overall	85 (53.8%)	76 (46.6%)
General disorders & administration site conditions	22 (13.9%)	23 (14.1%)
Multi-organ failure	21 (13.3%)	23 (14.1%)
Infections & infestations	14 (8.9%)	23 (14.1%)
Septic shock	9 (5.7%)	15 (9.2%)
Sepsis	2 (1.3%)	3 (1.8%)
Pneumonia	0	2 (1.2%)
Cardiac disorders	15 (9.5%)	10 (6.1%)
Cardiac arrest	6 (3.8%)	3 (1.8%)
Cardiogenic shock	4 (2.5%)	2 (1.2%)
Cardio-respiratory arrest	4 (2.5%)	2 (1.2%)
Respiratory, thoracic & mediastinal disorders	13 (8.2%)	9 (5.5%)
Respiratory failure	6 (3.8%)	6 (3.7%)
Acute respiratory failure	4 (2.5%)	1 (0.6%)
Acute respiratory distress syndrome	2 (1.3%)	0
Vascular disorders	5 (3.2%)	3 (1.8%)
Distributive shock	2 (1.3%)	1 (0.6%)
Nervous system disorders	3 (1.9%)	3 (1.8%)
Metabolism & nutrition disorders	2 (1.3%)	2 (1.2%)
Neoplasms benign, malignant & unspecified	5 (3.2%)	1 (0.6%)

Source: LJ501-CRH01 CSR Table 14.3.3.5
Note: Events occurring in ≥ 1% of patients in either treatment group are included. Sorted in order of descending frequency in the LJPC-501 treatment group. For each System Organ Class and Preferred Term, patients are counted once even if they experienced multiple events.

Only 1 death was reported as associated with a drug-related SAE. One patient, in the LJPC-501 treatment group, experienced an SAE of cardiogenic shock on Day 2 that was assessed by the investigator as possibly related to study drug. This case is confounded by history of coronary artery bypass graft, a preceding requirement for an intra-aortic balloon pump, and removal of the pump with weaning of inotropic support and subsequent documentation of severe left ventricular dysfunction. Given the history of cardiac disease and presenting symptoms, the cardiogenic shock was assessed as unlikely related to LJPC-501 by the applicant. Five other fatal events of cardiogenic shock were not thought by the respective investigators to be related to study drug (4 in the placebo group and 1 in the LJPC-501 group).

Other Serious Adverse Events

SAEs were reported in a smaller proportion of patients in the LJPC-501 group with 99 (60.7%) patients compared with the placebo group with 106 (67.1%) patients (Table 27). SAEs in the SOCs of Cardiac disorders and Respiratory, thoracic and mediastinal disorders were more common in the placebo group and SAEs in the SOC of Infections and infestations were more common in the LJPC-501 group. Most treatment-emergent SAEs were reported as single events. Only 4 SAEs were reported for at least 5% of patients in either treatment group: multi-organ failure with 25 (15.3%) patients in the LJPC-501 group versus 23 (14.6%) on placebo; septic shock with 18 (11.0%) patients in the LJPC-501 group versus 10 (6.3%) on placebo; respiratory failure with 8 (4.9%) patients in the LJPC-501 group versus 11 (7.0%) on placebo and cardiac arrest with 7 (4.3%) patients in the LJPC-501 group versus 9 (5.7%) on placebo.

Table 34 Treatment-emergent Serious Adverse Events with a Frequency of ≥ 2% in Either Treatment Group (Safety Population of LJ501-CRH01)

System Organ Class Preferred Term	Number (%) of Patients	
	Placebo (N=158)	LJPC-501 (N=163)
Any treatment-emergent serious adverse event	106 (67.1%)	99 (60.7%)
Infections & infestations	21 (13.3%)	30 (18.4%)
Septic shock	10 (6.3%)	18 (11.0%)
General disorders & administration site conditions	25 (15.8%)	27 (16.6%)
Multi-organ failure	23 (14.6%)	25 (15.3%)
Cardiac disorders	32 (20.3%)	27 (16.6%)
Cardiac arrest	9 (5.7%)	7 (4.3%)
Atrial fibrillation	5 (3.2%)	5 (3.1%)
Ventricular tachycardia	3 (1.9%)	5 (3.1%)
Cardio-respiratory arrest	5 (3.2%)	3 (1.8%)
Cardiogenic shock	4 (2.5%)	2 (1.2%)
Supraventricular tachycardia	4 (2.5%)	1 (0.6%)
Respiratory, thoracic & mediastinal disorders	25 (15.8%)	17 (10.4%)
Respiratory failure	11 (7.0%)	8 (4.9%)
Acute respiratory failure	5 (3.2%)	3 (1.8%)
Vascular disorders	15 (9.5%)	17 (10.4%)
Hypotension	3 (1.9%)	5 (3.1%)
Peripheral ischaemia	3 (1.9%)	5 (3.1%)
Distributive shock	4 (2.5%)	1 (0.6%)
Hepatobiliary disorders	5 (3.2%)	4 (2.5%)
Gastrointestinal disorders	8 (5.1%)	3 (1.8%)
Neoplasms benign, malignant and unspecified	5 (3.2%)	2 (1.2%)
Nervous system disorders	9 (5.7%)	7 (4.3%)

Source: LJ501-CRH01 CSR Table 14.3.3.1
Note: Number of patients experiencing events one or more times, the percentage is of all patients assessed for AEs.

Serious Adverse Events and deaths in Other Studies

Expanded Access Program LJ501-EAP01: SAEs were reported in 39 (73.6%) patients. The most common SAEs reported for at least 5% of patients: septic shock (12 patients, 22.6%), multiple organ dysfunction syndrome (7 patients, 13.2%), cardiac arrest (4 patients, 7.5%), peripheral ischaemia (4 patients, 7.5%), thrombocytopenia (4 patients, 7.5%), deep vein thrombosis (3 patients, 5.7%), and sepsis (3 patients, 5.7%). Fatal TEAEs occurred in 31 (58.5%) patients. Most common causes of death were septic shock (12 patients, 22.6%) and multiple organ dysfunction syndrome (7 patients, 13.2%).

Laboratory findings

Phase 3 Study LJ501-CRH01 in Patients with CRH

In the Phase 3 study, clinical laboratory evaluations of haematology and chemistry analytes were performed on blood collected at Baseline, Hour 3, and Hour 48. Laboratory results showed considerable variability both across patients and in individual patients. Many results are influenced by other treatments and procedures as well as progression of disease, confounding the results and limiting attribution to study drug. These confounders include haemodialysis/renal replacement therapy (RRT), fluid and electrolyte treatments, other medications, and the timing of these treatments relative to blood collections for laboratory tests.

Haematology Laboratory Results: There were no clinically notable differences between treatment groups in absolute change from Baseline to any time point for main hematological parameters. Thrombocytopenia was reported as a TEAE for 16 (9.8%) patients in the LJPC-501 group and in 11 (7.0%) patients in the placebo group. Of the 16 LJPC-501-treated patients with thrombocytopenia, 3 had thrombocytopenia, or disseminated intravascular coagulation as medical history prior to LJPC-501 treatment.

Clinical Chemistry Laboratory Results: Increases in severity of transaminase levels were similar between the placebo group and LJPC-501 group. There was a higher incidence of worsening hypoalbuminaemia in the placebo group and higher incidence of increases in total bilirubin and serum creatinine grades in the LJPC-501 group. However, there were no cases of elevations in transaminase levels or bilirubin levels that met the criteria for Hy's Law. Creatinine was also followed as an efficacy endpoint and patients on dialyses were excluded from those analyses. Most patients not on dialysis had serum creatinine levels above the upper limit of normal (ULN) at Baseline (67.8% LJPC-501, 73.5% placebo). The percent of patients with serum creatinine above the ULN had decreased at 48 Hours (56.8% LJPC-501, 50.6% placebo). The proportion of patients who had Grade 3/4 abnormal serum creatinine at Baseline decreased at Hour 48 in both groups, from 15.7% to 14.8% in the LJPC-501 group and 10.8% to 9.1% in the placebo group. Results for patients receiving haemodialysis were excluded in summaries of serum creatinine as they may confound the results.

Hyperglycaemia was reported in 7 (4.3%) patients in the LJPC-501 group and in 4 (2.5%) patients in the placebo group. Of the 7 LJPC-501-treated patients with hyperglycaemia, 1 had diabetes mellitus as medical history prior to LJPC-501 treatment, and 4 had blood glucose values above ULN at Screening. Of the 7 events, 2 events occurred during LJPC-501 administration, 1 event occurred on the day LJPC-501 administration was stopped, and 4 events occurred from 24 to 33 hours after the end of LJPC-501 administration. The laboratory data for glucose level do not suggest a marked difference between the two groups.

Safety in special populations

No dedicated studies in special populations have been conducted. The company states that since it is administered directly into the circulation and angiotensin II is has a short plasma half-life, predetermined adjustments to accommodate special groups or situations are not necessary. The following sections compare adverse event rates by intrinsic factors such as age, sex, race and by renal and hepatic function. Extrinsic factors such as geographical region are then discussed.

Intrinsic Factors

In study LJ501-CRH01, there were no statistically significant differences between treatment groups for any demographic characteristics. Across certain subgroups of patients analysed for comparisons of AEs, there were some statistically significant differences in Baseline characteristics.

Age: Patients 65 years or older comprised 48% of the safety population and 26% were 75 years or older. Mean age was 59.0 years, and 42.4% of patients were at least 65 years old. The youngest patients in each treatment group were 22 years old. Patients ≥ 75 years are also included in the ≥ 65 years subgroup. Study drug doses and exposure were similar between age subgroups. The incidence of TEAEs appeared to increase with age in the placebo treatment group but not in the LJPC-501 group. In patients 65 years or older, 51 (69.9%) patients in the LJPC-501 group experienced at least 1 Grade 3/4 TEAE versus 62 (76.5%) in the placebo group.

Sex: In study LJ501-CRH01, overall, 60.7% of patients were male and 39.3% were female. Study drug doses and exposure were similar for male and female subgroups. In the placebo group 52 (94.5%) women and 93 (90.3%) men experienced 1 or more TEAEs, compared with 61 (85.9%) and 81 (88.0%), respectively, in the LJPC-501 group. Males had higher incidences of TEAEs for atrial fibrillation in 16 (17.4%) males versus 6 (8.5%) females; thrombocytopenia with 11 (12.0%) males versus 5 (7.0%) females and hypokalaemia with 9 (9.8%) males versus 4 (5.6%) females.

Renal and hepatic function: Across the subgroups related to hepatic and renal function, overall adverse event rates were lower in the LJPC-501 group than the placebo group. For patients with Grade 2 to 4 elevations in serum bilirubin at Baseline, adverse event rates were 61 of 65 patients (93.8%) in the placebo group versus 43 of 47 patients (91.5%) in the LJPC-501 group, compared to 90.3% and 85.7%, respectively for patients with Grade 0 to 1 bilirubin. For patients with Grade 2 to 4 elevations in serum creatinine at Baseline, adverse event rates were 52 of 56 patients (92.9%) in the placebo group versus 58 of 62 (93.5%) patients in the LJPC-501 group, compared to 87.0% and 79.7%, respectively for patients with Grade 0 to 1 creatinine.

In the post-hoc defined AKI/RRT subgroup, overall adverse event rates were 57 of 60 patients (95.0%) receiving placebo and 40 of 45 patients (88.9%) receiving LJPC-501. The most frequently reported TEAEs were multi-organ failure (22.2% with LJPC-501 and 21.7% with placebo), hypotension (20.0% with LJPC-501 and 11.7% with placebo), and atrial fibrillation (15.6% with LJPC-501 and 11.7% with placebo).

Extrinsic Factors

Phase 3 Study LJ501-CRH01

In study LJ501-CRH01, 236 (73.5%) patients were treated in the US or Canada; the remaining patients were treated in Australia or New Zealand with 52 (16.2%) patients and Europe with 33 (10.3%) patients. The overall adverse event rates were lower in the LJPC-501 treatment group compared to placebo in each region. The difference was smallest in the US/Canada with 105 (90.5%) LJPC-501-treated patients and 110 (91.7%) on placebo.

Use in Pregnancy and Lactation

Phase 3 Study LJ501-CRH01: Pregnant women were excluded from participation in LJ501-CRH01. No pregnancies were reported during the study.

Studies from the Literature: In studies from the literature, angiotensin II has been administered to hundreds of pregnant women and pregnant adolescent girls (Busse 2017). Extensive evidence from the literature indicates that pressor sensitivity to exogenous angiotensin II is decreased in normal pregnancy (Schwarz 1971, Abdul-Karim 1961). Women who develop preeclampsia become hyper-responsive to the pressor effects of angiotensin II in late pregnancy; postpartum, angiotensin II responsiveness may remain elevated in this group, particularly among women with low sodium balance, reduced plasma volume or evidence of other underlying disorders (Hladunewich 2011, Saxena 2010, Spaanderman 2004). An increase in vascular resistance to angiotensin II in late-term normotensive pregnant women did not depend on volume expansion or a change in renin plasma levels (Gant 1973). Doses up to 64 ng/kg/min were reported in 43 pregnant women (Conti 1994). There was no difference in metabolic clearance of angiotensin II between 11 non-pregnant and 37 pregnant women (mean, 30 weeks; standard error of the mean, 0.3 weeks) administered pressor doses of angiotensin II (Magness 1994). Infusion of angiotensin II in pre-term pregnant women (26-35 weeks of gestation) was associated with a smaller drop in urine output and electrolyte excretion (Na^+ and Cl^-) when compared to non-pregnant women or pregnant women near term (Chesley 1963). Inulin clearance decreased by similar amounts in non-pregnant women and pregnant women near term (21%-28%) but decreased by a smaller amount in women at 26 to 35 weeks of gestation (8%-16%).

Adverse effects during infusions of angiotensin II to pregnant women included headache, dizziness, dyspnoea, chest oppression, palpitations, abdominal pain, dyspepsia (fish oil capsules also administered), bradycardia, and low backache (Adair 1996, Broughton Pipkin 1982, Schwarz 1971, Abdul Karim 1961).

Immunological events

Not provided.

Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies have been conducted with LJPC-501. Pharmacodynamic interactions between angiotensin II and other drugs are difficult to predict because of the complexity of counter-regulatory mechanisms to maintain fluid and electrolyte balance and potentially altered responses during vasodilatory shock.

All patients in study LJ501-CRH01 were receiving multiple concomitant medications prior to and during the treatment period. Most common were medications affecting the cardiovascular system, the nervous system, and systemic anti-infective medications. LJPC-501 was added to ongoing vasopressors. All vasopressor doses were converted to NEDs and summed to provide the total NED. Adverse events were more frequently reported for patients receiving higher doses of vasopressors at Baseline in both treatment groups but were less frequent in the LJPC-501 than placebo group within each Baseline vasopressor dose subgroup.

Discontinuation due to adverse events

In study LJ501-CRH01 (ATHOS-3), adverse events leading to permanent discontinuation of study drug were reported in 23 (14.1%) patients in the LJPC-501 group and 34 (21.5%) patients on placebo. Only 5 TEAEs were reported for more than one patient in either treatment group and frequencies were similar between the groups for 4 of these: multi-organ failure with 6 (3.7%) patients in the LJPC-501 group versus 6 (3.8%) on placebo; septic shock with 8 (4.9%) patients in the LJPC-501 group versus 4 (2.5%) on placebo; cardiogenic shock with 2 (1.2%) patients in the LJPC-501 group versus 4 (2.5%) on placebo and peripheral ischaemia with 1 (0.6%) patient in the LJPC-501 group versus 1 (0.6%) on placebo. Cardiac arrest led to discontinuation of study drug for 5 (3.2%) patients on placebo and none in the LJPC-501 group.

Only 3 patients in each treatment group experienced TEAEs that were considered by the investigator to be possibly related to study drug and that led to discontinuation. In the LJPC-501 group, these events were peripheral ischaemia, cardiogenic shock, and Stevens-Johnson syndrome. Peripheral ischaemia is a well known adverse reactions of vasopressors. Causality assessment of cardiogenic shock is complicated by the presence of multiple confounding factors. Finally, the causality assessment of a case of Stevens-Johnson syndrome (SJS) is also complicated by the multiple concomitant treatments that this patient received within two weeks of the first onset of SJS (i.e.: levetiracetam, carbamazepine, baclofen, cefepime, cetirizine, letrozole, amoxicillin and clavulanic acid, piperacillin sodium and tazobactam sodium and vancomycin). On the other hand, a literature search showed no evidence of causal relationship or known biological mechanism than implicates angiotensin II in SJS. Therefore, causal relationship between angiotensin-II and SJS seems unlikely.

Post marketing experience

Giapreza was approved for use in the US on 21 December 2017 and was available to market on 06 February 2018. There have been no spontaneous reporting of AEs or SAEs to the applicant up to the cut-off date of 01 March 2018.

2.6.1. Discussion on clinical safety

Safety data relevant to this application come primarily from the Phase III study LJ501-CRH01 in patients with the proposed indication. This study included 163 patients treated with angiotensin II and 158 with placebo. Median duration of exposure was 48 hours in both treatment groups. Twenty-five patients continued LJPC-501 after Hour 48. Maximum duration of study drug infusion was 60 hours in the placebo group and 168 hours (1 patient) in the LJPC-501 group; 13 patients received at least 72 hours of LJPC-501 compared with no patients in the placebo group. While the size of the safety database is modest, it can be considered adequate taking into account the high risk, the short half-life and the expected setting of use (an intensive care unit where patients will be monitored closely). The SmPC includes that *"GIAPREZA should be prescribed by a physician experienced in the treatment of shock and is intended for use in an acute and hospital setting"*.

Frequencies of fatal events were numerically lower in the LJPC-501 than in the placebo group (46.6% vs. 53.8%). Looking at the upper 95%CI of the HR in the final multivariate model provided for death (HR: 0.89; 95% CI, 0.64–1.24), a relative increase in mortality with angiotensin II ≥ 25% could be, in principle, ruled out. Anyway, given the scarce data available on top of high-dose vasopressor therapy and in the European population, further reassurance is needed in a post-marketing clinical trial. Multiorgan failures were the most common fatal events in both treatment groups accounting for 13.3% in placebo and 14.1% LJCP-501. Fatal cardiovascular disorders such as cardiac arrests, cardiogenic shock, and cardio-respiratory arrest were more common in the placebo group (9.5%) compared with LJPC-501 (6.1%), although 1 death due to cardiogenic shock was reported to be possibly related to LJPC-501 by the investigator. The applicant assessed the cardiogenic shock as unlikely related to LJPC-501 due to the subject's history of cardiac disease and presenting symptomatology, which was endorsed.

The expected adverse events for a vasopressor includes different types of ischemic events, tachycardia and hypertension. Thromboembolic events are normally unexpected for a vasopressor but have been linked to angiotensin II in the literature. These events are discussed hereafter.

Arterial ischemic events: The overall incidence of arterial ischaemic TEAEs was similar between treatment groups, but grade 3/4 ischaemic AESIs were reported for 13 (8.0%) patients in the LJPC-501 group and 8 (5.1%) patients on placebo. The difference was mainly driven by more cases of peripheral ischaemia with 5 (3.1%) patients in the LJPC-501 group versus 3 (1.9%) on placebo and more ischemias in the CNS (4 patients in the LJPC-501 arm vs. 1 in the placebo arm). In spite of the small number of events limiting the interpretation of the data, these findings are concerning. This risk is important because it is common and may be associated with serious long-term outcomes for the patient, such as the loss of a digit or impaired neurological function. The risk may be minimised by administering LJPC-501 under constant blood pressure monitoring at the lowest dose that is compatible with adequate arterial blood pressure and adequate tissue perfusion. Recommendations for acute and hospital use only and specialist supervision are included in SmPC section 4.2. Recommendations for managing peripheral ischaemia by administering the lowest dose compatible with adequate arterial blood pressure and tissue perfusion are included in SmPC section 4.4. The applicant proposed to continue to monitor and quantify ischemic events with LJPC-501 as part of routine pharmacovigilance and in the proposed post-authorisation study, LJ501-CRH06.

Thromboembolic events: there was a higher incidence of arterial and venous thromboembolic events in patients who received LJPC-501 than in the placebo group with 21 (12.9%) patients in the LJPC-501 group versus 8 (5.1%) patients on placebo. DVT was the most frequently one, occurring in 7 (4.3%) patients in the LJPC-501 group (Table 37). The percentage of patients in the angiotensin II and placebo groups with a history of embolic or thrombotic events at baseline was similar (52% versus 49%). The available data indicate that LJPC-501 can increase the risk of thromboembolic AEs in the intended patient population. Chronic angiotensin II infusion has prothrombotic potential through activation of platelet adhesion and aggregation. Angiotensin II may also contribute to thrombosis by reducing the activity of the endogenous fibrinolytic system. Such effects appear to be mediated by activation of platelet function, stimulation of the production of plasminogen activator inhibitor-1, promoting the production of superoxide radicals that scavenge free nitric oxide, and activation of nuclear factor-κB. These effects contribute to increased expression of tissue factor, the physiologic initiator of blood coagulation. Given the significant imbalance in thromboembolic events and biological plausibility, thromboembolism has been therefore considered an identified risk that may be minimised by antithrombotic prophylaxis. A recommendation to apply venous thromboembolism prophylaxis has been included in SmPC section 4.4: "*Concurrent venous thromboembolism prophylaxis (VTE) should be used unless contraindicated during treatment with GIAPREZA. Non-pharmacologic VTE prophylaxis may be considered where pharmacologic prophylaxis is contraindicated*". A description of thromboembolic events has been included in section 4.8.

MACE / MACE-plus: trends towards a higher number of different ischemic and cardiac events have been reported for angiotensin in the ATHOs-3 trial, together with transient hypertension. These events are not unexpected for a vasopressor like angiotensin II. The pre-specified events in the protocol were a mix of cardiovascular events of different clinical relevance and did not include a composite of major adverse cardiovascular events (MACE). There is an EMA Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015). The applicant was requested to analyse a composite of all major cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) as well as MACE-plus (unstable angina, need for revascularization, acute heart failure/worsening of existent heart failure, TIA and sudden death) in order to better characterize the cardiovascular risk profile of the product. Overall, the incidence of MACE (2.5% vs. 6.7%) and MACE-plus (7.4% vs. 11.4%) were numerically lower in the LJPC-5001 arm than in the placebo arm.

Tachycardia: sinus tachycardia, tachycardia and supraventricular tachycardia, not including tachyarrhythmias such as atrial or ventricular tachycardia was reported in 14 (8.6%) subjects treated with LJPC-501, and in 9 (5.7%) subjects in the control group in Study LJ501-CRH01. In animal models, angiotensin II has been shown to cause a central, dose-dependent reduction in vagal tone (Lee 1980). This action is normally antagonised by the reflex response to the vasopressor/hypertensive action of angiotensin II. Consequently, in situations where blood pressure is not elevated (for example, in severe sepsis), angiotensin II may cause an elevation in heart rate. In the setting of severe sepsis, many confounding factors are often present which can also influence heart rate. These include, in part, ongoing fluid status fluctuations, pharmacologic exposures, fever, and pain. The target population for Giapreza will require treatment in a critical care environment. In this environment, haemodynamic variables are normally monitored continuously in patients treated with vasopressors. The management of haemodynamic variables including heart rate should be routine in a critical care environment. The company proposed to include tachycardia as common adverse reaction in the SmPC, which was endorsed.

Arrhythmias: Most common was atrial fibrillation in LJPC-501 groups and placebo, occurring in 22 (13.5%) and 21 (13.3%) patients, respectively.

ECG parameters: Electrocardiogram results were compared at Screening/Baseline and at the Hour 48 time-point (Day 2 between Hour 24 and Hour 48). ECG abnormalities were reported as TEAEs for 3.8% of placebo-treated and 2.5% of LJPC-501-treated patients. There was no evidence of QTc prolongation in either treatment group. The mean (SD) change in QTcF was −2.1 (62.2) msec in the placebo group and +0.6 (61.1) msec in the LJPC-501 group (Table 47). QT prolongation (in the Investigations SOC) was reported as an adverse event for 1 (0.6%) patient in the LJPC-501 group and 4 (2.5%) patients on placebo.

Transient hypertension was reported in 37 (22.7%) patients during treatment with angiotensin II. The risk of transient hypertension has been included in section 4.8, as it is related to the drug, and the need for down-titration in these patients has been included in section 4.2, which is deemed acceptable.

Hypotensive events (hypotension): In the LJ501-CRH01 study, hypotensive events (including the preferred terms of hypotension, shock, septic shock, distributive shock, and cardiogenic shock) occurred in 40 (24.5%) patients in the LJPC-501 group and in 28 (17.7%) patients in the placebo group. According to the presented data, many of these AEs were reported some time after LJPC-501 was discontinued and reflects a recurrence of the underlying hypotension. A subset of hypotensive adverse events was reported at the time of LJPC-501 discontinuation and may reflect a direct link to the protocol-mandated down-titration of study drug at 48 hours. Due to the above-mentioned reasons, hypotension cannot be considered an adverse reaction to angiotensin II, and it is considered a back to the hypotensive state that the patient had before the angiotensin infusion. Its inclusion in section 4.8 of the SmPC was not endorsed by the CHMP and hypotension has been removed from this section. Recommendations for hospital use only and specialist supervision have already been included in SmPC section 4.2, and recommendations for gradual withdrawal of Giapreza and close monitoring of blood pressure in SmPC section 4.4. These preventive measures were deemed sufficient.

Adverse events leading to discontinuation were less common in the LJPC-501 group than in the placebo group (14.1% vs. 21.5%). The most frequent AE leading to discontinuation was “septic shock” (5% vs. 2% in the angiotensin II and placebo arms, respectively). During the hour 48 to the end of study treatment period, the incidence of septic shock increased over time with 10 (7.0%) patients in the LJPC-501 group versus 5 (3.9%) patients on placebo. Septic shock was also reported in 22.6% of patients in the LJ501-EAP01 expanded access study. The applicant was invited to discuss this finding and its possible link to a rebound effect (i.e.: worsening of septic shock after withdrawal of angiotensin II) or other causes (e.g.: greater use of corticosteroids or other immune-suppressive therapies in the experimental group). Most cases qualified as septic shock events correspond in fact to worsening hypotension/septic shock within 96 hour of LJPC-501 discontinuation (experimental drug discontinued after 48 hours, as per protocol), rather than a worsening of underlying infection. There were no major imbalances in prior or concurrent use of corticosteroids or other immunosuppressive therapies between treatment groups that could have led to the discrepancy in septic shock. To mitigate the risk of a patient being abruptly withdrawn from therapy, the applicant has included language in Sections 4.2 and 4.4 of the SmPC, instructing healthcare providers to gradually decrease the dose of GIAPREZA before discontinuing treatment.

Fungal infections: In Study LJ501-CRH01, fungal infection was reported in 10 (6.1%) subjects treated with LJPC-501, and in 2 (1.3%) subjects in the control group. Fungal infection, particularly overgrowth of Candida, is a frequent complication in patients treated for vasodilatory shock in a critical care environment, particularly when antibiotics and glucocorticoids are given concomitantly, and when the patient is intubated and mechanically ventilated. There was an imbalance in the use of hydrocortisone, with more patients receiving this drug in the angiotensin II group (see efficacy section). The applicant was requested to explore if the imbalance in fungal infections correlates with a wider use of glucocorticoids in the angiotensin II group. Data provided in response show a numerically higher rate of fungal infections in patients receiving glucocorticoids at baseline compared with patients not receiving glucocorticoids, but with no significant differences between treatment arms. In addition, fungal infections are common in critically ill patients and no fungal infection events were reported from previous clinical studies of angiotensin II in the literature (n = 31,281) (Busse 2017), in LJ501-EAP01. It was agreed not to include fungal infections as an adverse reaction associated with LJPC-501.

Thrombocytopenia: In Study LJ501-CRH01, thrombocytopenia was reported in 16 (9.8%) subjects treated with LJPC-501, and in 11 (7.0%) subjects in the control group. Thrombocytopenia is very common in the indicated population, with an estimated incidence of 20% to 40% at some point during an ICU stay (Venkata 2013, Drews 2000). A review of the literature reveals little information about a direct depression of the platelet count by angiotensin II. In fact, angiotensin II appears to stimulate the proliferation of hematopoietic progenitors and has been proposed as a possible agent to accelerate hematopoietic recovery after bone marrow injury (Rodgers 2000). Notably, clinical laboratory evaluations in LJ501-CRH01 did not show any clinically notable differences in platelets between treatment groups in absolute change from baseline to any time point. The adverse event has been listed in Section 4.8 of the SmPC. Given that there are many confounding factors, and that it is unexpected, it was not agreed to consider thrombocytopenia as adverse reaction of angiotensin II.

Delirium: The applicant stated that the imbalanced finding in delirium AEs [9 (5.5%) subjects treated with LJPC-501, and in 1 (0.6%) subjects in the control group] is potentially related to patients' background risk. However, a further discussion was required in order to rule out that these events were related to LJPC-501. Among patients who experienced delirium, there were no major imbalances in baseline Neurological SOFA score. Patients emerging from deep sedation/anaesthesia often suffer from delirium. The lack of mandated sedation interruption and appropriate detailed aetiology reporting of delirium hampers the ability to ascribe causation of delirium to angiotensin II. Delirium was removed from section 4.8. Routine pharmacovigilance can be considered sufficient regarding these events.

Acidosis: In Study LJ501-CRH01, acidosis (acidosis, lactic acidosis, metabolic acidosis, hyperlacticidaemia) was reported in 9 (5.5%) subjects treated with LJPC-501, and in 1 (0.6%) subjects in the control group. None of these AEs resulted in a fatal outcome. Vasoconstriction due to vasopressor administration may contribute to metabolic acidosis. Considering the laboratory findings, it is not clear whether LJPC-501 is associated with the risk of acidosis. Acidosis is common in this patient population and the applicant considers it likely that the reported AEs are associated with the progression of the underlying disease. There is no sufficient evidence for a causal relationship with LJPC-501. Routine pharmacovigilance can be considered sufficient regarding these events.

Hyperglycaemia: In Study LJ501-CRH01, hyperglycaemia was reported in 7 (4.3%) subjects treated with LJPC-501, and in 4 (2.5%) subjects in the control group (LJ501-CRH01 Supplemental Table 17.7). Nonclinical models have demonstrated that angiotensin II can affect glucose control via stimulation of gluconeogenesis and impairment of insulin sensitivity (Coimbra 1999, Ogihara 2002). Of the subjects with hyperglycaemia treated with LJPC-501, 1 had diabetes mellitus as medical history prior to LJPC-501 treatment, and 4 had blood glucose values above the upper limit of normal at screening. Two events occurred during LJPC-501 administration, 1 event occurred on the day LJPC-501 administration was stopped, and 4 events occurred from 24 to 33 hours after the end of LJPC-501 administration. Laboratory data do not suggest a difference between LJPC-501 treatment and controls. The target population for Giapreza will require treatment in a critical care environment. In this environment, clinical chemistry variables are normally monitored as frequently as is required to manage the patient. The management of blood glucose should be routine in a critical care environment.

Renal function: 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 favour of LJPC-501. The applicant acknowledged that among the patients with normal renal function, chronic kidney disease, or AKI not requiring RRT, neither the pre-morbid serum creatinine nor the recovery serum creatinine are available for assessment. However, the patients had complete follow up of AEs and SAEs to Day 28 and there were fewer renal events in the LJPC 501 arm than in the placebo arm. It is agreed that the short term administration of angiotensin II in patients with vasodilatory shock may be of benefit due to its effect in increasing MAP, thus increasing renal perfusion, and it is unlikely to exacerbate the acute kidney injury that is observed in up to 50% of patients with septic shock.

Multi-organ failure (MOF): the applicant discussed the similar frequency of this severe adverse event in both groups despite restoration of MAP and the imbalance between men and women. There is insufficient evidence to support a causal association between LJPC-501 therapy and the risk of MOF. The imbalance of baseline characteristics probably contributed to the imbalance of MOF between men and women. The development of MOF may be more likely to be associated with the progression of the underlying disease. The same explanation (imbalance in baseline characteristics) is applicable for the imbalance between women and men observed in some other TEAEs (e.g.: delirium, bradycardia, atrial fibrillation, thrombocytopenia, hypokalaemia).

Stevens-Johnson syndrome (SJS): a case was reported in the ATHOS-3 trial in association with angiotensin, but it was not included in section 4.8 of the SmPC as adverse reaction. Causality assessment was discussed by the applicant after the investigator changed the causality assessment from "possibly related to angiotensin II" to "related to levetiracetam". On the other hand, a literature search showed no evidence of causal relationship or known biological mechanism than implicates angiotensin II in SJS.

Safety in relevant subgroups:

In the responses to the D120 CHMP LoQ, the applicant provided the analyses of baseline characteristics, drug exposure (in LJPC-501 and NED levels) TEAEs (all grades and grades 3/4), deaths and other SAEs according to the vasopressin use at baseline (yes/no) , baseline NED (< or ≥ 0.5 µg/kg/min) and severity of APACHE II score at baseline.

There were no significant differences in demographic characteristics between the subsets of patients who were or were not receiving vasopressin at start of study drug administration, except regarding the geographic region: US/Canada patients were mainly under vasopressin at baseline (85.6% of patients receiving baseline vasopressin vs 49.1% of patients not receiving vasopressin), while the high majority of European patients was not treated with vasopressin at baseline (25.5% of patients not receiving vasopressin vs 2.8% of patients receiving baseline vasopressin, i.e only 6 European patients received vasopressin at baseline). According to the data provided, it can be considered that patients receiving vasopressin at baseline were rather more severe: notably more patients with MAP <65 mmHg (40.9% with baseline vasopressin vs 32.1% with no baseline vasopressin), APACHE II >30 (respectively 41.4% vs 32.1%), acute respiratory distress syndrome (respectively 31.6% vs 21.9%) or history of sepsis (respectively 87.4% vs 67%). TEAEs were not dramatically increased compared placebo in both subgroups of patients treated or not treated with vasopressin.

Patients receiving NED ≥0.5 microg/kg/min at start of study drug administration were younger (mean age of 56.7 years vs 64.2 years) and rather more severe: notably more patients with MAP <65 mmHg (63% in the group NED ≥0.5 microg/kg/min vs 32.5% in the group NED < 0.5 µg/kg/min), APACHE II >30 (respectively 41.3% vs 33.3%), acute respiratory distress syndrome (respectively 33.3% vs 21.4%) or vasopressin use prior to randomisation (respectively 76.1% vs 66.7%). Consistent with more severe disease and higher total dose administered, patients in the LJPC-501 group who had a baseline NED ≥0.5 µg/kg/min reported a greater incidence of AEs, Grade 3/4 AEs and fatal TEAEs when compared to patients who had a Baseline NED < 0.5 µg/kg/min. TEAEs were not dramatically increased compared to placebo in both subgroups of patients treated with baseline NED < 0.5 microg/kg/min or ≥0.5 microg/kg/min.

The subgroup with APACHE II > 30 included older patients; median age in this subgroup was 66 years, compared with 63 years for the subgroup with APACHE II ≤30. The high APACHE II subgroup also had morepatients with BMI > 30 kg/m2 (51.6% versus 39.7%). Mean Baseline APACHE II was 22.8 in the low APACHE II subgroup and 36.4 in the high APACHE II subgroup; within the high APACHE II group, 15.4% had a score of at least 41. Both Screening and Baseline MAP were similar between the APACHE II subgroups. Patients in the high APACHE II subgroup tended to have higher MELD score, higher acute respiratory distress syndrome and received slightly higher baseline NED doses than patients with lower APACHE II scores. TEAEs were not dramatically increased compared to placebo in both subgroups of patients with baseline APACHE II scores ≤30 and > 30.

Post-marketing experience:

Giapreza was approved for use in the US on 21 December 2017 and was available to market on 06 February 2018. There have been no spontaneous reporting of AEs or SAEs to the applicant up to the cut-off date of 01 March 2018. In the responses to CHMP D120 list of questions, the applicant provided an updated cumulative list of post-marketing cases with GIAREZA up to 30 November 2018 and no new safety signals were identified.

However, there was a particularly high incidence of SAEs in the expanded access study. It can be summarised that in this EAP study, many patients did not meet all study protocol entry criteria due to the critical conditions encountered. Therefore, patients in particularly serious medical situations experienced high rates of SAEs, which was not really unexpected. The most frequently unmet exclusion criteria were MELD score ≥ 30, absolute neutrophil count < 500 cells/mm3, and inclusion criteria was cardiac index > 2.3 l/min/m². However, this is particularly difficult to understand, since notably 38 patients with baseline MELD score ≥ 30 were also included in study LJ501-CRH01. Cardiogenic shock was requested by the CHMP to be clearly mentioned in section 4.4 as one of the clinical situations in which the use of Giapreza is not recommended, as there are no efficacy data in this clinical setting.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile for LJPC-501 can be considered acceptable, taking into account the high risk of the disease, the short half-life and the expected setting of use (acute or hospital settings) where patients will be monitored closely). The product information includes appropriate statements related to the safety aspects.

Angiotensin II has shown to be effective in increasing MAP in patients with vasodilatory or distributive shock on top of fluid and vasopressor therapy, but the effect of angiotensin II on morbidity and mortality has not been determined as morbidity and mortality were exploratory endpoints in the single pivotal trial. In addition, the available data indicate that LJPC-501 can increase the risk of thromboembolic AEs in the intended patient population. A recommendation to apply venous thromboembolism prophylaxis has been included in the SmPC. The potential benefit in morbidity and further reassurance regarding mortality will be further studied in the planned post-authorisation efficacy trial.

The CHMP considers the following measures necessary to address issues related to safety:

Post-authorisation efficacy study (PAES): In order to further investigate the efficacy and safety of Giapreza in the treatment of refractory hypotension in adults with septic or other distributive shock, the MAH should conduct and submit the results of a randomized, double-blind placebo-controlled multicentre study in adult patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy to provide: (1) data on the effect of the product on morbidity events and organ perfusion with and adequate representation of European patients, (2) reassurance that there is no detrimental effect on mortality at day 28, (3) additional safety data about ischemic and thromboembolic events associated with the use of the product and (4) the record of clinical global impression of the response to treatment.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	Thromboembolic events Transient Hypertension
Important potential risks	Peripheral ischaemia
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance activities. Routine pharmacovigilance is considered sufficient to identify, characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures.

However, a **post-authorisation efficacy study that is condition to the marketing authorisation** (imposed PAES, Study LJ501-CRH06) is planned to further characterise the efficacy uncertainty around catecholamine sparing effect but it will also aim at collecting additional safety data about ischemic and thromboembolic events aiming at further characterising the important identified risk of **thromboembolic events**.

Planned Post-Authorisation Efficacy Studies that is Condition to the Marketing Authorisation

Study / Status	**Summary of Objectives**	**Efficacy Uncertainties Addressed**	**Milestones**	**Due Date**
LJ501-CRH06 / Planned	Primary: • To compare the efficacy of LJPC-501 to placebo on reduction in doses of standard-of-care (SOC) vasopressors required for hemodynamic stability from baseline to Hour 2 in patients with vasodilatory shock and associated severe acute kidney injury Secondary: • To compare 28-day survival with LJPC-501 versus placebo treatment • To compare time to discontinuation of renal replacement therapy (RRT) with LJPC-501 versus placebo treatment • To compare clinical global impression of the response to treatment with LJPC-501 versus placebo • To assess safety and tolerability of LJPC-501 (adverse events and adverse events of special interest)	Catecholamine-sparing effect Safety	Results	2Q 2024

Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Important Identified risk – thromboembolic events	Routine risk communication: *SmPC sections 4.4 and 4.8.* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Intended to be used in hospital only under specialist supervision* *Instructions for venous thromboembolism prophylaxis is included in SmPC sections 4.4 and 4.8.* *Concurrent venous thromboembolism prophylaxis should be used unless contraindicated during treatment with GIAPREZA. Non-pharmacologic VTE prophylaxis may be considered where pharmacologic prophylaxis is contraindicated.* Other routine risk minimisation measures beyond the Product Information: None Legal status: Prescription only
Important Identified risk – Transient hypertension	Routine risk communication: *SmPC section 4.8* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for continuous intravenous infusion under close and continuous monitoring of hemodynamic are included in SmPC section 4.2* Other routine risk minimisation measures beyond the Product Information: None Legal status: Prescription only

Safety Concern	Risk Minimisation Measures
Important Potential risk – Peripheral ischaemia	Routine risk communication: *SmPC sections 4.4 and 4.8.* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations for continuous intravenous infusion under close and continuous monitoring of organ-specific parameters are included in SmPC section 4.2.* *Recommendations for managing peripheral ischaemia by administering the lowest compatible dose to achieve or maintain arterial blood pressure and tissue perfusion are included in SmPC section 4.4.* Other routine risk minimisation measures beyond the Product Information: None Legal status: Prescription only

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.12.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant has undertaken a comprehensive search of relevant databases in search of angiotensin products currently authorized in EU. Ile^5-angiotensin II has never been approved for marketing in EU. A different angiotensin II active substance, Hypertensin®, bearing a valine moiety instead of an isoleucine at amino acid 5 (Val^5-angiotensin II) was identified as having previously been on the market in the EU until its withdrawal in 1992. The applicant considered this comparator molecule as part of its justification.

The active metabolites produced by the Ile^5-angiotensin II metabolism [angiotensin III (angiotensin 2-8), angiotensin IV (angiotensin 3-8) and angiotensin (1-7)] always include the residue Ile^5. Consequently, Hypertensin® (Val^5-angiotensin II) does not share the same therapeutic moiety with Ile^5-angiotensin II. Therefore, the applicant has properly justified that angiotensin II contained in Giapreza (Ile5 angiotensin II acetate) does not expose the patient to the same therapeutic moiety as any active substance in a product already authorised in the EU.

The CHMP, based on the available data, considers angiotensin II acetate contained in Giapreza to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Giapreza (angiotensin II acetate) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Giapreza (angiotensin II) is for the treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

There is no universal consensus definition of distributive or vasodilatory refractory shock, and the causes of shock may be diverse. Therefore, the target population is difficult to define. The most common causes of distributive shock are sepsis, inflammation, vasoplegia, and severe drug reactions (Armstrong et al 2017). Proposed definitions include failure to achieve a BP goal despite vasopressor therapy, need for rescue vasopressor therapy, or need for high vasopressor doses [Jentzer et al. Chest 2018;154:416-426]. Clinical features of high-output distributive shock includes central venous oxygen saturation > 70% (either by oximetry catheter or by central venous blood gas) and central venous pressure (CVP) > 8 mmHg or Cardiac index > 2.3 L/min/m2. Inclusion criteria of the ATHOS-3 pivotal trial were consistent with these features.

3.1.2. Available therapies and unmet medical need

The treatment of distributive shock includes the treatment of the underlying causes (e.g.: infections in septic shock, etc.), fluid resuscitation and vasopressors.

A minimum of 30 ml/kg of crystalloids (1.5-3 litres) is advised for most patients to qualify as adequate fluid resuscitation. In ATHOS-3, actual volumes of fluid administered to meet inclusion criterion #4 (≥ 25 mL/kg in the previous 24 hours) were not recorded. The mean (SD) volume of fluid administered IV during the first three hours of study drug treatment was 665.41 (400.061) mL for patients in the placebo arm and 563.10 (539.995) mL for patients in the LJPC-501 arm (p = 0.0002), with median volumes of 602.5 mL and 447.0 mL, respectively. The mean CVP was 13.3 mmHg, and can be considered above the target CVP values of 8–12 mmHg [Rivers et al. N Engl J Med. 2001;345:1368–77]. Therefore, these data support that volume resuscitation was appropriate and even slightly above the target.

The main four vasoconstrictive hormones secreted in response to shock in order to defend blood pressure are epinephrine, norepinephrine, vasopressin and angiotensin. In Europe, where consensus guidelines are widely adopted, the most commonly recommended and used first-line vasopressors in this setting are catecholamines, particularly norepinephrine. Since their introduction, application of these guidelines has been shown to have improved patient outcomes including reducing mortality (Herrán-Monge 2017, Sánchez 2017, Ferrer 2008). With respect to refractoriness, a reasonable definition of refractory shock would be an inadequate response to high-dose vasopressor therapy (defined as ≥ 0.5 mg/kg/min norepinephrine-equivalent dose) [Bassi et al, Crit Care Pract. 2013]. However, in the pivotal ATHOS-3 trial, CRH was defined as requiring a total sum catecholamine dose of > 0.2 mcg/kg/min for the last 6-48 hours, to maintain a MAP between 55-70 mmHg. Therefore, patients were not necessarily receiving maximum catecholamine doses at baseline.

Second-line vasopressors include the posterior pituitary hormones vasopressin and arginine vasopressin (argipressin). Vasopressin is not authorised across all EU countries and is not commonly used to treat vasodilatory shock in Europe. In countries where vasopressin has a national marketing authorisation for any indication (e.g., the Netherlands), its use is reserved for off-label ‘rescue’ treatment in patients who fail to achieve an adequate MAP response with catecholamines. Empressin (argipressin or arginin-vasopressin) is another vasopressin analogue that is authorised in several EU countries “for the treatment of catecholamine refractory hypotension following septic shock in patients older than 18 years.” Therefore, angiotensin II may become the third approved second-line vasopressor drug (behind vasopressin and argipressin) for this patient group in the EU.

Both catecholamines and vasopressin have narrow therapeutic windows with toxic effects at higher doses (Dünser 2017, Dünser 2009), including cardiac and digital ischaemia with norepinephrine (Russell 2018, Russell 2008) and ischaemic skin lesions with vasopressin (Dünser 2003). It can be difficult to titrate vasopressin to achieve and maintain the desired MAP, and since it is not fast-acting (peak effect at 15 minutes; Vasostrict Prescribing Information), this may further complicate its use (Malay 2004) and leave patients hypotensive for longer. Only 45% of patients with vasodilatory shock who receive vasopressin have a blood pressure response (Sacha 2018), therefore there remains a significant unmet need for CRH patients who are also resistant to vasopressin.

Although glucocorticoid therapy in shock remains controversial with conflicting evidence regarding a mortality benefit, there is consistent and recent evidence supporting a more rapid resolution of shock [Annane D, et al. N Engl J Med 2018;378:809-18; Venkatesh et al. N Engl J Med. 2018; DOI: 10.1056/NEJMoa1705835], and they can also be considered among rescue therapies available in refractory shock.

A recent review (Bassi 2013) indicates patients requiring high dose vasopressors have a > 50% all-cause mortality. Thus, a significant unmet medical need exists for effective vasopressor therapies in patients with vasodilatory shock who remain hypotensive despite fluid and current standard of care vasopressor therapy. A vasopressor with a different mechanism of action compared with existing therapies would be a valuable addition to the protocols used to restore adequate MAP in these patients, provided that its efficacy and safety are demonstrated.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a single phase III multicenter, placebo-controlled, randomized study (LJ501-CRH01; ATHOS-3) to determine the safety and efficacy of angiotensin II in patients with distributive shock (mainly septic shock) refractory to catecholamines and other vasopressors. Angiotensin II was given at a starting dose of 20 ng/kg/min. The dose could be titrated as often as every 5 minutes based on current MAP, determined as the average of 3 MAP values at least 1 minute apart prior to change in infusion rate. The maximal maintenance dose was 40 ng/kg/min after 3 hours. Since eligible patients received standard-of-care fluid resuscitation prior to study drug treatment and continued to receive standard-of-care catecholamine and/or other vasopressor treatment during study drug treatment, placebo can considered to be an acceptable choice of control in a parallel treatment group.

The main inclusion criteria were high-output shock with hypotension resistant to catecholamines. High output shock was characterized by a central venous oxygen saturation > 70% (measured by oximetry catheter or central venous blood gas) and central venous pressure > 8 mmHg or a cardiac index > 2.3 L/min/m2. The CHMP agreed with this definition. The indication pursued (distributive or vasodilatory shock) inherently reflects the term "high-output shock" used in the ATHOS-3 study protocol. Hypotension was defined as a MAP < 65 mmHg and resistance to catecholamines with or without other vasopressors, defined as requiring a sum vasopressor dose (norepinephrine-equivalent dose, NED) > 0.2 µg/kg/min, since doses above 0.1 µg/kg/min in high-dose vasopressor-dependent shock were associated with mortality in excess of 50% across several studies. The definition of resistance to catecholamines was quite liberal in view of the CHMP, given that NED > 0.5 microg/kg/min are not unusual in these patients. The positive consequence was that the broad definition allowed to investigate the angiotensin II effect on MAP response on top of different NED ranges. On the contrary, the inclusion of patients not on maximum catecholamine doses, coupled with the recommendation of not increasing NED in the placebo group up to 3 hours (measurement of primary endpoint), were considered as features of a proof-of concept study under highly controlled conditions favouring the demonstration of a treatment effect.

The primary efficacy endpoint was a surrogate endpoint defined as the proportion of patients in each treatment group with an average MAP ≥ 75 mmHg or with a ≥ 10 mmHg increase in MAP above Baseline MAP at Hour 3, without an increase in standard-of-care vasopressor doses prior to Hour 3.

3.2. Favourable effects

The single pivotal study LJ501-CRH01 (ATHOS-3) was conducted at 128 sites in 10 countries and recruited 321 patients with refractory hypotension and shock.

The target MAP at Hour 3 (primary outcome) was obtained in 69.9% of patients receiving LJPC-501 and in 23.4% of patients receiving placebo (OR, 7.95; 95% CI: 4.76–13.3; p < 0.0001). Therefore, angiotensin II was clearly superior to placebo in increasing blood pressure to MAP target > 75 mmHg. The multivariate analysis of MAP response (OR, 12.4; 95% CI: 6.72-22.8; p < 0.0001) supported the results obtained in the primary univariate analysis.

Cardiovascular (CV) SOFA score was chosen by the sponsor as key secondary endpoint. Between group differences in CV SOFA score at 48 hours were 0.47 points, which was statistically significant but of uncertain clinical relevance, as the minimum difference of clinical relevance for CV SOFA score is not defined in the literature. In addition, CV SOFA score measured the same thing than the primary endpoint, as achieving a SOFA score = 0 (33% of patients in the experimental group vs. 23% in the placebo group), is driving the between-group difference in CV SOFA and equals to have a response with MAP $\geq$ 70 mmHg, the latter being the main component of the primary efficacy endpoint. Furthermore, the improvement in mean CV SOFA score at 48 hours by 0.47 points may be simply an artifact of the study design, which listed catecholamines but not angiotensin II on the CV SCOFA score calculation (sparing part of the protocol after 3 hours). Simply replacing a vasopressor by another (i.e.: epinephrine by angiotensin II) was not considered itself as clinically beneficial in the opinion of the CHMP, as there is no evidence that angiotensin is a safer vasoconstrictor than catecholamines.

Mortality at day 28 was 46% in the LJPC-501 group and 54% in the placebo group in the mITT population (8% absolute risk difference). In univariate analysis, the HR for all-cause mortality was 0.78 (95% CI: 0.57–1.07; unstratified logrank test). Randomization to LJPC-501 was not a factor associated with a lower mortality risk, and the hazard ratio for LJPC-501 versus placebo in the final multivariate model was 0.89 (95% CI, 0.64–1.24). Regarding causes of death, the majority of patients died from sepsis, while cardiac or vascular death rates were 7.9% and 12.7% in the angiotensin and placebo groups, respectively (a 4.7% absolute risk difference). The study was not powered/designed to show differences in mortality or morbidity, and therefore, the results of this, mainly proof-of-concept study, are within expected for a mortality exploratory outcome (i.e.: inconclusive). It was considered positive that survival tended to be in favor of the experimental group. However, the more conservative conclusion that we could take from this exploratory analysis at this stage is that, looking at the upper 95%CI of the HR in the final multivariate model for death provided, a relative increase in mortality with angiotensin II ≥ 25% could be, in principle, ruled out.

The sponsor analysed 18 different pre-specified subgroup analyses, which were generally consistent with those obtained in the overall population (i.e.: consistent effect of angiotensin II versus placebo in achieving MAP response and favourable trend in survival). The raising blood pressure effect was consistent regardless of baseline NED and, in the CHMP's opinion, there was no need to restrict the indication to those sicker patients with a NED ≥0.5 microg/kg/min, although from a recommendation of use in clinical practice, this sub-population can be considered the more refractory one. Data from subgroups also suggest that angiotensin II increases the MAP response regardless of the baseline angiotensin levels.

3.3. Uncertainties and limitations about favourable effects

The study was powered for the primary endpoint (increase in MAP), which is considered a surrogate pharmacodynamic endpoint, but underpowered for morbidity/mortality endpoints. Therefore the CHMP considered that the effects of angiotensin II on morbidity and mortality has not been determined in appropriate studies as also reflected in the SmPC. In patients with severe shock, prevention of progression (or reversal) of organ damage, as well as the reduction in all-cause mortality are considered the more relevant outcomes. In the 2018 CHMP follow-up SA, a post-authorisation placebo-controlled study in patients with shock and advanced kidney injury (AKI), powered to show an effect on resolution of organ failure and survival, was proposed to alleviate these concerns. This study according to the agreed protocol was included in Annex II as condition to the MA.

The ATHOS-3 pivotal study mainly included patients from North-America. Only 33 European patients contributed to the mITT/safety population (19 on angiotensin II and 14 on placebo). In Europe, there was less use of vasopressin and the doses of catecholamines were higher. There were also regional differences in angiotensin II concentrations at baseline, with North-American patients having the lowest values. In multivariate analyses of mortality, enrolment in North-America was an independent risk factor for death. Some clinical outcomes across sub-populations showed significant discrepancies at geographical level for instance for responder rates odd-ratio (OR=6.6, OR=9.5 et OR=28.2 respectively in US/Canada, AUS/NZL and EU), lack of response in the EU placebo arm (7% responder rate versus more than 20% in other regions placebo) or for the difference in mortality rates at 28 days between US and other countries involved in the trial (HR=1.80 with 95% CI [1.18 - 2.76], p=0.0066). Only about 6% of patients in the study received a high vasopressor dose at baseline (NED > 1 microg/kg/min), which was considered poorly representative of European practice. Therefore, the place of the treatment in the clinical practice and target population needed to be further discussed during the procedure and clearly defined. A revised wording of the indication and posology was agreed that defines the conditions of administration and the target population which could benefit from the LJPC-501 treatment while minimising the risk of adverse event.

The vast majority of patients (90%) had septic shock as the cause of hypotension. The following more frequent underlying cause was vasoplegia. Therefore, non-septic shocks were poorly represented. The trend towards better outcome in MAP response and survival was observed regardless of the type of shock. As patients with septic shock were the predominant population, a specific mention regarding septic shock was deemed appropriate and included in the wording of the indication.

No dedicated studies have been conducted in the elderly, renal or hepatic impairment. Main efficacy (MAP response, mortality) and safety data in ATHOS-3 trial were provided by age ranges, and also for patients with renal failure (on AKI/RRT at baseline) and patients with hepatic impairment in the ATHOS-3 study. Treatment effect was consistent in subgroups by age and presence of renal or hepatic impairment at baseline. However, elderly patients >75 yrs were poorly represented in the trial. Section 4.2 includes a statement to address the scarce data available in this aged population however it was also agreed that no special dose adjustment is required in patients over 75 years. The majority of patients had a dose decrease of LJPC-501 after a starting dose of 20 ng/kg/min, thus indicating a short onset of action in reaching MAP targets. At 30 minutes, most patients (67%) required doses below the 20 ng/kg/min starting dose, half of patients required 5 ng/kg/min or less and 24% of patients required 2.5 ng/kg/min or less. In addition, in the expanded access study that was provided as supportive, the recommended starting dose was 5 ng/kg/min instead of 20 ng/kg/min. The applicant was requested to discuss about the benefits and risks of recommending a 20 ng/kg/min starting dose instead of a 5 ng/kg/min starting dose recommended in the ongoing, at the time of the evaluation, expanded access study. The applicant provided additional safety data suggesting that a starting dose of 20 ng/kg/min (tested in the ATHOS-3 study) is not likely to cause harm in drug-sensitive patients, but a smaller subset of less sensitive patients might have an extended time with low MAP if drug needed to be up-titrated from 5 ng/kg/min to the maximum recommended dose of 80 ng/kg/min. Therefore, the proposed 20 ng/kg/min starting dose was considered acceptable.

As specified in the protocol, other vasopressors were not to be increased during Hour 0 to Hour 3 unless for safety reasons. This protocol feature, which is more reflective of a proof-of concept study than of a confirmatory study, allowed for an artificial comparison in which most patients in the placebo group did not receive the best standard of care during the first 3 hours (the rule was not to up-titrate concomitant vasopressors in the control group), while the vasopressor angiotensin dose could be up-titrated in the experimental group on demand. Even with the said protocol restriction, there was an increase in NED in the placebo group during the first 3 hours that can be explained by the "safety reason" exception included as a result of the expected life-threatening lack of efficacy of placebo in at least a proportion of these patients. Mortality rates were higher in patients in the placebo arm who received increases in SOC vasopressors during the first 3 hours (as measured by NED) regardless of changes in MAP at Hour 3. Patients in the placebo arm with an increase in NED during the first 3 hours of treatment tended to be older and have lower Baseline MAP within both “response” and “no response” subgroups. It was concluded that the delay of titration of standard-of-care vasopressors did not have a significant effect on 28-day mortality for patients in the placebo arm.

One of the exclusion criteria was the use of hydrocortisone > 500 mg/day or equivalent glucocorticoid medication. However, there was a significant use of hydrocortisone during the study, with a significant imbalance between treatment groups (48.5% of patients in the angiotensin II group and only 33.5% in patients on the placebo group were administered hydrocortisone; non-specified dose). As glucocorticoid therapy can be considered among the rescue therapies available in refractory shock, the potential influence of the imbalance in hydrocortisone use between treatment groups in the study results was explored. HR of MAP response tended to be lower in patients on hydrocortisone compared to the subgroup of patients not on hydrocortisone (HR: 5.88 vs. 10.2), but subgroup interaction was not statistically significant. The same trend of attenuated effect of angiotensin II was also found for the HR of day 28 mortality rates (HR: 0.90 vs. 0.67), but again subgroup interaction was not statistically significant. In addition, the post-hoc nature of these analyses, coupled with potential differences in baseline characteristics between subgroups not defined a priori, prevented from any meaningful conclusion.

In ATHOS-3 study, total SOFA score at baseline was approximately 11.77 points in the angiotensin group and 12.72 points in the placebo group, which was translated into a mortality rate of 46% in the angiotensin group and 54% in the placebo group at day 28. According to the calculation done during the procedure, the baseline imbalance in total SOFA score was statistically significant (angiotensin II SOFA score 11.77 points vs. placebo 12.72 points; Difference: -0.95; 95%CI: -1.63 to -0.27), suggesting that sicker patients were randomized to placebo. SOFA score at screening was not investigated as covariate for mortality. The applicant explained that a higher total SOFA score tended to be associated with poorer survival (HR = 1.38; 95% CI: 0.97-1.96), but the trend was not statistically significant (p = 0.0760), and therefore the final model did not include total SOFA score. However, a higher total SOFA score was significantly associated to a higher mortality risk within the placebo group (HR: 1.84; 95%CI: 1.19 to 2.84; p=0.0053). In addition, the analysis of the relative risk of death in patients with SOFA >12 (59%; 85 or 145) versus SOFA ≤12 (43%; 74 of 171) in the overall population of patients in the study (regardless of treatment group) was also statistically significant (RR: 1.35; 95%CI: 1.09 to 1.69); p=0.0067). Multivariate analyses including baseline SOFA score as covariate yields a HR 0.92 (0.66 - 1.27) p=0.6015 for the comparison between angiotensin-II and placebo in mortality. This point estimate is more realistic than the unadjusted HR reported in the publication (HR, 0.78; 95% CI, 0.57 to 1.07; P = 0.12) (Khanna et al. N Engl J Med 2017;377:419-30.).

Total SOFA score at 48 hours worsened 1.04 points in the angiotensin II group and 1.05 points in the placebo group (0.01 point difference). Therefore, on the basis of minimal changes obtained in the total SOFA score vs. placebo at 48 h, a beneficial effect of angiotensin in mortality cannot be anticipated. Finally, the lack of effect (no decrease vs. placebo) in total SOFA score at 48 hours was in favour of a spurious finding for the CV SOFA score.

In subgroup analyses, the group of sicker patients (i.e.: baseline MAP < 65 mmHg, Baseline APACHE-II > 30, baseline NED > 5 microg/kg/min) had less MAP response to angiotensin vs. placebo than the other subgroups, but on the contrary, a more favourable trend in survival. The applicant was requested to explore the individual correlation between both outcomes (i.e.: having a MAP response and survival; not having a MAP response and mortality) for all study patients and separately for angiotensin and placebo patients. With treatment groups combined, there were 62 deaths among 151 responders (41.0% mortality by Day 28) and 98 deaths among 170 non responders (57.6% mortality). By treatment group and MAP response, the best subgroup in mortality was comprised by the 114 responders to angiotensin-II (35% mortality), followed by 121 non-responders to placebo (52% mortality), 37 responders to placebo (59% mortality) and 49 non-responders to angiotensin (71% mortality). Therefore, MAP response was a predictor of survival in the angiotensin-II group but not in the placebo group. Overall, the data suggest that angiotensin-II may rescue some additional patients compared to placebo, and that the lack of response to angiotensin-II is a marker of poor prognosis. The potential benefit in morbidity and further reassurance regarding mortality will be further studied in the planned post-authorisation efficacy trial.

In order to alleviate to some extent the lack of proven benefit in mortality and morbidity, the investigators conducted a "post-hoc" subgroup analysis in patients with acute kidney injury (AKI) treated with renal replacement therapy (RRT) at initiation of angiotensin II or placebo (n= 45 and n= 60, respectively) [Tumlin et al, 2018. Crit Care Med. 2018;46:949-957]. This subgroup was defined post hoc and was reported in the Summary of Clinical Efficacy, but was not included in the ATHOS-3 CSR. Angiotensin was superior to placebo in the main outcome of MAP response also in this subgroup. The fact that angiotensin II raises blood pressure is well understood. In the AKI/RRT subgroup, among the 60 patients with AKI receiving placebo, 9 (15%) had discontinued RRT by Day 7, compared with 17 (38%) of the 45 patients with AKI receiving LJPC-501. However, this post-hoc analysis did not consider that, in the same period, in patients with no AKI/RRT at baseline, more patients in the angiotensin group (n=13) started RRT versus only 10 on placebo (LJ501-CRH01 CSR). The small sample size in this subgroup also prevents from firm conclusions regarding the potential benefit of angiotensin II in preventing/reversing renal failure. With respect to mortality, despite the publication claimed a "robust" survival benefit attributable to angiotensin II in the AKI/RRT subgroup, this conclusion was not supported by the data available according to the CHMP as the expected effect regarding mortality may have been overestimated in this exploratory post-hoc analysis. Mean/median SOFA scores were higher in the LJPC-501 group than the placebo group for patients with AKI/RRT (p = 0.0130). On the contrary, there were more patients with SOFA > 12 in the placebo group than in the LJPC-501 (78.3% vs. 65.9%; p =0.1582), which may suggest that the sickest patients with more advanced organ failure fell in the placebo group. The dossier included an interim analysis, dated on 17 March 2018, with 53 patients included in an ongoing prospective cohort expanded access protocol with similar inclusion criteria than the ATHOS-3 study (adult patients with distributive or vasodilatory shock who remained hypotensive despite fluid and vasopressor therapy). Overall, 31 of 53 (59%) patients have died up to day 28, including 21 (40%) patients who died on or before Day 7. No effectiveness or demographic data are available, and between study comparisons are fraught with risk. Notwithstanding, mortality reported with angiotensin II in the expanded access protocol (59%) seemed similar or even higher than that reported with placebo in the ATHOS-3 trial (54%), and much higher than the mortality rates reported with angiotensin II in the overall population ATHOS-3 trial (46%) and in the high-risk subgroup with AKI/RRT at baseline (47%). These data highlights the need for controlled data on mortality/morbidity versus best standard of care, to assess whether an increase in MAP versus placebo shown in the ATHOS-3 trial would translate into benefits in morbidity and/or mortality.

3.4. Unfavourable effects

Safety data relevant to this application come primarily from the only pivotal trial in patients ATHOS-3 trial. This study included 163 patients treated with angiotensin II and 158 with placebo. Median duration of exposure was 48 hours in both treatment groups. Twenty-five patients continued LJPC-501 after Hour 48. Maximum duration of study drug infusion was 60 hours in the placebo group and 168 hours (1 patient) in the LJPC-501 group; 13 patients received at least 72 hours of LJPC-501 compared with no patients in the placebo group. While the size of the safety database is modest, it was considered sufficient taking into account the supportive safety data available from an expanded access protocol and literature, the short half-life of the product and the setting of use (acute and hospital settings where patients will be monitored closely).

Frequencies of fatal events were numerically lower in the LJPC-501 than in the placebo group (46.6% vs. 53.8%). Looking at the upper 95%CI of the HR in the final multivariate model provided for death (HR: 0.89; 95% CI, 0.64–1.24), a relative increase in mortality with angiotensin II ≥ 25% could be, in principle, ruled out. Multiorgan failures were the most common fatal events in both treatment groups. Fatal cardiovascular disorders such as cardiac arrests, cardiogenic shock, and cardio-respiratory arrest were more common in the placebo group (9.5%) compared with LJPC-501 (6.1%).

The expected adverse events for a vasopressor like angiotensin II include different types of ischemic events, tachycardia and hypertension. Thromboembolic events are normally unexpected for a vasopressor but have been linked to angiotensin II in the ATHOS-3 pivotal trial and also in the literature. These events are discussed hereafter.

The overall incidence of arterial ischaemic TEAEs was similar between treatment groups, but grade 3/4 ischaemic AESIs were reported for 13 (8.0%) patients in the LJPC-501 group and 8 (5.1%) patients on placebo. The difference was mainly driven by more cases of peripheral ischaemia and more cases of ischemia in the CNS. In spite of the small number of events limiting the interpretation of the data, these findings are concerning. This risk is important because it is common and may be associated with serious long-term outcomes for the patient, such as the loss of a digit or impaired neurological function. The risk may be minimised by administering LJPC-501 under constant blood pressure monitoring at the lowest dose that is compatible with adequate arterial blood pressure and adequate tissue perfusion.

Thromboembolic events have also been linked to angiotensin II in the ATHOS-3 pivotal trial versus placebo (12.9% vs. 5.1%). DVT was the most frequently one, occurring in 7 (4.3%) patients in the LJPC-501 group. Angiotensin is known to induce platelet adhesion and aggregation, and also to reduce the activity of the endogenous fibrinolytic system by activations of the plasminogen activator inhibitor-1. Given the significant imbalance in thromboembolic events and biological plausibility, thromboembolism has been therefore considered an identified risk that may be minimised by antithrombotic prophylaxis. A recommendation to apply venous thromboembolism prophylaxis, unless contraindicated, has been included in SmPC section 4.4.

The pre-specified cardiovascular events in the protocol were a mix of cardiovascular events of different clinical relevance and did not include a composite of major adverse cardiovascular events (MACE). The applicant was requested to analyse a composite of all major cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) as well as MACE-plus (unstable angina, need for revascularization, acute heart failure/worsening of existent heart failure, TIA and sudden death) in order to better characterize the cardiovascular risk profile of the product in line with the *EMA Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)*. The incidence of MACE (2.5% vs 6.7%) and MACE-plus (7.4% vs 11.4%) were numerically lower in the LJPC-5001 arm than in the placebo arm, which is reassuring.

Sinus tachycardia, tachycardia and supraventricular tachycardia, not including tachyarrhythmias such as atrial or ventricular tachycardia was reported more frequently with angiotensin than with placebo (8.6% vs. 5.7%). It was agreed to include tachycardia as common adverse reaction in the SmPC. A formal QT study was not conducted. However ECG parameters were measured in the ATHOS-3 pivotal trial. There was no evidence of QTc prolongation in either treatment group. QT prolongation (in the Investigations SOC) was reported as an adverse event for 1 (0.6%) patient in the LJPC-501 group and 4 (2.5%) patients on placebo.

Transient hypertension was reported in 37 patients during treatment with angiotensin II. "Transient hypertension" is derived from the primary mechanism of action of the drug and has been included as adverse reaction in the SmPC.

In the LJ501-CRH01 study, hypotensive events (including the preferred terms of hypotension, shock, septic shock, distributive shock, and cardiogenic shock) occurred in 40 (24.5%) patients in the LJPC-501 group and in 28 (17.7%) patients in the placebo group. According to the presented data, many of these AEs were reported some time after LJPC-501 was discontinued and reflect a recurrence of the underlying hypotension. A subset of hypotensive adverse events was reported at the time of LJPC-501 discontinuation and may reflect a direct link to the protocol-mandated down-titration of study drug at 48 hours. Due to the above-mentioned reasons, hypotension is not considered an adverse reaction to angiotensin II and has been removed from section 4.8 of the SmPC. It is, however, an identified risk that can be prevented with the recommendations for use under continuous monitoring and gradual withdrawal of Giapreza as described in the in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Safety database seems, in principle, sufficient to reasonably rule out a relative increase in mortality with angiotensin II ≥ 27% (amending multivariate analyses considering SOFA score at baseline as covariate), but it is insufficient to characterize the risk of worsening in renal function and to fully characterize thromboembolic events as well as infrequent adverse events. The laboratory results indicated a slightly worse renal profile in the LJPC- 501 arm compared to the placebo arm. A potential harmful effect of LJPC- 501 on renal function cannot be ruled out based on the drug's 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 favour of LJPC-501. In principle, the short term administration of angiotensin II in patients with vasodilatory shock may be of benefit due to its effect in increasing MAP, thus increasing renal perfusion, and it is unlikely to exacerbate the acute kidney injury that is observed in up to 50% of patients with septic shock. The effects on renal function will be tested further in the post-authorisation efficacy study. Thromboembolic events and infrequent adverse events will be evaluated as well in this trial. As angiotensin has been tested as add-on therapy, there are no head to head comparisons with other vasopressors. Whether the substitution of catecholamines or vasopressin by angiotensin II represents a safety advantage is pending to be established.

Finally, Giapreza was approved for use in the US on 21 December 2017 and was available on the market from 06 February 2018. There have been no spontaneous reporting of AEs or SAEs up to the cut-off date of 01 March 2018 and no new signals were identified up to 30 November 2018. However, there was a particularly high incidence of SAEs in the expanded access study (EAP). It can be summarised that in this EAP study, many patients did not meet all study protocol entry criteria due to the critical conditions encountered. Therefore, patients in particularly serious medical situations experienced high rates of SAEs, which was not unexpected. The most frequently unmet exclusion criteria were MELD score ≥ 30, absolute neutrophil count < 500 cells/mm3, and inclusion criteria was cardiac index > 2.3 l/min/m². However, this is particularly difficult to understand, since notably 38 patients with baseline MELD score ≥ 30 were also included in study LJ501-CRH01. It was agreed to mention cardiogenic shock as non-indicated in the SmPC, since there is a demonstrated risk of misuse in the critical emergency situations, while there are no efficacy data in this clinical setting. Indeed, real life patients are also expected to be similar to patients of the LJ501-EAP01 study (rather than the selected patients of LJ501-CRH01). The CHMP agreed that the risk of misuse will be diminished with addition of the amendments to the SmPC (i.e.: qualifying the target populations as those with refractory vasodilatory shock and including a warning about not using the product in patients with other types of shock, like cardiogenic shock).

3.6. Effects Table

Table 35 Effects Table for Giapreza (angiotensin II) for the treatment of hypotension in patients with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

Effect	Short Description	Unit	Giapreza	Placebo Control	Uncertainties / Strength of evidence	Ref.
Favourable Effects						
MAP	Percentage of patients with MAP response at hour 3	%	69.6%	23.4%	Robust effect in different subgroups and ancillary analyses, but surrogate PD endpoint.	1
CV SOFA score	Mean change in CV SOFA score from screening to hour 48	Mean (SD)	-1.75 (1.77)	-1.28 (1.65)	Statistically significant decrease (0.0129), but a -0.47 point difference is of uncertain relevance. Closely related to the primary endpoint. Potential bias in outcome definition.	1
Uncertain effects (exploratory analyses of relevant outcomes)*						
Total SOFA	Mean change in total SOFA score from screening to hour 48	Mean (SD)	+1.05 (5.50)	+1.04 (5.336)	Increased score in both groups, directly correlated with higher mortality (one point increase or difference is clinically relevant). Between-treatment difference was minimal: +0.01.	1
All-cause mortality	Death to day 28	%	46%	54%	8% difference (exploratory, not significant). Most patients died from underlying disease (sepsis).	1
Mortality due cardiac or vascular disorders	CV deaths to day 28	%	7.9%	12.7%	4.8% difference (exploratory, not significant). For a vasopressor, CV death may be more reflective of drug effect than all-cause death.	Table 26. Summary of Clinical Safety
Unfavourable Effects						
Thromboembolism	Study period	%	12.9%	5.1%	5.5% vs. 2.5% were serious. Most of the difference is due to DVT (4.3% vs. 0%). Consistent with prothrombotic effects of angiotensin (platelet activation, blocking of fibrinolysis). Identified risk. Could be minimized with antithrombotic prophylaxis.	1
Peripheral ischemia	Study period	%	4.3%	2.5%	Of them 3.1% in the experimental group and 1.9% in the placebo group were of grade 3/4 severity. This is an identified risk. Further quantification of the risk of ischemic events is needed post-authorisation (not only limited to peripheral ischemia, but including cerebral, cardiac and liver ischemia as well).	Table 31. Current report.

Effect	Short Description	Unit	Giapreza	Placebo Control	Uncertainties/ Strength of evidence	Ref.
Transient hypertension†	First 3 hours of treatment	%	22.7%	0%	The recommended starting dose (20ng/kg/min) had no impact on patient's safety and therefore it is deemed appropriate. Posology section of the SmPC reflects the need for careful dose titration.	1
(Post-treatment) hypotension	Study period	%	24.5%	17.7%	Not an adverse event but an identified risk. Mainly occurred in ATHOS-3 study after protocol mandatory drug down-titration after 48 hours. Manageable with the warnings in the SmPC (slow down-titration at withdrawal) and in the context of continuous monitoring in the ICU.	1
Tachy-arrhythmias	Study period	%	8.6%	5.7%	Difference mainly driven by non-serious tachycardia. Included as adverse reaction.	1

1 = Clinical Assessment Report; CV = cardiovascular; DVT = deep vein thrombosis; ICU = intensive care unit; MAP = mean arterial pressure; SD = standard deviation; SOFA = sequential organ failure assessment.
*In this application is equally important what the company has provided (a robust effect in increasing blood pressure) and what the company has not provided (i.e.: evidence on a beneficial effect in mortality, prevention/recover of organ failure)
† This transient hypertension is distinct from hypertension recorded as an AE throughout the study. The frequency of hypertension recorded as an AE through Day 28 was 5.5% in the LJPC-501 group and 5.7% in the placebo group (Summary of Clinical Safety).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal trial ATHOS-3 shows a robust effect of angiotensin II in increasing MAP in patients with vasodilatory or distributive shock on top of fluid and vasopressor therapy. It is known that failure to achieve MAP > 70 mmHg in shock is associated with very high mortality rates exceeding 50%. It could be argued if vasopressor therapy in patients recruited into the ATHOS-3 trial could be further optimised as only 29% of patients were on maximum doses of vasopressors (i.e.: NED > 0.5 ng/kg/min). The blood pressure raising effect of angiotensin II was achieved in all patients regardless of baseline equivalent norepinephrine doses (NED) (above or below 0.5 microg/kg/min at baseline).

The primary outcome (MAP response) was considered a surrogate endpoint. The more relevant outcome in patients with refractory distributive/vasodilatory shock is all-cause mortality. The effect on all-cause mortality tended to be in favour of angiotensin II in the ATHOS-3 trial compared to placebo. However, the sample size was insufficient to reach meaningful conclusions and further reassurance regarding the potential effect on mortality will be further evaluated in the post-authorisation study but is difficult to predict, mainly because most patients in this setting die from sepsis, and a vasopressor is unlikely to reduce the risk. It could be expected that in patients with no other treatment alternatives who are refractory despite maximum vasopressor doses, the addition of angiotensin could result in a benefit in mortality due to cardiocirculatory collapse. However, angiotensin is also associated with ischemic and thrombotic events, which could offset this potential benefit.

In general, the adverse events reported with angiotensin II were within those described in the literature for other forms of angiotensin (i.e.: bovine angiotensin) and, in general for vasopressors, like ischemic events (mainly, but not limited, to peripheral events) and tachycardia. These events could be manageable by using the lowest angiotensin effective dose during the shorter possible time after patient's improvement. The main and important difference with other vasopressors is the risk of thromboembolic events, which were reported in 13% of patients (mainly DVTs) compared with 5% on placebo. These events are frequent in immobilised patients at the ICU, and could be prevented by the application of appropriate thromboprophylaxis. The main issue is that many of ICU patients with septic shock have thrombocytopenia or are at risk of bleeding, and therefore not all of them will be candidates to chemical thromboprophylaxis (with LMWH). In patients with contraindications to chemical thromboprophylaxis, mechanical thromboprophylaxis should be applied.

3.7.2. Balance of benefits and risks

Angiotensin II has shown to be effective in increasing MAP in patients with vasodilatory or distributive shock on top of fluid and vasopressor therapy, but the effect of angiotensin II on morbidity and mortality has not been determined as morbidity and mortality, were exploratory endpoints in the single pivotal trial.

Although the restoration of blood pressure is of main clinical relevance, there was uncertainty about whether this restoration conferred a clinical benefit, as there was a lack of improvement of total SOFA score over placebo and lack of significant improvement in the overall mortality at both Day 7 and Day 28 or any other objective assessment that would indicate clinical benefit other than increased blood pressure. Moreover, when considering observed adverse events, safety data did not show any improvement of the well-known vasopressor toxicity or on the worsening of the disease in the LJPC-501 arm compared to placebo. The applicant discussed whether the effect of LJPC-501 on blood pressure can be associated with a particular clinical benefit. Looking at subgroup analyses, the treatment effect of LJPC-501 in raising and then supporting MAP when added to SOC vasopressors was particularly high in the group of patients in whom SOC vasopressors are ineffective, as evidenced by a failure to achieve the international consensus minimum target MAP of 65 mmHg. In this group, LJPC-501 was found to be nearly 3 times more effective in achieving a MAP > 65 mmHg when compared with placebo, with both arms receiving SOC vasopressors. A correlation has also been found from the literature and from exploratory analysis between achieving a MAP > 65 mmHg and survival benefit. Therefore, although the ATHOS-3 trial was not powered for mortality, the effect in raising MAP is likely to be correlated to a positive effect in survival. The same positive trend in mortality found in the subgroup of "Baseline MAP < 65 mmHg" was also found in other high risk-subgroups (e.g.: baseline APACHE II > 30; baseline AKI on RRT; baseline SOFA score >12; MELD score ≥ 20). The survival trend in the subgroup of patients with AKI represents a group of patients who may have a pronounced clinical benefit, which may be linked to increased renal perfusion. The extent of that benefit will be assessed in the planned post-authorisation clinical trial.

On the other hand, LJPC-501 treatment allowed for substantial vasopressor sparing, (mean change in CV SOFA −1.75 versus −1.28; p = 0.0129). Of particular clinical relevance, 40.5% of patients in the LJPC-501 group no longer required SOC vasopressors at Hour 48 compared with 28.5% of patients in the placebo group (Section 2.5.4.1.4.1.1). In exploratory analyses, patients who had at least a 50% reduction of vasopressor doses (NED) at Hour 24 were twice as likely to survive to Day 28 (p < 0.0001). Therefore, the vasopressor sparing effect (≥ 50% reduction in NED) can also be related to a better patient outcome. The applicant was also invited to discuss whether there is any subset of patients or any biomarkers (e.g., measure of glomerular filtration, cardiac function, intestinal perfusion) predictive of clinical benefit beyond the improvement of blood pressure. All available data supporting beneficial effect on vital organ perfusion were submitted. In the subgroup of patients with AKI who were on RRT at baseline, treatment with LJPC-501 led to improvements in key metrics of organ function, such as significantly more patients discontinuing RRT and ventilation, and more patients being discharged from the ICU and hospital by Day 28. This suggests a beneficial effect of treatment with LJPC-501 on kidney function, which may be due to increased kidney perfusion. A major limitation is that no direct measurements of organ perfusion of the heart, lungs, liver, kidney, intestine or brain were taken during the study. No other relevant data were available. A study protocol for the post-authorisation efficacy study (PAES) was agreed by the CHMP during the procedure. The proposed post-marketing study data will be periodically evaluated by a Data Safety Monitoring Committee (DSMC). The applicant will submit the study report at the latest by mid-2024.

3.7.3. Additional considerations on the benefit-risk balance

The CHMP is of the opinion that a post-authorization efficacy study (PAES) in a subpopulation at high risk of morbidity-mortality events (e.g.: patients with renal failure on AKI/RRT, with or without liver failure with MELD score ≥ 30, ARDS, SOFA score at baseline >15, baseline MAP < 65 mmHg, APACHE II score > 30, baseline NE-equivalent dose ≥ 0.5 µg/kg/min) with adequate representation of European patients/centers, is needed to further investigate the potential benefit in preventing organ damage and prolonging survival, as well as to provide additional safety data about ischemic and thromboembolic events. The protocol of the proposed PAES was agreed by CHMP (A phase 4, randomised, double-blind, placebo-controlled, multicentre study of LJPC-501 in adult patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy). The intention of this study is to confirm the potential clinical benefit imparted via improved haemodynamics. This will be done by providing data on the effect on morbidity events and organ perfusion, reassurance that there is no detrimental effect on mortality, additional safety data about ischemic and thromboembolic events and the record of clinical global impression of the response to treatment. The primary endpoint will be the change in NED from Baseline to Hour 2. The study drug must generate an increase in blood pressure response in order for the clinician to safely decrease the NED. The secondary endpoints will include mortality.

This study was included in Annex II as condition to the marketing authorization. It was agreed as well that the proposed study falls within the following criteria according to the EC DELEGATED REGULATION (EU) No 357/2014 as regards situations in which post-authorisation efficacy studies may be required: (a) an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions.

3.8. Conclusions

The overall B/R of Giapreza is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Giapreza is favourable in the following indication:

Giapreza is indicated for the treatment of refractory hypotension in adults with septic or other distributive shock who remain hypotensive despite adequate volume restitution and application of catecholamines and other available vasopressor therapies (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy and safety of Giapreza in the treatment of refractory hypotension in adults with septic or other distributive shock, the MAH should conduct and submit the results of a randomized, double-blind placebo-controlled multicentre study in adult patients with vasodilatory shock and associated severe acute kidney injury requiring renal replacement therapy to provide: (1) data on the effect of the product on morbidity events and organ perfusion with and adequate representation of European patients, (2) reassurance that there is no detrimental effect on mortality at day 28, (3) additional safety data about ischemic and thromboembolic events associated with the use of the product and (4) the record of clinical global impression of the response to treatment.	Submission of study results: 30 June 2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that angiotensin II acetate contained in Giapreza to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.