

Angiotensin II for catecholamine-resistant vasodilatory shock in patients with acute kidney injury: a post hoc analysis of the ATHOS-3 trial

Anis Chaba, Alexander Zarbock, Lui G. Forni, Johanna Hästbacka, Elena Korneva, Giovanni Landoni, Peter Pickkers, and Rinaldo Bellomo. *Shock*. 2025;63(1):88-93. doi:10.1097/SHK.0000000000002481

Angiotensin II is marketed in the United States as GIAPREZA® (angiotensin II) injection for intravenous infusion, indicated to increase blood pressure in adults with septic or other distributive shock¹

The ATHOS-3 trial assessed whether the addition of GIAPREZA to background vasopressors would improve blood pressure in adult patients with septic or other distributive shock.¹

This post hoc subgroup study evaluated effects of GIAPREZA on mortality, blood pressure, and renal outcome in patients with AKI at baseline (63%) from the ATHOS-3 randomized trial population.²

Limitations of the analysis presented: This analysis did not intend to make a conclusion regarding additional effects of GIAPREZA. Because the analysis was not prespecified and multiplicity adjustments were not applied, the data require cautious interpretation and do not represent an additional benefit of GIAPREZA. Other limitations presented include²

- These outcomes represent a post hoc analysis of the ATHOS-3 data, which was not designed to test the hypotheses described
- There was inability to test if the outcomes were reached at the expense of other measures of clinical status
- The management of patients with stage 3 AKI may have changed since ATHOS-3 with a shift toward a more delayed approach to RRT initiation
- The impact of sex on the response to GIAPREZA or on clinical outcomes cannot be assessed
- The number of patients with stage 1 (n=25) and stage 2 (n=42) AKI was too small to obtain statistically robust assessments, with most patients having stage 3 (n=136) AKI
- The generalizability of the results presented in this analysis is limited, and the findings need to be considered only as hypothesis generating

Disclosures: Innoviva Specialty Therapeutics, Inc., in partnership with La Jolla Pharmaceutical Company, markets GIAPREZA, and both companies have a financial interest in the product. The outcomes presented in this publication have not been evaluated in a prospective manner and may be due to random chance.² GIAPREZA is approved to increase blood pressure in adults with septic or other distributive shock.¹ Numerous financial disclosures are referenced in the published Chaba et al study. Namely, some authors have received consultant fees, grants, or other financial benefit from the manufacturer of GIAPREZA. The ATHOS-3 trial and the analysis of the data were funded in full by La Jolla Pharmaceutical Company.

AKI=acute kidney injury; ATHOS-3=Angiotensin II for the Treatment of High-Output Shock; RRT=renal replacement therapy. The ATHOS-3 trial protocol is freely accessible at <https://www.nejm.org/doi/full/10.1056/NEJMoa1704154>.

SELECTED IMPORTANT SAFETY INFORMATION

Indication

GIAPREZA® (angiotensin II) increases blood pressure in adults with septic or other distributive shock.

Contraindications

None.

Please see additional Important Safety Information throughout. Before administering, please see the [Full Prescribing Information](#) for GIAPREZA.

ATHOS-3 trial design and results for overall population

GIAPREZA® (angiotensin II) was studied in ATHOS-3, an international, randomized, double-blind, placebo-controlled trial of 321 patients with distributive shock who remained hypotensive despite fluid and vasopressor therapy.^{1,2}

- Treatment arms: GIAPREZA plus SOC vasopressors (n=163) vs placebo plus SOC vasopressors (n=158)^{1,*}
- Primary endpoint: An increase in MAP at hour 3 of ≥ 10 mmHg, or a MAP of ≥ 75 mmHg, without an increase in baseline vasopressor dosing¹
- Secondary endpoints: Mean change in cardiovascular SOFA score at hour 48 and mean change in total SOFA score at hour 48³
- Exploratory endpoint: All-cause mortality through day 28³

MAP response: 70% of patients (114/163) achieved target MAP with GIAPREZA plus SOC vs 23% (37/158) with placebo plus SOC ($P < 0.0001$).¹

Patient survival: 54% of patients (88/163) were alive at day 28 with GIAPREZA plus SOC vs 46% (73/158) with placebo plus SOC.¹

- Not statistically significant. Mortality through day 28 was an exploratory endpoint in ATHOS-3. The trial was not powered to detect a difference in mortality³

Fewer patients treated with GIAPREZA experienced safety and tolerability events³:

- In the GIAPREZA group, 142 (87.1%) patients experienced adverse events vs 145 (91.8%) in the placebo group
- In the GIAPREZA group, 23 (14.1%) patients discontinued treatment due to adverse events vs 34 (21.5%) in the placebo group
- In the GIAPREZA group, 99 (60.7%) patients experienced serious adverse events vs 106 (67.1%) in the placebo group[†]

Adverse reactions occurring in $\geq 4\%$ of patients treated with GIAPREZA and $\geq 1.5\%$ more often than in placebo-treated patients included thromboembolic events, including arterial and venous thrombosis events (12.9% vs 5.1%), deep vein thrombosis (4.3% vs 0.0%), thrombocytopenia (9.8% vs 7.0%), tachycardia (8.6% vs 5.7%), fungal infection (6.1% vs 1.3%), delirium (5.5% vs 0.6%), acidosis (5.5% vs 0.6%), hyperglycemia (4.3% vs 2.5%), and peripheral ischemia (4.3% vs 2.5%).¹

Thromboembolic events:

- The Prescribing Information presents both serious adverse events and adverse events, including thromboembolic events, under a single category^{1,3}
- The incidence of patients with a grade 3 or 4 (severe or life-threatening) thromboembolic event was 9 (5.5%) events in the GIAPREZA group vs 5 (3.2%) in the placebo group^{4, §, ¶}
- In the GIAPREZA group, 12/25 (48%) thromboembolic events occurred within 3 days of treatment discontinuation in comparison to 7/8 (87.5%) events in the placebo arm⁴

Use concurrent venous thromboembolism (VTE) prophylaxis.¹

^{*}SOC vasopressors included norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin.¹

[†]Doses of GIAPREZA or placebo were titrated to a target MAP of ≥ 75 mmHg during the first 3 hours of treatment while doses of other vasopressors were maintained. From hour 3 to hour 48, GIAPREZA or placebo was titrated to maintain a MAP between 65 mmHg and 70 mmHg while reducing doses of other vasopressors.¹

[‡]Serious adverse events with frequency $\geq 1\%$ in either study group.³

[§]Grade 3 thromboembolic event: thrombosis; medical intervention indicated.⁵

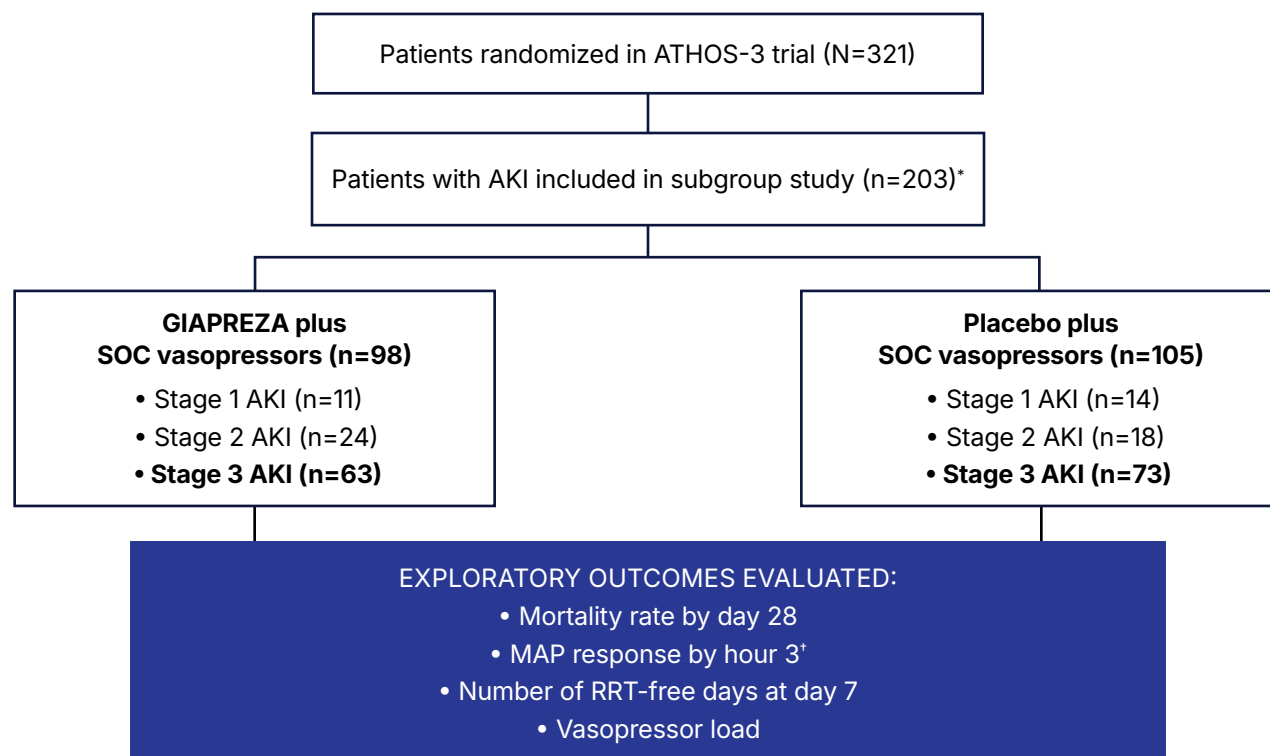
[¶]Grade 4 thromboembolic event: life-threatening consequences with hemodynamic or neurologic instability; urgent medical intervention indicated.⁵

MAP=mean arterial pressure; SOC=standard of care; SOFA=sequential organ failure assessment.

Please see additional Important Safety Information throughout. Before administering, please see the [Full Prescribing Information](#) for GIAPREZA.

Subgroup study of ATHOS-3: Impact of GIAPREZA on patient outcomes by AKI stage²

Most patients in the subgroup study had stage 3 AKI



Baseline characteristics of AKI stage 3 patients included in the study

	GIAPREZA + SOC (n=63)	Placebo + SOC (n=73)
Median age, years (min-max)	63 (26-88)	63 (22-87)
Median APACHE II score (min-max)	32 (11-54)	31 (17-51)
Median serum creatinine, mg/dL (min-max)	2.9 (0.4-11.9)	2.7 (0.6-8.8)
Median NED dose, mcg/kg/min (min-max)	0.4 (0.1-2.6)	0.4 (0.1-3.8)
RRT usage, n (%)	47 (75)	63 (86)

*118 patients from ATHOS-3 trial without AKI or missing baseline creatinine excluded from the subgroup study.

*Defined as an increase in MAP at hour 3 of ≥ 10 mmHg from baseline, or a MAP of ≥ 75 mmHg, without an increase in baseline vasopressor dosing.

APACHE II=Acute Physiology and Chronic Health Evaluation II; NED=norepinephrine-equivalent dose.

SELECTED IMPORTANT SAFETY INFORMATION

Warnings and Precautions

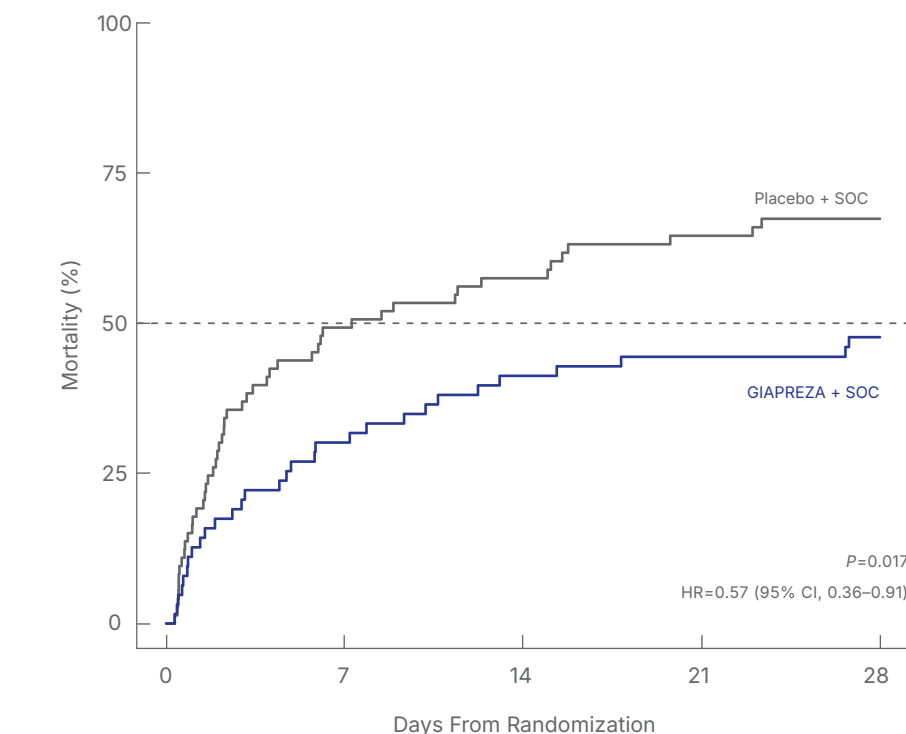
The safety of GIAPREZA was evaluated in 321 adults with septic or other distributive shock in a randomized, double-blind, placebo-controlled study, ATHOS-3. There was a higher incidence of arterial and venous thrombotic and thromboembolic events in patients who received GIAPREZA compared to placebo-treated patients in the ATHOS-3 study (13% vs. 5%). The major imbalance was in deep venous thromboses. Use concurrent venous thromboembolism (VTE) prophylaxis.

Please see additional Important Safety Information throughout. Before administering, please see the [Full Prescribing Information](#) for GIAPREZA.

Increased survival with GIAPREZA® (angiotensin II) plus SOC for AKI stage 3 patients from the ATHOS-3 trial²

Based on post hoc analysis of the ATHOS-3 clinical trial data: Because these analyses were not prespecified and multiplicity adjustments were not applied, these data require cautious interpretation.

43% reduction in risk of death for AKI stage 3 patients with GIAPREZA plus SOC by day 28



More AKI stage 3 patients were alive at day 28 with GIAPREZA plus SOC (52% vs 33% with placebo plus SOC; $P=0.024$).

Results for all patients with AKI:

- 25% reduction in risk of death for patients with any stage AKI with GIAPREZA plus SOC ($P=0.121$)
- 47% of patients with any stage AKI were alive at day 28 with GIAPREZA plus SOC vs 37% with placebo plus SOC ($P=0.2$)

SELECTED IMPORTANT SAFETY INFORMATION

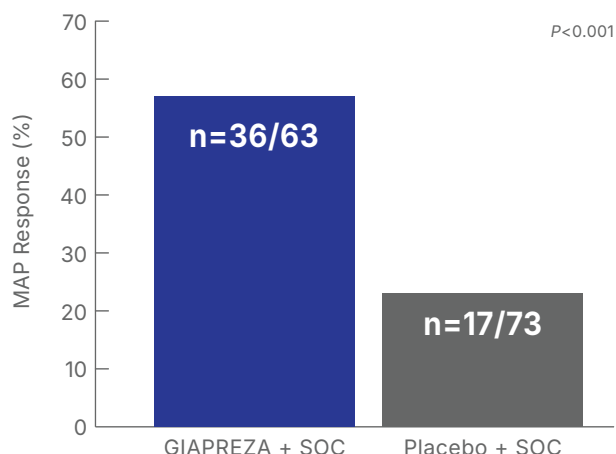
Adverse Reactions

The most common adverse reactions reported in greater than 10% of GIAPREZA-treated patients were thromboembolic events. Adverse reactions occurring in $\geq 4\%$ of patients treated with GIAPREZA and $\geq 1.5\%$ more often than placebo-treated patients in the ATHOS-3 study were thromboembolic events (including deep vein thrombosis), thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia.

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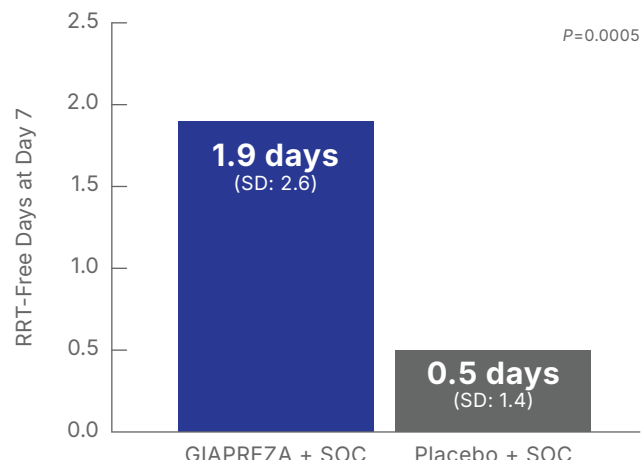
Observed improvements in AKI stage 3 patients: MAP response, RRT-free days, and vasopressor load (post hoc analysis)^{2,6}

More AKI stage 3 patients achieved target MAP with GIAPREZA plus SOC⁶



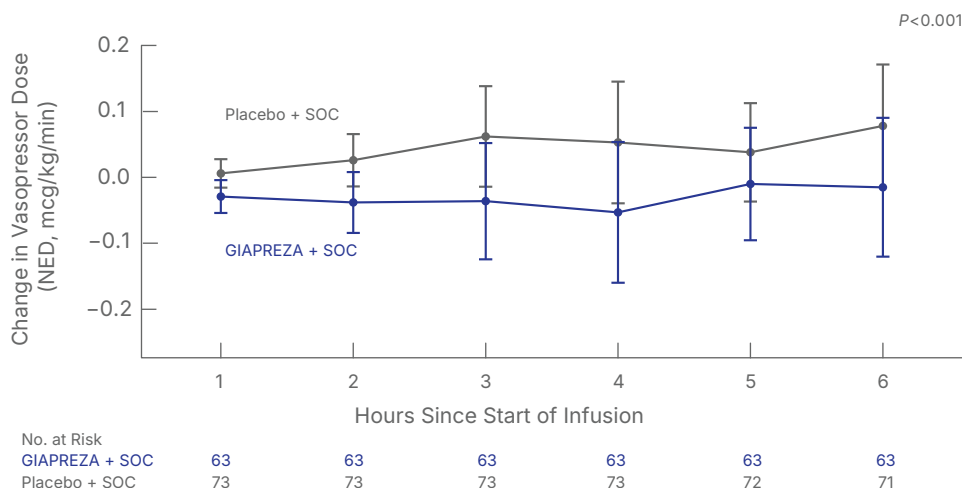
Results for all patients with AKI: 59 out of 98 patients with any stage AKI achieved target MAP with GIAPREZA plus SOC vs 30 out of 105 with placebo plus SOC ($P < 0.001$).²

More RRT-free days for AKI stage 3 patients with GIAPREZA plus SOC²



Results for all patients with AKI: 2.2 RRT-free days for patients with any stage AKI with GIAPREZA plus SOC vs 1.3 with placebo plus SOC ($P = 0.0182$).²

With GIAPREZA plus SOC, AKI stage 3 patients needed lower mean doses of SOC vasopressors⁶



Results for all patients with AKI: With GIAPREZA plus SOC, lower mean doses of SOC vasopressors needed for patients with any stage AKI vs placebo plus SOC ($P < 0.001$).^{2,6}

SD=standard deviation.

SELECTED IMPORTANT SAFETY INFORMATION

Drug Interactions

Angiotensin converting enzyme (ACE) inhibitors may increase response to GIAPREZA. Angiotensin II receptor blockers (ARBs) may reduce response to GIAPREZA.

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GIAPREZA® (angiotensin II) improved survival, blood pressure, and renal outcomes in patients with stage 3 AKI^{2,6}

Please see front cover for the limitations of the post hoc analysis presented in Chaba et al.

ATHOS-3 trial primary endpoint: achievement of target MAP¹

- In the overall ATHOS-3 trial population, 70% of patients (n=114/163) achieved target MAP with GIAPREZA plus SOC vs 23% of patients (n=37/158) with placebo plus SOC ($P<0.0001$)
- MAP response: An increase in MAP at hour 3 of ≥ 10 mmHg, or a MAP response of ≥ 75 mmHg, without an increase in baseline vasopressor dosing

Exploratory post hoc subgroup analysis: GIAPREZA plus SOC for AKI stage 3 patients from the ATHOS-3 trial^{2,6}

- A greater proportion of AKI stage 3 patients were alive at day 28 with GIAPREZA plus SOC (52% vs 33% with placebo plus SOC; $P=0.024$)²
- A greater proportion of AKI stage 3 patients achieved target MAP with GIAPREZA plus SOC vs placebo plus SOC ($P<0.001$)⁶
- A greater proportion of AKI stage 3 patients experienced RRT-free days at day 7 with GIAPREZA plus SOC (1.9 days vs 0.5 days with placebo plus SOC; $P=0.0005$)²
- AKI stage 3 patients needed lower mean doses of SOC vasopressors with GIAPREZA plus SOC vs placebo plus SOC ($P<0.001$)⁶

No differences were observed in AKI stage 1 and 2 patients; however, the small number of patients in these groups limits the ability to make reliable inferences.^{2,6}

"Our findings also demonstrate that AKI patients had high baseline renin levels. Previous studies have shown that high renin level was associated with hemodynamic deficiency, adverse renal outcome, and increased mortality. ... [GIAPREZA] treatment in patients with stage 3 AKI was associated with 28-day lower mortality, a greater MAP response than placebo, and more days alive and free from RRT up to day 7."

— Chaba et al 2025

References: 1. GIAPREZA. Prescribing information. La Jolla Pharmaceutical Company; 2021. 2. Chaba A, Zarbock A, Forni LG, et al. Angiotensin II for catecholamine-resistant vasodilatory shock in patients with acute kidney injury: a post hoc analysis of the ATHOS-3 trial. *Shock*. 2025;63(1):88-93. doi:10.1097/SHK.0000000000002481 3. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med*. 2017;377(5):419-430. doi:10.1056/NEJMoa1704154 4. Data on File. Innoviva Specialty Therapeutics; 2023. 5. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Published June 14, 2010. 6. Supplementary appendix to: Chaba A, Zarbock A, Forni LG, et al. Angiotensin II for catecholamine-resistant vasodilatory shock in patients with acute kidney injury: a post hoc analysis of the ATHOS-3 trial. *Shock*. 2025;63(1):88-93. doi:10.1097/SHK.0000000000002481

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Contraindications

None.

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