Appendix 1. This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Table 1. Schedule of study procedures

Activity	Screening[1]	Day 1 (0–3 hours)	Day 1 (3–24 hours)	Day 2 (24–48 hours)	Days 3–6	Day 7 (EOS[2])	Day 28 (Safety)
Informed consent[3]	X						
Titrate SOC vasopressors[4]	X						
Inclusion/exclusion criteria evaluation	X						
Demographics	X						
Medical/surgical history	X						
Concomitant medications and concomitant procedures[5]	X	X	X	X	X	X	
Limited physical exam[6]	X					X	
Chest x-ray	X						
Hemodynamic vital signs[7]	X	X	X	X	X	X	
Other vital signs[8]	X	X	X	X	X	X	
12-Lead ECG[9]	X			X			
Central venous pressure[10]	X	X	X	X			
Cardiac output[10]	X	X	X	X			
Urine output[11]	X	X	X	X			
Arterial blood gas[12]	X	X					

SOFA scoring[13] a. Respiratory system (PaO_2/FiO_2) b. Nervous system (Glasgow Coma Scale) c. Cardiovascular system (MAP or vasopressors required) d. Liver (bilirubin) e. Coagulation (platelets) f. Renal (creatinine or urine output)	X	X		X			
Hematology[14]	X	X		X			
Serum chemistry[14]	X	X		X			
Blood for serum angiotensin I and II concentrations	X	X					
Blood for banked storage sample[15]	X						
Routine urinalysis[16]	X						
Randomise to study	X						
Pharmacy ANGII preparation	X						
ANGII administration/titration[17]		X	X	X	X	X	
Safety assessments (AEs/SAEs)[18]		X	X	X	X	X	X

AE = adverse event. ECG = electrocardiogram. ANGII = angiotensin II. EOS = end of study. FiO_2 = fraction of inspired oxygen. HR = heart rate. MAP = mean arterial pressure. PaO_2 = partial pressure of dissolved oxygen. SAE = serious adverse event. SOC = standard of care. SOFA = Sequential Organ Failure Assessment.

1. Screening procedures may be conducted up to 48 hours prior to the anticipated initiation of ANGII dosing.
2. EOS to be performed no earlier than 168 hours (7 days) ± 12 hours after initiation of ANGII. All patients will be followed for a minimum of 72 hours (3 days) ± 6 hours following discontinuation of ANGII.
3. Informed consent must be obtained before any study-related activities can occur.
4. All patients will have their SOC vasopressors titrated for a minimum of six hours but not for longer than 48 hours prior to initiation of ANGII dosing. The screening MAP is defined as the average of six hourly MAP measurements collected during the period of time SOC vasopressors are being titrated.

5. Record all concomitant medications taken (including all vasopressors), any procedures performed within two days of administration of ANGII, and continue to do so through Day 7/EOS. Record any concomitant anti-hypertensive medications, including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, taken within seven days of administration of ANGII through Day 7/EOS.
6. A limited physical examination should be performed at screening that includes documentation of body weight and height.
7. It is anticipated that patients will be continuously monitored during the first 48 hours following initiation of ANGII. Haemodynamic vital signs (ie, HR and MAP) must be documented hourly during screening for a minimum of six hourly readings. The average of these six readings will determine the screening MAP for purposes of randomisation and stratification. MAP must be measured −30 minutes, −15 minutes, and 0 minutes (or just prior) to initiation of ANGII. The average of these three MAP values will determine the baseline MAP (ie, how a patient should begin ANGII dose titration). MAP and HR will be recorded on Day 1 prior to every dose titration and minimally every 15 minutes during hours 0–3:15, and prior to any dosing adjustments, and a minimum of hourly thereafter beginning with Day 1 at 4 hours through Day 2 at 48 hours. During hours 0–3, MAP will be measured in triplicate and averaged to determine MAP value for dosing modifications. Evaluation of MAP and HR should continue once daily on Days 3–7. If a patient remains on ANGII beyond Day 2 at 48 hours, documentation of MAP and HR should continue as during hours 3–48 (ie, just prior to any dose adjustment and a minimum of hourly through discontinuation of ANGII).
8. Other vital signs (blood pressure, respiratory rate, body temperature) should be assessed at screening, just prior to initiation of dosing on Day 1, Day 1 at 3 hours, Day 1 at 24 hours, Day 2 at 48 hours and once daily on Days 3–7.
9. ECG assessments will be performed at screening and on Day 2 at 48 hours.
10. An assessment of cardiac output will be conducted by an acceptable method at screening to determine eligibility, if available. A central venous pressure measurement will be conducted at screening to determine patient eligibility. In addition, cardiac output (if available) and central venous pressure will be collected a minimum of every 15 minutes during hours 0–3, and a minimum of hourly during hours 3–48.
11. Urine output will be measured and recorded hourly in the six hours prior to the initiation of ANGII. Upon start of ANGII titration, urine output will be measured and recorded hourly from hours 0–3. Urine output between hours 0–3 should be summed and documented in the chart. The total amount of intravenous fluid administered during hours 0–3 will also be documented in the chart. Hourly urine output measurement and recording should continue during hours 3–48.
12. An arterial blood gas will be conducted during screening and just prior to initiation of ANGII dosing on Day 1 at hour 0.
13. The screening cardiovascular SOFA score must be determined with data obtained within six hours prior to initiation of ANGII dosing. All parameters of the SOFA index should be performed at screening, on Day 1 at 3 hours and on Day 2 at 48 hours.
14. Blood for clinical chemistry and haematology will be collected at screening, on Day 1 at 3 hours and on Day 2 at 48 hours.
15. Blood will be collected to bank as a storage sample that may be evaluated at a later time point for measures to be determined.
16. It is not necessary to wait for results of the screening routine urinalysis to randomise the patient to the study, if otherwise eligible, at the investigators' discretion.
17. See Table 5 for study periods and dose titration schemes.

18. Safety will be evaluated at every time point. On Day 28, a follow-up phone call to the patient, the patient's primary care physician and/or a chart review will be conducted to determine if reportable safety events occurred between Day 7/EOS and Day 28. Investigators should pay particular attention to signs of vasopressor toxicity. Information about these events will be systematically collected throughout the duration of the study on a once-daily basis.

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Table 1. Corticosteroid conversion table*

Glucocorticoid	Approximate equivalent dose (mg)	Half-life (hr)
	Short-acting	
Cortisone	25	8–12
Hydrocortisone	20	8–12
	Intermediate-acting	
Methylprednisolone	4	18–36
Prednisolone	5	18–36
Prednisone	5	18–36
Triamcinolone	4	18–36
	Long-acting	
Betamethasone	0.60–0.75	36–54
Dexamethasone	0.75	36–54

* Conversions based on published values.[1–3]

References

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3. Singer M, Webb AR. Oxford Handbook of Critical Care. 2nd ed. New York: Oxford University Press, 2005.