Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial

Peter Pickkers, MD, PhD; Ravindra L. Mehta, MD; Patrick T. Murray, MD; Michael Joannidis, MD; Bruce A. Molitoris, MD; John A. Kellum, MD; Mirjam Bachler, PhD; Eric A. J. Hoste, MD, PhD; Kenneth Krell, MD; Marlies Ostermann, MD, PhD; Wim Rozendaal, MD; Miia Valkonen, MD, PhD; David Brealey, MD, PhD; Albertus Beishuizen, MD, PhD; Ferhat Meziani, MD, PhD; Raghavan Murugan, MD, MS, FRCP; Hilde de Geus, MD, PhD; Didier Payen, MD, PhD; Erik van den Berg, MSc; Jacques Arend, MD; for the STOP-AKI Investigators

IMPORTANCE Sepsis-associated acute kidney injury (AKI) adversely affects long-term kidney outcomes and survival. Administration of the detoxifying enzyme alkaline phosphatase may improve kidney function and survival.

OBJECTIVE To determine the optimal therapeutic dose, effect on kidney function, and adverse effects of a human recombinant alkaline phosphatase in patients who are critically ill with sepsis-associated AKI.

DESIGN, SETTING, AND PARTICIPANTS The STOP-AKI trial was an international (53 recruiting sites), randomized, double-blind, placebo-controlled, dose-finding, adaptive phase 2a/2b study in 301 adult patients admitted to the intensive care unit with a diagnosis of sepsis and AKI. Patients were enrolled between December 2014 and May 2017, and follow-up was conducted for 90 days. The final date of follow-up was August 14, 2017.

INTERVENTIONS In the intention-to-treat analysis, in part 1 of the trial, patients were randomized to receive recombinant alkaline phosphatase in a dosage of 0.4 mg/kg (n = 31), 0.8 mg/kg (n = 32), or 1.6 mg/kg (n = 29) or placebo (n = 30), once daily for 3 days, to establish the optimal dose. The optimal dose was identified as 1.6 mg/kg based on modeling approaches and adverse events. In part 2, 1.6 mg/kg (n = 82) was compared with placebo (n = 86).

MAIN OUTCOMES AND MEASURES The primary endpoint was the time-corrected area under the curve of the endogenous creatinine clearance for days 1 through 7, divided by 7 to provide a mean daily creatinine clearance (AUC1-7ECC). Incidence of fatal and nonfatal (serious) adverse events (S[A]Es) was also determined.

RESULTS Overall, 301 patients were enrolled (men, 70.7%; median age, 67 years [interquartile range (IQR), 59-73]). From day 1 to day 7, median ECC increased from 26.0 mL/min (IQR, 8.8 to 59.5) to 65.4 mL/min (IQR, 26.7 to 115.4) in the recombinant alkaline phosphatase 1.6-mg/kg group vs from 35.9 mL/min (IQR, 12.2 to 82.9) to 61.9 mL/min (IQR, 22.7 to 115.2) in the placebo group (absolute difference, 9.5 mL/min [95% CI, −23.9 to 25.5]; P = .47). Fatal adverse events occurred in 26.3% of patients in the 0.4-mg/kg recombinant alkaline phosphatase group; 17% in the 0.8-mg/kg group, 17.4% in the 1.6-mg/kg group, and 29.5% in the placebo group. Rates of nonfatal SAEs were 21.0% for the 0.4-mg/kg recombinant alkaline phosphatase group, 14.3% for the 0.8-mg/kg group, 25.7% for the 1.6-mg/kg group, and 20.5% for the placebo group.

CONCLUSIONS AND RELEVANCE Among patients who were critically ill with sepsis-associated acute kidney injury, human recombinant alkaline phosphatase compared with placebo did not significantly improve short-term kidney function. Further research is necessary to assess other clinical outcomes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02182440

JAMA. 2018;320(19):1998-2009. doi:10.1001/jama.2018.14283
Published online October 24, 2018.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The STOP-AKI Investigators are listed at the end of this article.

Corresponding Author: Peter Pickkers, MD, PhD, Department of Intensive Care Medicine, Radboud University Nijmegen Medical Center, PO Box 9101, Internal Post 710, 6500HB Nijmegen, the Netherlands (peter.pickkers@radboudumc.nl).
Acute kidney injury (AKI) occurs in up to 60% of patients in intensive care units (ICUs), and its incidence is increasing. Development of AKI in patients with sepsis is associated with increased mortality, and survivors are at risk of developing chronic kidney disease, resulting in a burden for both patient and society. Sepsis-associated AKI is a multifactorial syndrome with inflammatory, nephrotoxic, and ischemic insults occurring simultaneously with other pathophysiological responses rapidly leading to kidney impairment. Currently, no pharmacologic interventions are available to prevent or treat AKI.

Alkaline phosphatase is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of various compounds, including bacterial endotoxins and proinflammatory mediators such as extracellular adenosine triphosphate. In animal sepsis models, treatment with alkaline phosphatase attenuated systemic inflammation and organ dysfunction and improved survival rates. Based on these results, a human recombinant form of alkaline phosphatase was developed that combined the properties of 2 human isoenzymes, intestinal and placental alkaline phosphatase. Replacing the crown domain of intestinal alkaline phosphatase (the most biologically active isoenzyme) with the crown domain of placental alkaline phosphatase (which has the longest half-life) created a highly stable, biologically active enzyme. The therapeutic effects of human recombinant alkaline phosphatase were confirmed in various AKI models. In human proximal tubular epithelial cells, recombinant alkaline phosphatase was able to dephosphorylate endotoxin and adenosine triphosphate, resulting in an attenuated inflammatory response. In rats, renal ischemia–induced and inflammation-induced AKI was attenuated by recombinant alkaline phosphatase.

The intent of the current clinical trial was to determine the optimal therapeutic dose, effect on kidney function, and adverse effects of recombinant alkaline phosphatase in patients with sepsis-associated AKI.

Methods

Trial Design and Participants

The study protocol and informed consent form were reviewed and approved by the institutional review board or independent ethics committee at each participating site. The trial was conducted in accordance with ethical principles of Good Clinical Practice. Prior to initiation of any study-related procedures, written informed consent was obtained from the patient or the patient’s legal representative. Race and ethnicity information was self-reported or from a first-degree relative in accordance with the US Food and Drug Administration guidance. Data were obtained from all sites, except those from France, where it is prohibited to collect data on race/ethnicity. The reason for inclusion of race/ethnicity in this study was that this was the first inpatient trial with recombinant alkaline phosphatase and therefore differences in, for example, pharmacokinetics could be possible.

The STOP-AKI trial was an international randomized, double-blind, placebo-controlled, 4 parallel-group, dose-finding, adaptive phase 2a/2b trial conducted in critically ill adults with sepsis-associated AKI. The protocol, including slight changes in eligibility criteria (upper age limit from 80 years to 85 years, weight limit from ≤100 kg to ≤115 kg, sepsis time window from <72 hours to <96 hours, and the time window in which the creatinine increase should be observed from <24 hours to <48 hours) implemented after inclusion of 120 patients, was published previously (Supplement 1 and Supplement 2). Patients admitted to the ICU who were aged 18 to 85 years with a diagnosis of sepsis, a diagnosis of AKI, and were not expected to have a rapidly fatal outcome were eligible for study participation (for an overview of all inclusion and exclusion criteria, see eMethods 1 in Supplement 3). Prior to the administration of the study drug, to ensure that patients with prerenal AKI were not enrolled, the AKI diagnosis needed to be confirmed. In practice, patients were volume resuscitated and only when AKI demonstrated to be nonresolving (as defined by a sustained increase in serum creatinine corrected for fluid resuscitation or ongoing oliguria), the patient remained eligible.

Patients enrolled during the first part of the study were randomly assigned to receive either placebo or 1 of 3 recombinant alkaline phosphatase doses (0.4, 0.8, or 1.6 mg/kg) once daily for 3 days using a 1:1:1 allocation ratio.

The data and safety monitoring board (DSMB) performed regular, unblinded safety evaluations. After the inclusion of 120 patients, futility or superiority of the intervention on the primary end point data and the fit to an assumed maximum effect attributable to the drug ($E_{max}$) model dose-response curve was assessed (eMethods 2 in Supplement 3). The adaptive design directed the cessation of 2 treatment groups at the interim analysis, as described in the statistical analysis plan. The DSMB was provided with the time-corrected (ie, measured per day) AUC of the endogenous creatinine phosphatase.
clearance for days 1 through 7, divided by 7 to provide a mean daily creatinine clearance (AUC7-1 ECC) (primary end point) and safety data of the patients in part 1 of the study. The DSMB was instructed to select the highest dose, provided that the Emax model applied and that no safety concerns prohibited the selection of this dose. This dose selection method was based on the observation that biologics exhibit a linear or Emax dose response correlation. Patients were randomized to either placebo or the selected dose of recombinant alkaline phosphatase in part 2.

Trial Oversight
All study medication was manufactured by Nova Laboratories (Leicester, UK) according to Good Manufacturing Practice regulations. The design of the study was discussed with European and US regulatory agencies. Following the interim analysis, an adjudication committee was installed as advised by the DSMB and steering committee to adjudicate the day 1 to 7 ECC data of all patients (eMethods 3 in Supplement 3).

Randomization and Study Medication
The randomization schedule was stratified by site. An independent statistician generated a permuted block randomization schedule (per 8 in part 1 and per 4 in part 2) for an interactive voice/web response system, which linked sequential patient randomization numbers to treatment codes. Study drug dose rationale is explained in eMethods 4 in Supplement 3. The lowest dose was chosen with predicted trough plasma concentrations below the assumed effective concentration. The middle and high doses were chosen based on trough concentrations reaching or exceeding, respectively, the estimated effective concentration. Study drug was administered as a 1-hour intravenous infusion within 24 hours after sepsis-associated AKI was first diagnosed, and then 24 hours (±1 hour) and 48 hours (±1 hour) following administration of the first dose. Administration of nephrotoxic drugs was avoided where possible, as recommended by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Personnel involved in this study were blinded to treatment assignment. To maintain the blinding, clinicians were not allowed to measure circulating alkaline phosphatase concentrations until day 14 (details on blinding in eMethods 5 in Supplement 3).

Outcome Measures
Primary End Point
The primary objective of this study was to determine the optimal therapeutic dose and adverse effects (AEs) of recombinant alkaline phosphatase, and to evaluate its effect on kidney function (AUC7-1 ECC). In view of the limitations of serum creatinine values in patients who are not in a steady state and the limited feasibility to use other measures of kidney function, ECC was chosen as the primary efficacy end point. All patients had an indwelling catheter to ensure accurate measurements of urine volume, with a urine collection period of 6 hours (±1 hour) daily. In patients who were anuric, an ECC of 0 mL/min was imputed. The mean value of the serum creatinine concentration measured at the beginning and at the end of the urine collection period was used for ECC calculations.

Key Secondary End Point
Requirement for renal replacement therapy (RRT) was the main related clinical parameter. Sites were advised to follow criteria for the initiation and termination of RRT. Only continuous forms of RRT were allowed during the first 7 days following enrollment to prevent a rebound effect on ECC by intermittent hemodialysis.

Secondary End Points
Kidney secondary end points included ECC and blood urea nitrogen clearance up through day 28, urine volume, serum creatinine, blood urea nitrogen, proteinuria, and estimated glomerular filtration rate. Nonkidney secondary end points were liver function, pulmonary function, shock-free days, Sequential Organ Failure Assessment (SOFA) scores, biomarker assessment, and mortality. A priori exploratory subgroup analyses were planned to determine whether recombinant alkaline phosphatase treatment demonstrates different levels of efficacy in specific patient groups.

Other End Points
Other exploratory end points included composite major adverse kidney events (MAKE) scores at days 28, 60, and 90; serology; ICU and hospital length of stay; and quality of life. All end points are specified in eMethods 6 in Supplement 3.

Adverse Events
Incidence of fatal and nonfatal (serious) AEs (S)AEs), tolerability, pharmacokinetics (in the first 120 patients), immunogenicity, laboratory assessments, vital signs, and electrocardiography data were included in the safety analysis.

Statistical Analyses
Custom-programmed simulations were performed using SAS software (SAS Institute), version 9.2, to determine power and type I error rate of the chosen sample size and design in a number of different dose-response scenarios. Each scenario assumed a standard deviation of 49 mL/min for the primary end point with an assumed response of 60 mL/min for the placebo group, and from 60 mL/min (no treatment effect) to 79 mL/min (strong treatment effect) for the recombinant alkaline phosphatase dose groups. These estimations and standard deviation were taken from the previous trial using bovine alkaline phosphatase. A sample size was planned of 30 patients per treatment group in part 1 with an additional 85 patients recruited to the optimal recombinant alkaline phosphatase dose and placebo treatment groups in part 2, (eMethods 7 in Supplement 3). Missing values were imputed by interpolation between measured values and extrapolation based on last observation carried forward, according to predefined rules described in the statistical analysis plan. The safety data set consisted of all patients who were assigned to a treatment group and received at least 1 dose of study drug. Efficacy and exploratory end points were analyzed according to the intention-to-treat (ITT)
Figure 1. Flow of Patients Through the STOP-AKI Trial of Recombinant Alkaline Phosphatase in Acute Kidney Injury (AKI)

AKI indicates acute kidney injury; ITT, intention-to-treat; RRT, renal replacement therapy; and STOP-AKI, Safety, Tolerability, Efficacy, and Quality of Life Study of Human Recombinant Alkaline Phosphatase in the Treatment of Patients With Sepsis-Associated Acute Kidney Infection. Part 1 of the trial identified the optimal dose of recombinant alkaline phosphatase. Part 2 compared the optimal dose (1.6 mg/kg) with placebo.

The ITT population included patients from whom informed consent was obtained and who were randomized to a treatment group. The ITT population did not include patients who were randomized during interim analysis and who were assigned to the human recombinant alkaline phosphatase 0.4 mg/kg or 0.8 mg/kg treatment group because these 2 treatment groups were dropped following interim analysis.

An unblinded interim analysis was conducted on the part 1 data to determine the optimal recombinant alkaline phosphatase dose for part 2. This analysis compared the primary efficacy end point and a selection of the safety data for the 4 treatment groups from part 1. The interim analysis was conducted when the first 7 days of laboratory data had been collected for 120 patients from part 1.

A hierarchical method was employed to address any multiplicity arising from the analysis of the key secondary end point. In case of a nonsignificant effect on the primary outcome measure, RRT requirement is viewed as an exploratory end point. All analyses performed on the other secondary end points were for exploratory purposes only; therefore, no further multiplicity adjustment was used. The analysis of the primary efficacy end point was performed by analysis of variance with site as a fixed effect.
| Characteristics | Recombinant Alkaline Phosphatase Groups, No. (%) | Placebo Group (n = 116), No. (%) |
|-----------------|-----------------------------------------------|----------------------------------|
| Age, median (IQR), y | 67.0 (61.0-72.0) | 68.0 (61.0-75.0) |
| Men | 23 (74.2) | 84 (72.4) |
| Women | 8 (25.8) | 32 (27.6) |
| Race/ethnicity |                                |                                  |
| White | 25 (80.6) | 95 (81.9) |
| Black | 0 | 1 (0.9) |
| Asian | 2 (6.5) | 1 (0.9) |
| Other (specifics not obtained) | 0 | 0 |
| Not collected | 4 (12.9) | 16 (13.8) |
| Weight, median (IQR), kg | 78.0 (70.0-86.0) | 79.2 (70.0-86.5) |
| Height, median (IQR), cm | 172.5 (165.0-184.0) [n=30] | 174.0 (165.0-178.0) [n=115] |
| BMI, median (IQR) | 25.8 (22.4-28.4) [n=31] | 26.3 (23.9-29.4) [n=115] |
| Disease severity, median (IQR) | | |
| APACHE II score | 30.0 (25.0-35.0) | 26.0 (20.0-33.5) |
| SAPS II | 52.0 (42.0-70.0) [n=30] | 47.0 (39.0-60.0) [n=97] |
| SOFA score | 10.0 (8.0-13.0) [n=29] | 10.0 (8.0-12.0) [n=108] |
| Mechanical ventilation | 23 (74.2) | 68 (58.6) |
| Vasopressor/inotropic therapy use | 28 (90.3) | 103 (88.8) |
| Vital signs | | |
| Heart rate, median (IQR), beats/min | 93.0 (77.0-115.0) [n=31] | 98.0 (85.0-111.0) |
| Systolic BP, median (IQR), mm Hg | 108.0 (100.0-119.0) | 112.0 (101.5-131.5) |
| Diastolic BP, median (IQR), mm Hg | 54.0 (49.0-62.0) | 56.5 (51.0-63.5) |
| Body temperature | 31 (100) | 114 (100) |
| <36°C | 4 (12.9) | 11 (9.5) |
| ≥36°C<38°C | 20 (64.5) | 76 (65.5) |
| >38°C | 7 (22.6) | 27 (23.3) |
| Kidney function | | |
| eGFR, median (IQR), mL/min\d | 27.2 (20.0-42.4) [n=27] | 37.5 (23.9-50.8) [n=102] |
| ECC, median (IQR), mL/min\e | 25.6 (20.4-40.7) [n=28] | 29.7 (20.5-46.5) [n=98] |
| Day 0 | 14.4 (8.8-58.0) [n=10] | 31.8 (14.7-62.5) [n=49] |
| Day 1 | 28.3 (4.3-64.4) [n=30] | 35.9 (12.2-82.9) [n=103] |
| AKI stage\f | 31 (100) | 112 (100) |
| 1 (Least affected) | 22 (71.0) | 91 (78.4) |
| 2 | 5 (16.1) | 16 (13.8) |
| 3 (Most affected) | 4 (12.9) | 5 (4.3) |
| Urine output, median (IQR), mL/h | 50.0 (21.7-101.7) [n=13] | 60.0 (21.8-99.3) [n=51] |
| Serum creatinine, median (IQR), mg/dL | 2.3 (1.5-2.8) [n=29] | 1.8 (1.3-2.4) [n=113] |

Abbreviations: AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index—weight in kilograms divided by height in meters squared; BP, blood pressure; ECC, endogenous creatinine clearance; eGFR, estimated glomerular filtration rate; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

\* APACHE II scores range from 0-71, with higher scores indicating greater severity. For example, a patient with APACHE II score of 26 at admission, on mechanical ventilation and vasopressor support, could be elderly (eg, 76 y [6 points]), with a temperature of 39.5°C (3 points), mean arterial pressure 62 mm Hg (2 points), heart rate 145/min (3 points), respiratory rate 37/min (3 points), Pao\textsubscript{2} 65 mm Hg (1 point), arterial pH 7.25 (2 points), serum Na\textsuperscript{+} 152 mEq/L (1 point), creatinine 140 mg/dL (2 points), hematocrit 47% (1 point), and white blood cell count 29 x10\textsuperscript{9}/L (2 points).

\d SAPS II ranges from 0-163, with higher scores indicating greater severity.

\e SOFA scores range from 0-24, with higher scores indicating more severe dysfunction. The maximal deviation from normal in 24 h at baseline was used for heart rate, blood pressure, body temperature, and AKI stage.

\f The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.\textsuperscript{24}

\g Study drug infusion was administered as soon as possible, and investigators did not wait until data of day 0 were completed. Therefore, data are given as change from day 1, the day of study drug infusion.

\h AKI stage was stratified according to the AKI-Network definition.\textsuperscript{25}
A Cox proportional hazards model including treatment was fitted to the data together with each of the prognostic factors. The prognostic factor having the lowest \( P \) value on overall survival was chosen to be in the model. A model containing this factor, treatment, and each of the remaining factors was then fitted to the data and the second most influential factor was chosen based on the lowest \( P \) value. This process was continued until the introduction of any new factor did not affect overall survival significantly (\( P > .10 \)).

All statistical tests performed on the ITT population were conducted with SAS (SAS Institute), version 9.4, and with a 2-sided \( P \) value less than .05 for significance.

**Results**

**Participants**

From December 2014 through May 2017, of 326 patients who passed an initial screen, 301 patients (men, 70.7%; median age, 67 years [interquartile range (IQR), 59 to 73]) were enrolled across 53 sites in 11 countries in the European Union and United States (eTable 1 in Supplement 3). Sites were active for 17 months (±8 months). Follow-up was conducted for 90 days and the final visit took place on August 14, 2017. The safety analysis included 294 patients and ITT included 290 patients. In the ITT data set, patients received recombinant alkaline phosphatase doses of 0.4 mg/kg (n = 31), 0.8 mg/kg (n = 32), 1.6 mg/kg (n = 29 in part 1 and n = 82 in part 2), or placebo (n = 30 in part 1 and n = 86 in part 2) (Figure 1). Randomization resulted in well-balanced demographic and patient characteristics (Table 1; for exploratory subgroup analyses, see eFigures 1-23 in Supplement 3).

**Primary End Point**

In part 1, the dose-finding part of the trial, the median \( AUC_{1-7} \) ECC was \( 47.0 \text{ mL/min (IQR, 6.6 to 88.4) in the 0.4-mg/kg recombinant alkaline phosphatase group, 63.5 mL/min (IQR, 8.1...
to 96.8) in the 0.8-mg/kg recombinant alkaline phosphatase group, and 60.7 mL/min (IQR, 3.7 to 92.4) in the 1.6-mg/kg recombinant alkaline phosphatase group compared with 46.2 mL/min (IQR, 21.5 to 114.6) in the placebo group.

Following the interim analysis, the DSMB advised continuing the study with 1.6 mg/kg of recombinant alkaline phosphatase. As per the statistical analysis plan, only the effects of the 1.6-mg/kg recombinant alkaline phosphatase group were compared with those of the placebo group in the primary end point analysis. From day 1 to day 7, median ECC increased from 26.0 mL/min (IQR, 8.8 to 59.5) to 65.4 mL/min (IQR, 26.7 to 115.4) in the 1.6-mg/kg recombinant alkaline phosphatase group vs from 35.9 mL/min (IQR, 12.2 to 82.9) to 61.9 mL/min (IQR, 22.7 to 115.2) in the placebo group, resulting in an AUC$_{1-7}$ ECC of 55.1 mL/min (IQR, 15.0 to 93.9) in the 1.6-mg/kg recombinant alkaline phosphatase group vs 45.6 mL/min (IQR, 17.7 to 112.4) in the placebo group (absolute difference, 9.5 mL/min [bootstrap 95% CI, −23.9 to 25.5]; $P = .47$ (Figure 2). For the primary endpoint, 10.2% of data were missing and following the judgment of the adjudication committee, 3.1% of data were discarded. Missing or discarded data were imputed according to the prespecified method.

**Secondary End Points**

The requirement of RRT (days 1-28) was 36.0% in the 1.6-mg/kg recombinant alkaline phosphatase group vs 29.3% in the

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### Table 2. Adverse Events and Serious Adverse Events in the First 28 Days Among Patients Who Were Critically Ill With Sepsis-Associated Acute Kidney Injury Treated With Recombinant Alkaline Phosphatase vs Placebo, in the Safety Data Population

| Adverse Event                                      | Recombinant Alkaline Phosphatase Groups | Placebo Group | Recombinant Alkaline Phosphatase Groups | Placebo Group |
|----------------------------------------------------|----------------------------------------|---------------|----------------------------------------|---------------|
|                                                     | 0.4 mg/kg (n = 38)                     | 0.8 mg/kg (n = 35) | 1.6 mg/kg (n = 109) | 0.4 mg/kg (n = 38) | 0.8 mg/kg (n = 35) | 1.6 mg/kg (n = 109) |
|                                                     | 1.6 mg/kg (n = 112)                   |               |                                        |               |                   |
| Total events                                        | 277                                   | 252           | 898                                    | 806           |
| Nonfatal events                                     | 24                                    | 13            | 57                                     | 56            |
| Patients with a fatal event                         | 10 (26.3)                             | 6 (17.1)      | 19 (17.4)                              | 33 (29.5)     |
| Patients with at least 1 event                     | 35 (92.1)                             | 31 (88.6)     | 103 (94.5)                             | 111 (99.1)    |
| Gastrointestinal disorders                         | 17 (44.7)                             | 16 (45.7)     | 63 (57.8)                              | 49 (43.8)     |
| Infections and infestations                         | 16 (42.1)                             | 16 (45.7)     | 60 (55.0)                              | 47 (42.0)     |
| Metabolism and nutrition disorders                  | 13 (34.2)                             | 13 (37.1)     | 49 (45.0)                              | 41 (36.6)     |
| General disorders and administration site conditions| 10 (26.3)                             | 13 (37.1)     | 44 (40.4)                              | 43 (38.4)     |
| Cardiac disorders                                  | 11 (28.9)                             | 12 (34.3)     | 43 (39.4)                              | 44 (39.3)     |
| Psychiatric disorders                              | 12 (31.6)                             | 13 (37.1)     | 42 (38.5)                              | 39 (34.8)     |
| Respiratory, thoracic, and mediastinal disorders    | 14 (36.8)                             | 14 (40.0)     | 40 (36.7)                              | 52 (46.4)     |
| Vascular disorders                                 | 12 (31.6)                             | 9 (25.7)      | 36 (33.0)                              | 40 (35.7)     |
| Investigations                                     | 8 (21.1)                              | 10 (28.6)     | 30 (27.5)                              | 30 (26.8)     |
| Blood and lymphatic system disorders                | 10 (26.3)                             | 8 (22.9)      | 24 (22.0)                              | 22 (19.6)     |
| Skin and subcutaneous tissue disorders              | 7 (18.4)                              | 5 (14.3)      | 22 (20.2)                              | 17 (15.2)     |
| Nervous system disorders                            | 6 (15.8)                              | 10 (28.6)     | 19 (17.4)                              | 15 (13.4)     |
| Kidney and urinary disorders                        | 6 (15.8)                              | 2 (5.7)       | 16 (14.7)                              | 12 (10.7)     |
| Injury, poisoning, and procedural complications     | 13 (34.2)                             | 7 (20.0)      | 14 (12.8)                              | 15 (13.4)     |
| Musculoskeletal and connective tissue disorders     | 3 (7.9)                               | 1 (2.9)       | 13 (11.9)                              | 14 (12.5)     |
| Hepatobiliary disorders                            | 1 (2.6)                               | 1 (2.9)       | 9 (8.3)                                | 9 (8.0)       |
| Endocrine disorders                                | 1 (2.6)                               | 1 (2.9)       | 3 (2.8)                                | 4 (3.6)       |
| Eye disorders                                       | 3 (7.9)                               | 1 (2.9)       | 3 (2.8)                                | 2 (1.8)       |
| Ear and labyrinth disorders                        | 0                                     | 0             | 2 (1.8)                                | 1 (0.9)       |
| Neoplasm benign, malignant, and unspecified (including cyst and polyps) | 0                                     | 0             | 1 (0.9)                                | 1 (0.9)       |
| Congenital, familial, and genetic disorders         | 0                                     | 0             | 1 (0.9)                                | 0             |
| Reproductive system and breast disorder             | 0                                     | 0             | 1 (0.9)                                | 0             |

* Adverse events and serious adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 19.0. All patients who died were analyzed and classified as a fatal serious adverse event. Patients were counted once for each event category, even if they had multiple events in that category. Only patients who received at least 1 dose of study drug were included in the safety analysis data set.
placebo group (odds ratio, 1.4 [95% CI, 0.8 to 2.4]; P = .28). However, due to the null primary end point and the requirement for hierarchical testing, this finding does not represent a formal analysis.

The exploratory end point, treatment effect of recombinant alkaline phosphatase compared with placebo on ECC improvement up to day 28, showed that the 1.6-mg/kg recombinant alkaline phosphatase group exerted a differential treatment effect during the 28-day period (P = .04 for interaction), driven by day 21 (mean difference, 16.3 mL/min [95% CI, 3.07 to 29.5]; P = .02) and day 28 (mean difference, 18.5 mL/min [95% CI, 5.3 to 31.7]; P = .006) (Figure 2). All-cause mortality at day 28 was lower in the 1.6-mg/kg recombinant alkaline phosphatase group (n = 16 [14.4%]) vs the placebo group (n = 31 [26.7%]; difference, 12.3% [95% CI, 1.9%-22.7%]; P = .02). This effect persisted to day 90, 17.1% in the 1.6-mg/kg recombinant alkaline phosphatase group (n = 19) vs 29.3% in the placebo group (n = 34) (difference, 12.2% [95% CI, 1.3% to 23.0%]; P = .03) (eFigure 24 in Supplement 3). Kidney injury biomarkers, as well as other nonkidney secondary end points, were not significantly influenced by recombinant alkaline phosphatase treatment (eTable 2 in Supplement 3). Per-protocol analyses yielded comparable results. Data of other exploratory secondary end points are provided in eTable 3 in Supplement 3.

Statistically significant differences in the effects on the primary end point and key secondary end point were not observed in the a priori defined exploratory subgroups (eFigures 1-8 in Supplement 3).

Other End Points
Treatment with recombinant alkaline phosphatase did not affect MAKE at 28 days, but resulted in a significantly lower incidence of MAKE at 60 days (27.0% in the 1.6-mg/kg recombinant alkaline phosphatase group [n = 30] vs 39.7% in the placebo group [n = 46]; hazard ratio [HR], 1.8 [95% CI, 1.0 to 3.1]; P = .045) and MAKE at 90 days (26.1% in the 1.6-mg/kg recombinant alkaline phosphatase group: [n = 29] vs 39.7% in the placebo group [n = 46]; HR, 1.9 [95% CI, 1.1 to 3.3]; P = .03), mainly driven by a difference in survival (for MAKE definitions at each measurement, see eTable 2 in Supplement 3). Inflammatory biomarkers, quality of life, and other exploratory end points were not significantly influenced by recombinant alkaline phosphatase treatment (eTables 2-3 and eFigures 9-23 in Supplement 3).

Adverse Events
In the safety data population (Table 2), 68 fatal SAEs were reported during the study. Fatal SAEs were reported in 26.3% of the 0.4-mg/kg recombinant alkaline phosphatase group, 17.1% of the 0.8-mg/kg recombinant alkaline phosphatase group, 17.4% of the 1.6-mg/kg recombinant alkaline phosphatase group, and 29.5% in the placebo group. eTable 4 in Supplement 3 provides a summary of cause of death by organ class and Figure 3 illustrates the cumulative incidence of fatal SAEs over time for all treatment groups. Nonfatal SAEs were reported for 8 patients (21.0%) in the 0.4-mg/kg recombinant alkaline phosphatase group, 5 patients (14.3%) in the 0.8-mg/kg recombinant alkaline phosphatase group, 28 patients (25.7%) in the 1.6-mg/kg recombinant alkaline phosphatase group, and 23 patients (20.5%) in the placebo group. Adverse events were reported for the majority of patients in each of the groups (0.4-mg/kg recombinant alkaline phosphatase group, 35 [92.1%]; 0.8-mg/kg recombinant alkaline phosphatase group, 31 [88.6%]; 1.6-mg/kg recombinant alkaline phosphatase group, 103 [94.5%]; placebo, 111 [99.1%]), with most AEs in each treatment group being either mild or moderate in severity. No recombinant alkaline phosphatase dose-dependency in the incidence and nature of (S)AEs was observed. Anti-drug antibody titers were just above the detection limit in 9 patients treated with recombinant alkaline phosphatase.

Post Hoc Analyses
Post hoc, MMRM sensitivity analysis, mixed-effects regression, with random terms for time of measurement and site without imputation, resulted in a mean difference of 27.6 mL/min (95% CI, 8.7 to 46.6; P = .004) for day 21 and a mean difference of 18.2 mL/min (95% CI, 2.5 to 38.9; P = .08) for day 28. Baseline and day 1 ECC strongly correlated with AUC(7 ECC (F = 0.87; common slope, 1.01 [95% CI, 0.93-1.09]; P < .001). Also, a lower baseline ECC correlated with a log-linear higher relative HR for mortality according to a Cox model (eFigure 25 in Supplement 3). To test the robustness of the recombinant alkaline phosphatase–mediated effect on survival, a forward stepwise multivariable analysis was conducted. Of the various covariates tested, recombinant alkaline phosphatase treatment, baseline APACHE II score, baseline ECC, and time to recombinant alkaline phosphatase treatment remained...
significant additive prognostic factors included in the model with a resulting treatment effect for mortality (HR, 0.47 [95% CI, 0.25 to 0.88]) was statistically significant with a 2-sided P value of .02 (eTable 5 in Supplement 3).

Discussion

Among patients with sepsis-associated AKI, human recombinant alkaline phosphatase compared with placebo did not significantly improve short-term kidney function. There are a number of explanations for this finding, the first of which is that this medication is not an effective treatment for sepsis-associated AKI. However, there are alternative possible explanations including, second, that creatinine and its clearance are recognized to be of limited precision to estimate kidney function, especially during nonsteady state conditions; however, a suitable clinical alternative is currently not available. Third, despite randomization, there was a slight imbalance in kidney function between groups. Previous work as well as the current trial, illustrate that the degree of initial kidney dysfunction is prognostic for the extent of kidney recovery and survival, as more severe kidney failure correlates with worse outcomes. Therefore, the somewhat-more-impaired kidney function in the recombinant alkaline phosphatase group may account for the absence of a significantly more pronounced improvement of ECC in the first week. Fourth, the 7-day timeframe was possibly too short, as differences in recovery of ECC between treatment groups emerged on day 21 and day 28. Fifth, the exploratory finding of lower mortality in the recombinant alkaline phosphatase–treated group may have had an influence on the primary outcome because poor kidney function in the most severely ill—but surviving—patients in the treatment group may have attenuated the increase in ECC of the recombinant alkaline phosphatase group.

In sepsis, injury is known to be heterogeneous throughout the kidney with patchy tubular damage being the most common histological finding. In contrast, ECC is a nonspecific, late functional marker. Consequently, acute measures of organ function may not reflect underlying organ damage that only becomes evident later. Therefore, an interventional therapy that reduces damage and improves organ function by attenuating severity and duration of AKI, may prevent maladaptive repair mechanisms and fibrosis, with manifestation of recovery only after weeks. Longer-term exploratory kidney end points indicated that recombinant alkaline phosphatase resulted in more complete long-term recovery of kidney function compared with placebo. Although these beneficial effects are more patient-centered and clinically relevant, it is important to emphasize that these were exploratory end points of this study, so effects of recombinant alkaline phosphatase on longer-term kidney function and survival should be interpreted as only hypothesis-generating.

In view of the detoxifying properties of alkaline phosphatase, therapeutic properties were investigated in animal models of sepsis, demonstrating improved outcomes. It remains unclear to what extent kidney protection is mediated through effects directly on tubular cells or through systemic effects indirectly preventing damage to the kidneys, or whether kidney function improves as part of a general effect of improving sepsis or a combination of the above. Alkaline phosphatase is depleted in the kidney following an ischemic insult, and recombinant alkaline phosphatase attenuates the inflammatory response in isolated human proximal tubule cells. However, systemic detoxifying properties may lead to more swift normalization of circulating inflammatory markers indirectly benefitting the kidneys. As this latter observation could not be confirmed in the current trial, the direct effects on kidney tissue could be more important.

Adverse effects were reported in the majority of patients, independent of treatment with recombinant alkaline phosphatase or placebo. In accordance with the safety data from the previously reported phase 1 studies, no compound-specific or dose-related adverse effects emerged. Fatal SAEs occurred in patients treated with recombinant alkaline phosphatase (17.4%) and placebo (29.5%).

Limitations

This study has several limitations. First, despite randomization, a small but potentially relevant difference in baseline ECC was present that may account for the lack of an effect on the primary outcome measure. Second, the large number of secondary end points may have introduced a type 1 error related to the significant differences between groups, all of which need to be interpreted as exploratory and hypothesis-generating. Third, the exploratory analyses performed to investigate the robustness of the observed mortality difference, were not preplanned and should be interpreted with caution. Fourth, although no signals were observed in this trial for AEs related to treatment, low incidence AEs may be detected in larger trials only.

Conclusions

Among patients who were critically ill with sepsis-associated acute kidney injury, human recombinant alkaline phosphatase compared with placebo did not significantly improve short-term kidney function. Further research is warranted to assess other clinical outcomes.
Effect of Human Recombinant Alkaline Phosphatase on Kidney Function in Sepsis-Associated AKI

Original Investigation Research

Nijmegen, the Netherlands (Hoiting); Internal Medicine, Eastern Idaho Regional Medical Center, Idaho Falls, Idaho; St. Thomas Hospital, King’s College London, London, United Kingdom (Ostermann); Intensive Care, Jeroen Bosch Hospital, ’s-Hertogenbosch, the Netherlands (Rozendaal); Division of Anesthesia and Intensive Care Medicine, Helsinki University Central Hospital, Helsinki, Finland (Valkonen); Division of Critical Care, University College London Hospitals National Institute for Health Research Biomedical Research Centre, London, United Kingdom (Brealey); Bloomberg Institute of Intensive Care Medicine, University College Hospital, London, United Kingdom. (Brealey); Intensive Care, Medisch Spectrum Twente, Enschede, the Netherlands (Beishuizen); Faculté de Médecine, Service de Réanimation, Université de Strasbourg, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France (Meziani); Department of Critical Care Medicine, Center for Critical Care Nephrology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Murugan); Department of Intensive Care, Erasmus Medical Centre, Rotterdam, the Netherlands (de Geus); Unité Mixte de Recherche INSERM 1610, University Paris 7 Denis Diderot, Paris, France (Payan); Department of Anesthesiology and Critical Care, Hôpital Lariboisière, Assistance Publique–Hôpitaux de Paris, Paris (France) (Payan); Clinical Department, AM-Pharma BV, Bunnik, the Netherlands (van den Berg, Arend).

Author Contributions: Dr Pickkers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Pickkers is the principal investigator and chaired the steering committee, which also included Drs Mehta, Murray, and Joannidis. Dr Kellum served as national PI for all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Pickkers is the principal investigator and chaired the steering committee. Concept and design: Pickkers, Mehta, Murray, Joannidis, van den Berg, Arend. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Pickkers, van den Berg, Arend.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Pickkers reported receiving travel reimbursements and fees for medical monitoring of this trial from AM-Pharma. Dr Mehta reported receiving consulting fees from AM-Pharma. Dr Murray reported receiving consulting fees from AM-Pharma. Dr Joannidis reported receiving travel reimbursements and consulting fees from AM-Pharma; consulting fees from Baxter Healthcare; speakers’ fees from CSL Behring and Astute Medical; and a research grant and speakers’ fees from Fresenius. Dr Moltorris reported adjudicating being a coauthor in the study, which was paid for by AM-Pharma, and has conducted preclinical studies for AM-Pharma. Dr Kellum reported receiving consulting fees from AM-Pharma. Dr Bachler reported receiving travel reimbursements for meetings of this trial from AM-Pharma; personal fees and travel grants from LFB Biomedicaments; travel grants from Baxter; travel grants and research funding from CSL Behring and Mitsubishi Tanabe; and nonfinancial support from TEM International outside the submitted work. Dr Hoste reported receiving travel reimbursements from AM-Pharma; and speakers’ fees from Alexion. Dr Krell reported receiving support from AM-Pharma for attendance to the CRRT meeting in San Diego 2017. Dr Murugan reported receiving financial support from AM-Pharma to screen and enroll patients in the trial; financial support for other trials through the University of Pittsburgh from La Jolla Pharmaceuticals; grant support from the National Institute of Diabetes and Digestive and Kidney Diseases; and grant funding from Bioporo Inc. Dr van den Berg is an employee of AM-Pharma and holds equity interest in the company; he also has patents or licenses filed via AM-Pharma for which he receives no personal compensation. Dr Arend is an employee of AM-Pharma and holds equity interest in the company; he also has patents or licenses filed via AM-Pharma for which he receives no personal compensation. Funding/Support: This work was supported by AM-Pharma.

Role of the Funder/Sponsor: The role of the sponsor in the design of the study was to coordinate and facilitate processes, where the scientific input was provided by the members of the protocol committee, steering committee, and specific input by external experts in data management and statistics. The sponsor contracted an external contract research organization to operationally conduct the study at the study sites. The contract research organization was responsible for setting up the technical systems, data collection, quality control, pharmacovigilance, statistics, and further overall management of the study, under coordination and supervision of the sponsor. The statistical analysis plan was prepared by the contract research organization with input by principal investigator, sponsor, and external experts in statistics. The analyses were performed by external contract research organizations. Data were interpreted by the members of the steering committee, and, in a later phase, all coauthors and external experts, coordinated by the sponsor, could provide input. The principal investigator was responsible for preparation of the manuscript. All coauthors reviewed, made adjustments, and approved the manuscript. The decision to submit the manuscript was made by the principal investigator and other coauthors.

STOP-AKI Investigators: Jacques Arend, MD, Clinical Department, AM Pharma BV, Bunnik, the Netherlands; Mirjam Bachler, PhD, Medical University Innsbruck, Department of General and Surgical Critical Care Medicine, Austria; Albertus Beishuizen, MD, PhD, Medisch Spectrum Twente, Intensive Care, Enschede, the Netherlands; Erik van den Berg, Clinical Department, AM Pharma BV, Bunnik, the Netherlands; David Brealey, PhD, MRCP, FRCA, Division of Critical Care, University College London Hospitals NHS Trust, Biomedical Research Centre and Bloomberg Institute of Intensive Care Medicine, University College London, UK; Hilde de Geus, MD, PhD, Erasmus Medical Centre, Department of Intensive Care, Rotterdam, the Netherlands; Oscar Hoiting, MD, Canissius Wilhelmina Hospital, Intensive Care, Nijmegen, the Netherlands; Eric Hoste, MD, PhD, Ghent University, Intensive Care, Ghent, Belgium, and Clinical Research Foundation Flanders (FWO), Brussels, Belgium; Michael Joannidis, MD, Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria; John Kellum, MD, Center for Critical Care Nephrology, Department of Critical Care Medicine, School of Medicine, Pittsburgh, Pennsylvania; Kenneth Krell, MD, Eastern Idaho Regional Medical Center, Internal Medicine, Idaho Falls, Idaho; Ravindra Mehta, MD, Department of Medicine, Indiana University, Indianapolis, Indiana; Patrick Murray, MD, School of Medicine, University College Dublin, Dublin, Ireland; Raghaven Murugan, MD, MS, FRCPC, FCCM, Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Marlies Ostermann, MD, PhD, King’s College London, Guy’s & St Thomas’ Hospital, London, UK; Didier Payen, MD, PhD, UMR INSERM 1610, University Paris 7 Denis Diderot Paris Cité Sorbonne & Lariboisière Hospital—AP–H, Paris, France; Peter Pickkers, MD, PhD, Department of Intensive Care Medicine, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; Wim Rozendaal, MD, Jeroen Bosch Hospital, Intensive Care, Hertogenbosch, the Netherlands; Mina Valkonen, MD, PhD, Division of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital and Helsinki University Central Hospital, Helsinki, Finland; Antonio Arjona, MD, PhD, Hospital de Sabadell de Barcelona, Centro de Criticos, Sabadell, Spain; Frederic Bellec, MD, Centre Hospitalier de Montauban, Montauban, France; Antonio Bettbske Røg, MD, PhD, Hospital de La Santa Cruz i Sant Pau, Medicina Intensiva, Barcelona, Spain; Azar Ibnouz, MD, University of Florida, Gainesville; Thierry Bouain, MD, Centre Hospitalier Régional d’Orléans, Orléans, France; Edward Cordasco, MD, Remington Davis Inc, Columbus, Ohio; Dianna Cruz, MD, University of California San Diego; Jacques Devrient, MD, CHU Brugmann, Soins intensifs, UCL, Bruxelles, Belgium; Brian Dive, MD, PhD, CHU UCL Namur asbl—Site Godinne, Soins Intensifs, Yvoir, Belgium; Joseph Eustace, MD, Cork University Hospital, PIN, Cork, Ireland; Liu G, Forni, MD, PhD, Royal Surrey County Hospital, Intensive Care, Guildford, UK; Kevin Finkel, MD, University of Texas Houston Medical School, Bruno Francois, MD, Centre Hospitalier Universitaire de Limoges, CHU Dupuytren, Rénovation polyvalente, Limoges, France; Rita Galeiras, MD, PhD, Hospital Universitario Arco Iris, A Coruña, Spain; Herwig Gerlach, MD, PhD, Vivantes Klinikum Neukölln, Berlin, Germany; Richard Gerritsen, MD, Medisch Centrum Leeuwarden, Leeuwarden, the Netherlands; Matthias Gründling, MD, PhD.
University of Greifswald, Klinik für Anästhesiologie, Intensivmedizin, Notfallmedizin und Schmerzmedizin, Greifswald, Germany; Luis Jauregui-Peredo, MD; ID Clinical Research Ltd, Toledo, Ohio; Olivier Joannes-Bouy, MD, CHU de Bordeaux, Pessac, France; Luis Juncos, MD, University of Mississippi Medical Center, Jackson; Sari Karlsson, MD, PhD, Tampere University Hospital, Department of Intensive Care Medicine, Tampere, Finland; Kalloori Kofale, MD, Royal Infirmary of Edinburgh, Anaesthesia, Critical Care and Pain Medicine, Edinburgh, UK; Andreas Kortgen, MD, PhD, Universitätsklinikum Jena, Klinik für Anästhesiologie und Intensivtherapie, Jena, Germany; Giacomo Monti, MD, Department of Anesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy; Raili Laru-Sompa, MD, Kski Suomen Keskussairaala, Jyväskylä, Finland; Pierre-François Laterre, MD, PhD, Cliniques universitaires Saint-Luc, Soins Intensifs, Bruxelles, Belgium; Jean-Yves Lefrant, MD, PhD, CHU de Nîmes; Fédération Médicale, LAM, Marseille, France; Nicolas Lerrole, MD, CHU Angers, Service de Réanimation Médicale et Médecine Hyperb, Angers, France; Bruno Levy, MD, CHRU Nancy, Vandenoue lès Nancy, France; Andrew Lewington, MD, St James University Hospital, Leeds, UK; Carole Llorente, MD, PhD, Hospital Universitario de Getafe, Getafe, Spain; Rafael Manez Mendiluce, MD, PhD, Hospital Universitario de Bellvitge, Llobregat, Spain; Laurent Martin-Lefevre, MD, Centre Hospitalier Départemental de Vendée, Réanimation médico-chirurgicale, La Roche-sur-Yon, France; Martin Matijevic, MD, PhD, University Hospital Pizen, 1st Department of Internal Medicine, Pilsen, Czech Republic; Andreas Meier-Hellmann, MD, PhD, Helios Klinikum Erfurt, Erfurt, Germany; Emmanuelle Mercier, MD, Hôpital Bretonneau, Tours, France; Martin Novacek, MD, Oblastní nemocnice Kolín, a.s., Anestesiologicko-rezuscitace a klinika, Kolín, Czech Republic; Alistair Nichol, MD, FCICM, FFICMC, FCARCSI, MB, BCH, Victoria Hospital—University of Cincinnati Medical Center, Cincinnati, Ohio; Ashita J. Tolwani, MD, University of Alabama at Birmingham; Teresa Maria Tomasina Irigui, MD, Hospital Universitario Germans Trias i Pujol, Servicio de Medicina Intensiva, Badalona, Spain; Pieter R. Tuinman, MD, PhD, VU Medical Center, Intensive Care Medicine, Amsterdam, the Netherlands; Ari Uusaro, MD, PhD, Kuopio University Hospital, Department of Anesthesiology and Intensive Care, Kuopio, Finland; Bernt Veber, MD, PhD, Hôpital Charles Nicolle, Réanimation Chirurgique, Rouen, France; Jean-Louis Vincent, MD, PhD, Jacques Creteur, MD, Hôpital Erasme, Bruxelles, Belgium; Anitha Vijayan, MD, Washington University, St Louis, Missouri; Norbert Weiler, MD, Universitätsklinikum Schleswig-Holstein, Klinik für Anästhesiologie und operative Intensivmedizin, Kiel, Germany; James Welker, MD, Anne Arundel Medical Center, Annapolis, Maryland; Tobias Welte, MD, PhD, Medizinische Hochschule Hannover, Hannover, Germany; Jason Wilson, MD, MA, FFAEM, FACEP, Tampa General Hospital, Division Emergency Medicine, Tampa, Florida; Kai Zacharowski, MD, PhD, ML, FRCA, University Hospital Frankfurt, Anaesthesie, Intensive Care Medicine and Pain Therapy, Frankfurt am Main, Germany; Pleun Hemelaar, MD, PhD, Intensive care, Nijmegen, the Netherlands; Rob ten Pas, Global clinical trial director, Clinical Department, AM Pharma BV, Bunnik, the Netherlands; Willem Raaben, Project manager, Clinical Department, AM Pharma BV, Bunnik, the Netherlands; Annelies Resink, Global Clinical Research Director, AM Pharma BV, Bunnik, the Netherlands.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank all co-investigators, their research nurses, and their intensive care teams at each of the recruitment sites for their contributions to this trial. Editorial assistance was provided by Pleun Hemelaar, MSc (Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; no compensation received). Rob ten Pas, MSc, Willem Raaben MSc, and Annelies Resink, PhD (all employees of AM-Pharma BV, Bunnik, the Netherlands). Also, we thank the DSM8 members, chaired by A. Shaw, MB, FRCA, FFICM, FCICM (University of Alberta, Canada), for their willingness to perform interim and safety analyses.

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Original Investigation Research

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