FDA Approval of Angiotensin II for the Treatment of Hypotension in Adults with Distributive Shock

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Abstract

Distributive shock is a subset of shock marked by decreased systemic vascular resistance, organ hypoperfusion and altered oxygen extraction. Despite the use of intravenous fluids and either higher dose of catecholamines or other additional exogenous vasopressors to maintain blood pressure in the target range, the rate of mortality remains higher in patients with septic shock. Therefore, there is clearly an unmet need for additional safe and effective treatments. The use of angiotensin II to raise the mean arterial pressure (MAP) could provide additional therapy and the opportunity to evaluate a catecholamine-sparing effect by decreasing the dose of concomitant catecholamines while maintaining a target MAP. ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock phase 3; ClinicalTrials.gov number, NCT02338843) was an adequate and well-controlled trial. The primary endpoint was the rate of MAP response at hour 3 of treatment with study drug, defined as either a 10-mmHg increase from baseline in MAP or a MAP of at least 75 mmHg. The secondary endpoints were changes from baseline in Sequential Organ Failure Assessment (SOFA) scores (total and cardiovascular). Mortality was an exploratory endpoint. The trial provided substantial evidence of the effectiveness of angiotensin II in raising blood pressure over placebo in patients with distributive shock, while keeping catecholamine levels constant. There was no change in the secondary endpoint of total SOFA scores relative to placebo when catecholamine use was reduced in lieu of angiotensin II treatment. There was a slight decrease in the secondary endpoint of cardiovascular SOFA score relative to placebo during the catecholamine-sparing phase, reflecting the catecholamine-sparing effect. There was a consistent trend in decreased mortality relative to placebo over the 28-day study period. Based on the agreements emanating from the special protocol assessment to assess blood pressure effects, the data from this single study supported approval of angiotensin II by the Food and Drug Administration for marketing in the USA.

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Key Points

Angiotensin II (Giapreza[®]) was shown to be efficacious in raising the mean arterial pressure (MAP) to target levels > 75 mmHg or 10 mmHg from baseline in patients at high risk of death.

The regulatory thinking behind approving a drug in distributive shock is to raise the MAP to provide time to treat the underlying condition.

The data from this trial did not conclusively demonstrate a clinical benefit other than raising the blood pressure.

1 Introduction

Distributive shock occurs in nearly 200,000 US adults yearly. It is often fatal despite intensive monitoring and treatment. It occurs despite normal cardiac function and a euvolemic state [1]. The cause of distributive shock is systemic inflammation that renders blood vessels unresponsive to endogenous vasoconstrictors. This causes redistribution of blood flow from the arterial system to the venous system resulting in adverse consequences for organ perfusion. The hemodynamic profile in distributive shock includes increased cardiac output, normal or decreased filling pressures, and a decreased systemic vascular resistance (SVR) [2]. By far the most frequent cause of distributive shock is sepsis. Other causes include pancreatitis, burns, toxic shock syndrome, anaphylaxis, adrenal insufficiency, reaction to drugs/toxins, heavy metal poisoning, hepatic insufficiency, and damage to the central nervous system.

The management of shock is based on a multitude of metrics, including heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urinary output, and hemodynamic measurements of cardiac status [3]. The “Surviving Sepsis Campaign Bundle: 2018” guidelines recommend fluid resuscitation and consideration of vasopressors within the first hour of the recognition of shock [4]. When rapid fluid replacement fails to restore adequate perfusion pressure (e.g., mean arterial pressure [MAP] to > 65 mmHg), exogenous vasopressors are introduced (catecholamines and non-catecholamines). The most widely used catecholamines include epinephrine and norepinephrine. These are neuromodulators of the sympathetic nervous system that have a direct effect on vascular smooth muscle cells. Dopamine, phenylephrine, and vasopressin are also used. The latter of these is a non-catecholamine vasoconstrictor that also promotes renal fluid retention and has been approved by the US Food and Drug Administration (FDA) to increase blood pressure in patients with severe hypotension. A compilation of drugs used to treat septic shock is listed in Table 1.

Most patients will respond to either volume replacement or vasopressors. However, approximately 6% of critically ill patients will develop refractory shock. Norepinephrine doses exceeding $0.1 \mu\text{g/kg/min}$ or rescue therapy with vasopressin is generally associated with mortality rates greater than 50%, whereas 94% of patients requiring doses above $100 \mu\text{g/min}$ of norepinephrine or epinephrine die [5]. The greater the number of vasopressors required, the higher the death rate; use of three pressors infused at full dose is associated with a mortality rate of 92% [6].

Septic shock that is refractory to catecholamine treatment is a life-threatening condition with significant mortality. This condition represents an important unmet medical need as

the currently available vasopressor therapies only leverage the vasopressin and adrenergic systems [3]. A third possible leverage point is the renin-angiotensin-aldosterone system, a homeostatic system that regulates blood pressure and fluid and electrolyte balance [7]. Angiotensin II, the principal hormone of the system, is a potent vasoconstrictor [7], and might be able to reverse the vasoplegia associated with septic shock [8]. This is the therapeutic context addressed in the ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock phase 3) trial of angiotensin II.

Use of angiotensin II as a pressor dates back to 1941, and there are reports of administration to healthy subjects for up to 11 days [8, 9]. Several reports of clinical use of angiotensin II to treat severe hypotension in septic shock have been published [3, 8, 10–13]. Based on a literature search, 31,281 subjects in 1124 studies have received angiotensin II (0.05 – 3780 ng/kg/min) [8]. Hypertensin[®], a modified bovine angiotensin II, was approved for treatment of shock and circulatory collapse by the US FDA in 1962, but the sponsor (Ciba-Geigy) subsequently withdrew the marketing application for reasons unrelated to safety.

The new drug application (NDA) for angiotensin II (Giapreza[®]) was submitted by La Jolla Pharmaceutical company, San Diego, CA (the Applicant), in June 2017 and approved by the agency on December 21, 2017. The standard time between NDA submission and approval is 12 months. The rapidity of this NDA review and subsequent approval was based on its Priority Review status, high submission quality, ease of review based on a small sample size relative to a standard cardiovascular clinical outcome phase 3 trial, and timely and high-quality responses from the Applicant to information requests from the review team.

2 Regulatory Review

2.1 Chemistry

The drug substance in Giapreza[®] is the acetate salt of synthetic angiotensin II, an octapeptide identical to endogenous human angiotensin II. The active pharmaceutical ingredient, a synthetic Ile5-angiotensin II acetate (human sequence) of Giapreza[®] was classified as a New Molecular Entity because it did not have exactly the same amino acid sequence, chemical form and origin as the previously marketed Hypertensin[®] (synthetic Val5-angiotensin-II amide; NDA 12-791). Both the N- and the C-terminus of the sequence are unmodified.

- Human angiotensin II: Asp¹-Arg-Val-Tyr-Ile⁵-His-Pro-Phe⁸ (This sequence is identical to the recently approved product, Giapreza[®]).

Table 1 Summary of treatment armamentarium relevant to proposed indication Source: Drug labels for FDA approved drugs

Product(s) name	Relevant indication	Year of approval	Dosing/administration	Efficacy information	Important safety and tolerability issues	Other comments
FDA approved treatments						
Epinephrine/NDA 205029	Hypotension and shock	2014	0.05–2.0 mcg/kg/min	Achieves MAP goal > 70 mmHg	Cardiac arrhythmias, renal impairment, caution with narrow-angle glaucoma, heart disease, diabetes	Hyperglycemia, impaired insulin sensitivity, lactic acidosis, worsening symptoms of Parkinson disease
Norepinephrine/NDA 007513	Hypotension and shock	1950	8–12 mcg/min initial, then 2–4 mcg/min maintenance	Maintains MAP 80–100 mmHg	Ischemic injury due to potent vasoconstrictor action and tissue hypoxia. Reflex bradycardia. Respiratory difficulty. Extravasation necrosis	Transient headache. Anxiety
Phenylephrine/NDA 203826	Hypotension and shock	2012	0.5–6 mcg/kg/min	Increase MAP via titration to effect	Exacerbation of heart failure, heart failure and pulmonary hypertension	Headache, vomiting, reflex bradycardia, AV block, ventricular extra systoles
Vasopressin/NDA 204485	Vasodilatory shock	2014	0.01–0.07 units/min	Increases MAP in septic shock	Skin and subcutaneous necrosis. Periphereal and visceral ischemia	
Dopamine/NDA 019099	Shock syndrome	Originally 1982; NDA 019099 approved 1996	Initial: 2–5 mcg/kg/min. Titrate to effect. If > 50 mcg/kg/min is required, check urine output	MAP requirements met at 20 mcg/kg/min in > 50% subjects	Decreased cardiac output, bradycardia, tachycardia, tachyarrhythmia, coronary, mesenteric, and digital ischemia	Increased bilirubin and liver transaminase, decreased platelets
					Hypovolemia, hypoxia, ventricular arrhythmia, occlusive vascular disease, local necrosis	Nausea, vomiting, dyspnea, cardiac conduction defects, headache

AV atrioventricular, FDA Food and Drug Administration, MAP mean arterial pressure, NDA new drug application

- Bovine angiotensin II: Asp¹-Arg-Val-Tyr-Val⁵-His-Pro-Phe⁸.
- Hypertensin[®] (Ciba-Geigy): Asn¹-Arg-Val-Tyr-Val⁵-His-Pro-Phe⁸ (Variation in the amino acid from human angiotensin II is shown in *italic*).

Angiotensin II injection for intravenous (IV) infusion drug product (Giapreza[®]) is a sterile, aqueous solution containing 2.5 mg/mL angiotensin II (equivalent to an average of 2.9 mg angiotensin II acetate) and 25 mg/mL mannitol in water, adjusted to pH 5.5, and is supplied in single-dose vials. Giapreza[®] is supplied in two strengths: 2.5 mg angiotensin II/vial (2.5 mg/mL) and 5 mg angiotensin II/vial (2.5 mg/mL). The drug product is diluted in 0.9% (volume/volume) sodium chloride solution prior to administration by IV infusion and is titrated to effect. Results from an in-use study demonstrate that the drug product is stable and compatible when diluted in normal saline IV bags of both the PVC and non-PVC bag types for up to 36 h at 25 °C. These worst-case scenario in-use stability data adequately support product administration instructions that state that diluted solution may be stored at room temperature or under refrigeration and should be discarded after 24 h. Regarding the undiluted product, the current stability data support a shelf-life of 18 months for the product when stored at 2–8 °C in the approved commercial container closure system.

2.2 Assessment of the Clinical Data

The approval of this NDA was based almost entirely on the ATHOS-3 trial that had undergone a special protocol assessment (SPA). The original hypothesis set forth by the Applicant was the potential catecholamine-sparing benefit associated with use of angiotensin II in patients with catecholamine-resistant distributive shock who have been administered high catecholamine doses. During the SPA and concomitant discussion with the Applicant, there was an agreement that the goal of the trial was to establish the efficacy of angiotensin II in raising MAP to a clinically adequate level. To accomplish this, the trial design was required to maintain all other pressors constant such that increases in MAP could be attributed to study drug during the first 3 h of treatment. After 3 h, the trial permitted titration of study drug and catecholamines in order to evaluate study-drug-induced maintenance of MAP while sparing the use of catecholamine.

The original NDA was based on the 505(b)(2) regulatory pathway. In a 505(b)(2) application, the applicant relies upon published literature or FDA's finding of safety and efficacy for one or more drugs on the FDA's list of approved drug products (available online at <http://www.accessdata.fda.gov/scripts/cder/ob/>). In a 505(b)(1) application, the applicant owns or has a right of reference to all the included

information that is relied upon to support the safety and efficacy of the product. The Applicant submitted a dossier to support safety and efficacy including the full report of the ATHOS-3 trial as well as nine supportive clinical publications. Eight of these were small trials with sample sizes ranging from 6 to 50 for a total of 93 subjects (approximately 50% healthy and 50% in shock). These studies were conducted between 1966 and 2014. The ninth supportive publication was a systematic literature review of 31,281 subjects in 1124 studies published from 1941 to 2016 [14]. These studies were not prospectively designed to collect safety data. Of these, 982 studies did not mention safety and 75 studies reported no adverse events. Eight studies reported dose reductions due to excess blood pressure responses, and the remaining 59 studies reported adverse events, most commonly headache, chest pressure/tightness, dyspepsia/nausea, bradycardia, and orthostatic hypotension.

The wide variability in time when the supportive studies were conducted led us to conclude that time-dependent standard of care may have confounded the assessment of safety. The lack of safety assessment in 87% of the studies comprising the systematic review led us to conclude that the supportive safety data was suboptimal. The NDA review team therefore assessed the ATHOS-3 trial as both essential and sufficient to support approvability of angiotensin II (Giapreza[®]). Because none of the publications were essential to support approval, the 505(b)(2) pathway was changed to a 505(b)(1) pathway.

2.3 ATHOS-3 Trial

The trial results were published in 2017 [15]. This was a multicenter, placebo-controlled, double-blind, randomized clinical trial in 344 adults with refractory distributive shock, defined as persistent hypotension (MAP 55–70 mmHg) after treatment with fluids and high-dose vasopressors. Subjects were randomized 1:1 to receive angiotensin II starting at 20 ng/kg/min or placebo (saline), in addition to standard of care. Subjects were titrated on study drug until the endpoint response was achieved. The primary endpoint was the rate of response at 3 h of treatment with study drug, defined as either a 10-mmHg increase from baseline in MAP or an MAP of at least 75 mmHg. A logistic regression was used for the primary endpoint analysis adjusted by fixed covariates of baseline MAP (<65 mmHg vs ≥65 mmHg), Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, vasopressin use over the 6 h prior to randomization (yes vs no), and average norepinephrine equivalent dose (NED) over the 6 h prior to randomization, using the modified intent-to-treat (mITT) population, defined as randomized patients who received at least one dose of the study drug.

There were two study periods: period 1 covered baseline to 3 h, and period 2 covered 3–48 h. Study drug (placebo or angiotensin II) was initiated at hour 0 and titrated to restore MAP during period 1. Study drug administration continued during period 2 with mandatory down-titration and discontinuation at hour 48. However, the protocol provided for optional re-initiation of angiotensin II from hours 48–168. The trial hypothesis focused on period 1, during which background vasopressor and fluid dosing were not changed. In period 2, the catecholamine doses were down-titrated to evaluate whether angiotensin II could maintain MAP with lower catecholamine doses. However, the trial was not designed to evaluate the catecholamine-sparing effect.

3 Study Outcomes

3.1 Baseline Characteristics of Subjects in the ATHOS-3 Trial

A total of 404 patients were screened. Of these 60 were excluded (54 did not meet eligibility criteria, three withdrew consent, one died, one moved to hospice, and one for reasons unknown). The remaining 344 patients were randomized 1:1 (i.e., 172 per arm) and were included in the intent-to-treat (ITT) population. Of these, 13 in the placebo arm and 10 in the angiotensin II arm did not receive study drug. Also, one subject initially randomized to the placebo arm was re-randomized to angiotensin II, and was considered an angiotensin II arm subject for analysis. Thus, there were 158 and 163 subjects in the placebo and angiotensin II arms, respectively, in the mITT population. The baseline characteristics between subjects in the placebo and angiotensin II arms were similar (Table 2). The mITT population was 61% male, 81% white, and 10% black, had a mean age of 62 years (range 22–89 years), and 74% were from the USA/Canada. The mean baseline values were MAP 66 mmHg, APACHE II score 28, Model of End-stage Liver Disease (MELD) score 21, cardiovascular Sequential Organ Failure Assessment (SOFA) score 4.00, and total SOFA score 12.00. The values were evenly distributed between the arms of the trial. The APACHE II score is based on common physiological variables measured during the initial 24 h in the intensive care unit (ICU) [16], and it is correlated with mortality [17]. The SOFA score is sepsis related and evaluates major organ systems serially over time [18], and it is also correlated with mortality [19]. The MELD score provides an estimate of mortality at 3 months from liver disease [20].

The mean NED was 0.5 $\mu\text{g/kg/min}$ during 6 h prior to randomization and continued during randomization. Vasopressin, whose doses were calculated as part of the NED, was administered to 70% of the ITT population in both arms during 6 h prior to randomization. The level of NED and

the inclusion of vasopressin indicated a population with a significant mortality risk.

3.2 Dosing, Pharmacodynamics and Pharmacokinetics

During period 1 and period 2, the study drug titration scheme (Table 3) allowed for titration every 5 to every 15 min based upon the MAP relative to the target range.

During period 1, the NED remained constant. Following initiation of angiotensin II infusion at 20 ng/kg/min , at least 50% of patients achieved target MAP by 5 min, and the response was a function of the baseline MAP. As the blood pressure effects of angiotensin II reached steady state within 5 min of constant infusion, and doses were permitted to be up-titrated or down-titrated quickly to achieve target MAP, the starting dose of 20 ng/kg/min was considered reasonable for the intended patient population irrespective of the baseline MAP. The dosing pattern of angiotensin II showed an initial down-titration followed by a steady increase in the average angiotensin II infusion rate (Fig. 1). The mean angiotensin II doses (ng/kg/min) at hours 0–1, 1–2, and 2–3 were 16, 24 and 32, respectively (Table 4). The mean placebo doses (ng/kg/min) in the same three time periods were 51, 91, and 113, respectively (Table 4). The maximum allowed dose during the first 3 h of treatment was 200 ng/kg/min , but none of the 21% of patients who received doses $> 80 \text{ ng/kg/min}$ achieved the target MAP. Therefore, labeling recommended the maximum dose of angiotensin II of 80 ng/kg/min during the first 3 h of infusion.

During period 2, the overall mean angiotensin II dose remained constant at 19 ng/kg/min . The NED decreased from a mean of 0.49 $\mu\text{g/kg/min}$ to a mean of 0.43 $\mu\text{g/kg/min}$ in the placebo group, and decreased from a mean of 0.43 $\mu\text{g/kg/min}$ to a mean of 0.34 $\mu\text{g/kg/min}$ in the angiotensin II group (Table 5). The greater decrease of the NED in the angiotensin II arm compared to the placebo arm in period 2 was likely a consequence of the angiotensin II effect, whereas the decline in both arms appeared to be associated with management and resolution of the underlying cause of distributive shock.

Serum levels of angiotensin II were similar between baseline and after 3 h of infusion. However, the serum levels of angiotensin I were reduced by approximately 40%. This could be possibly due to a negative bio-feedback mechanism, which could have suppressed renin secretion and reduced the formation of angiotensin I from renin. Therefore, angiotensin II levels remain unchanged, but angiotensin I levels were reduced in the circulation. The published literature reports were reviewed to provide additional pharmacokinetic information for angiotensin II. Briefly, angiotensin II reaches steady-state plasma concentrations in 5 min after IV infusion [21]. It is metabolized to angiotensin (1–7) and angiotensin 2–8 (angiotensin III) by aminopeptidase A and angiotensin

Table 2 Subject demographics and baseline ICU parameters (mITT population)

Demographic parameters	Placebo (<i>N</i> = 158)	Giapreza® (<i>N</i> = 163)	Total (<i>N</i> = 321)
Gender, <i>n</i> (%)			
Male	103 (65)	92 (56)	195 (61)
Female	55 (35)	71 (44)	126 (39)
Age			
Mean years (SD)	63 (15)	62 (16)	62 (15)
Median (years)	65	63	64
Min–max (years)	22–89	22–89	22–89
Age group, <i>n</i> (%)			
< 17 years	0	0	0
≥ 17 to < 65 years	77 (49)	90 (55)	167 (52)
≥ 65 years	81 (51)	73 (45)	154 (48)
≥ 65 to < 75 years	39 (25)	32 (20)	71 (22)
≥ 75 years	42 (27)	41 (25)	83 (26)
Race, <i>n</i> (%)			
White	122 (77)	135 (83)	257 (81)
Black or African American	19 (12)	14 (9)	33 (10)
Asian	8 (5)	5 (3)	13 (4)
American Indian or Alaska Native	0	1 (0.6)	1 (0.3)
Native Hawaiian or other Pacific Islander	1 (0.6)	0	1 (0.3)
Other	8 (5)	8 (5)	16 (5)
Ethnicity, <i>n</i> (%)			
Hispanic or Latino	7 (4)	10 (6)	17 (5)
Not Hispanic or Latino	151 (96)	153 (94)	304 (95)
Region, <i>n</i> (%)			
United States/Canada	120 (76)	116 (71)	236 (74)
Rest of the world			
Europe	14 (9)	19 (12)	33 (10)
Australia/New Zealand	24 (15)	28 (17)	52 (16)
Baseline ICU values			
MAP (mmHg), mean (SD)	65 (6)	66 (5)	66 (5)
APACHE II, mean (SD)	29 (8)	27 (8)	28 (8)
MELD, mean (SD)	22 (7)	20 (7)	21 (7)
Number of pressors, mean (SD)	2.0 (0.7)	1.9 (0.0)	2.0 (0.8)
NED (μg/kg/min), mean (SD)	0.5 (0.4)	0.5 (0.3)	0.5 (0.4)
Vasopressin usage, <i>n</i> (%)	111 (70)	113 (69)	224 (70)

Source of data: NDA dataset

APACHE Acute Physiologic Assessment and Chronic Health Evaluation, ICU intensive care unit, MAP mean arterial pressure, MELD Model of End-stage Liver Disease, mITT modified intent-to-treat, NDA new drug application, NED norepinephrine equivalent dose during 6 h prior to randomization, SD standard deviation

converting enzyme 2 (ACE2) [7, 22, 23], respectively. The plasma half-life of angiotensin II is less than a minute [24].

3.3 Review of Efficacy

In the angiotensin II arm, the MAP rose from a mean of 66 mmHg to a mean of 77 mmHg, corresponding to a 70% responder rate, on a mean dose of 21 (standard deviation [SD] 21) ng/kg/min. In the placebo arm, the MAP rose from

a mean of 65 mmHg to a mean of 70 mmHg, corresponding to a 23% responder rate (odds ratio 8; 95% confidence interval [CI] 5–13, $P < 0.00001$) (Table 6). The results were consistent across all evaluated subgroups, including those based on age, gender, race, body mass index (BMI), or geographic region.

The secondary endpoint was the change from baseline in total and cardiovascular SOFA scores. The mean change from baseline at hour 3 in the cardiovascular SOFA score

Table 3 Study drug titration scheme

MAP (mmHg)	Initial drug dose (ng/kg/min)	Ang II titration interval (min)	Ang II dose titration (ng/kg/min)	Ang II maximal dose (ng/kg/min)	Ang II minimal dose (ng/kg/min)
Titration scheme: 0–3 h					
≤ 59	20	5	Increased to 80 ^a then by increments of 20	200	2.5
60–74	20	15	Increased by 10	200	2.5
75–84	NA	15	Maintain dose	200	2.5
≥ 85	NA	5	Decreased by 10 ^b	200	2.5 ^c
Titration scheme: 3–48 h					
≤ 59		5	Increased to 40	40	2.5
60–64		15	Increased by 10	40	2.5
65–70		15	Maintain dose ^a	40	2.5
≥ 70		15	Decreased by 10 ^b	40	2.5 ^c

Ang II angiotensin II, DSMB data safety monitoring board, MAP mean arterial pressure, NA not applicable

^aDoses may be modified to 60–120 ng/kg/min based on the recommendations from DSMB

^bIf a dose of 10 ng/kg/min has been reached, study drug may be further reduced to half in each titration until the minimum dose is achieved

^cDosing may be reduced to as low as 1.25 ng/kg/min for those patients considered hyper-responders (MAP remains ≥ 85 mmHg despite discontinuation of other vasopressors)

Fig. 1 Pattern of study drug dosing and MAP for hours 0–3. Data represents mean ± SEM. Ang II angiotensin II, MAP mean arterial pressure, SEM standard error of the mean

was -0.01 (SD 0.11) in the placebo arm and -0.13 (SD 0.55) in the angiotensin II arm. Given that the norepinephrine equivalent infusion rates were constant in this period, the cardiovascular SOFA score should have remained constant. The mean change from baseline at hour 48 in the cardiovascular SOFA score was -1.28 (SD 1.65) in the placebo group and -1.75 (SD 1.77) in the angiotensin II

Table 4 Study drug dose during initial 3 h of treatment

Statistics	Dose (ng/kg/min)	
	Placebo (<i>N</i> = 158)	Giapreza® (<i>N</i> = 163)
Hours 0–1	<i>N</i> = 158	<i>N</i> = 163
Mean (SD)	51 (37)	16 (16)
Median (range)	35 (13–171)	9 (2–92)
Hours 1–2	<i>N</i> = 156	<i>N</i> = 163
Mean (SD)	91 (53)	24 (32)
Median (range)	75 (3–200)	10 (0–183)
Hours 2–3	<i>N</i> = 156	<i>N</i> = 163
Mean (SD)	113 (53)	32 (46)
Median (range)	115 (0.3–200)	10 (0–200)

SD standard deviation

arm. These changes were attributable to standard-of-care response in both arms, as well as catecholamine sparing in the angiotensin II arm via replacement of catecholamines with angiotensin II that is not listed in the cardiovascular SOFA calculation. The mean change from baseline at hour 3 in the total SOFA score was $+0.47$ (SD 1.82) in the placebo arm and $+0.81$ (SD 1.93) in the angiotensin II arm. Similarly, the mean change from baseline at hour 48 in the total SOFA score was $+1.04$ (SD 5.34) in the placebo arm and $+1.05$ (SD 5.50) in the angiotensin II arm. The total SOFA score changes from baseline suggested no clinical benefit of angiotensin II over placebo in the ICU setting for distributive shock. Despite this, mortality over the course of the study was numerically lower in the angiotensin II arm (Fig. 2).

Table 5 Norepinephrine equivalent dose by study period

	NED ($\mu\text{g/kg/min}$)	
	Placebo ($N=158$)	Giapreza [®] ($N=163$)
Baseline	$N=158$	$N=163$
Mean (SD)	0.48 (0.45)	0.45 (0.35)
Median (range)	0.34 (0.05–3.80)	0.33 (0.08–2.58)
Hours 0–3	$N=158$	$N=163$
Mean (SD)	0.49 (0.48)	0.43 (0.37)
Median (range)	0.34 (0.05–4.46)	0.31 (0.01–2.58)
Hours 3–48	$N=157$	$N=162$
Mean (SD)	0.43 (0.62)	0.34 (0.59)
Median (range)	0.21 (0.02–3.92)	0.13 (0–4.43)

NED norepinephrine equivalent dose, SD standard deviation

Table 6 Primary efficacy analysis of MAP at hour 3 (mITT population)

Analysis	Placebo ($N=158$)	Giapreza [®] ($N=163$)	Total ($N=321$)
Number responding (n)	37	114	151
Percentage responding	23.4	69.9	47.0
Odds ratio (95% CI) ^a	7.95 (4.76–13.3)		
P value	< 0.0001		

APACHE Acute Physiologic Assessment and Chronic Health Evaluation, CI confidence interval, MAP mean arterial pressure, mITT modified intent-to-treat

^aChi-squared test from logistic regression model adjusting baseline MAP (<65 mmHg/ $\geq$ 65 mmHg), baseline APACHE II score, vasopressin use 6 h prior to randomization (yes/no), and mean norepinephrine equivalent dose over the 6 h prior to randomization

3.4 Review of Safety

The major safety concern was an excess of arterial and venous thromboembolic events: 21 subjects (12.9%) on angiotensin II versus eight subjects (5.1%) on placebo. The most common of these events was deep vein thrombosis (DVT), which occurred in seven versus no subjects. The standard care of patients with sepsis includes anticoagulant treatment for prophylaxis, although such prophylaxis was not required by the protocol and was not provided to all subjects in the ATHOS-3 trial. Our exploratory analyses showed that anticoagulation with heparin or related drugs was similar in both arms (~50%) prior to treatment and was more frequent in the angiotensin arm during the study (52% vs. 32%). Thus, the higher incidence of thromboembolic events in the angiotensin II arm could not be attributed to a lower

Fig. 2 Kaplan–Meier plot of mortality to day 28. The cumulative mortality rate on day 28 was 54% in the placebo arm and 46% in Giapreza[®] arm. The hazard ratio (95% CI) was 0.78 (0.57–1.07). CI confidence interval

use of prophylactic anticoagulation in that arm. Considering that the preclinical data indicate that angiotensin II has prothrombotic effects through various mechanisms [25], the totality of evidence suggests that the risk of thromboembolic events could be drug related. Hence, a warning regarding thrombotic risk along with a recommendation for prophylactic anticoagulation was added in labeling of angiotensin II.

There were other minor safety signals observed in the ATHOS-3 trial; however, it was difficult to distinguish which adverse events were likely to be causally related to angiotensin II, because of the small safety database and the extremely ill population. Despite these limitations, the result of a favorable trend in mortality was reassuring of safety. Table 7 summarizes the adverse reactions at incidence of at least 4 and 1.5% higher in the angiotensin II arm than in the placebo arm.

4 Assessment of Effectiveness

The use of an increasing number of vasopressors in refractory distributive shock poses a risk of end-organ damage due to excess vasoconstriction. In the setting of adequately improving the mean arterial blood pressure to clinical target levels, the safety database from the ATHOS-3 trial did not demonstrate end-organ damage for subjects with refractory shock treated with angiotensin II relative to placebo.

None of the drugs labeled in the USA for distributive shock were approved with data indicating that they reduced

Table 7 Adverse reactions occurring in $\geq 4\%$ of patients treated with Giapreza® and $\geq 1.5\%$ more often than in placebo-treated patients in ATHOS-3 (mITT population)

Adverse event	Placebo (<i>N</i> = 158)	Giapreza® (<i>N</i> = 163)
Thromboembolic events ^a	8 (5.1%)	21 (12.9%)
Deep vein thrombosis	0 (0.0%)	7 (4.3%)
Thrombocytopenia	11 (7.0%)	16 (9.8%)
Tachycardia	9 (5.7%)	14 (8.6%)
Fungal infection	2 (1.3%)	10 (6.1%)
Delirium	1 (0.6%)	9 (5.5%)
Acidosis	1 (0.6%)	9 (5.5%)
Hyperglycemia	4 (2.5%)	7 (4.3%)
Peripheral ischemia	4 (2.5%)	7 (4.3%)

ATHOS-3 Angiotensin II for the Treatment of High-Output Shock phase 3, *mITT* modified intent-to-treat

^aIncluding arterial and venous thromboembolic events

mortality. We have not required sponsors to show a benefit other than an increase in blood pressure to support approval of drugs to treat hypotension in the setting of shock. We have accepted the belief prevalent in the medical community that treatment of hypotension in patients with shock will improve tissue perfusion to allow needed time for specific treatment of the underlying cause of shock, and thereby decrease death and serious morbidity, although this hypothesis has never been rigorously evaluated. However, given the high rate of death in patients with septic shock despite treatment, there is clearly an unmet need for additional safe and effective treatments.

Although the sponsor conducted only one controlled trial, the trial was adequate to demonstrate effectiveness in raising mean arterial blood pressure. Several of the criteria for finding effectiveness based on one study that are described in FDA's 1998 guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", are present here. The ATHOS-3 trial was a well-conducted, placebo-controlled, superiority trial with no important flaws in conduct or imbalances in the study arms. The difference between the study arms for the primary endpoint, the MAP response rate, was large and favored angiotensin II. Despite the lack of a confirmed benefit for any outcome other than MAP, the benefits of angiotensin II were determined to outweigh its risks in the studied population. This study population is representative of patients in the USA with distributive shock, so the results of ATHOS-3 can be extrapolated to US patients.

In the ATHOS-3 trial, subjects received study drug against a background of other vasopressors. However, data from outside the ATHOS-3 trial indicate that angiotensin II also raised blood pressure in subjects who had not received other vasopressors, including patients with distributive

shock [13]. Consequently, the regulatory decision to approve Giapreza® did not restrict use to subjects who were on maximum levels of catecholamines. Given that Giapreza® was administered in a controlled clinical setting, the dose was titrated to effect that was achieved in less than 5 min. No formal drug interaction studies or pharmacokinetic studies in patients with renal impairment or hepatic impairment were conducted. No specific distribution, metabolism and excretion studies were conducted using Giapreza®. Age and gender did not influence the pharmacokinetics of angiotensin II as observed in the phase 3 study.

5 Conclusions

The ATHOS-3 trial provided substantial evidence demonstrating that angiotensin II increased MAP in patients with distributive shock receiving a variety of other vasopressors. Results for mortality favored angiotensin II, but the advantage was not statistically significant. Adverse events occurring at a higher rate in the angiotensin II arm than in the placebo arm included thrombotic events, peripheral ischemia, lactic acidosis and delirium. None of these are rare in ICU patients with distributive shock treated with other pressor agents. Overall, the data suggested that the hemodynamic benefits of angiotensin II in patients with distributive shock outweighed its risks. The results of ATHOS-3 supported approval of this drug by the FDA for marketing in the USA. Full prescribing information for angiotensin II in the treatment of distributive shock is available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209360s000lbl.pdf.

Compliance with Ethical Standards

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Conflict of interest Fortunato Senatore, Gowraganahalli Jagadeesh, Martin Rose, Venkateswaran C. Pillai, Sudharshan Hariharan, Ququan Liu, McDowell Tzu-Yun, Mohan K. Sapru, Mary Ross Southworth, and Norman Stockbridge declare that they have no conflicts of interest relevant to the content of this article.

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