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

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[+] **Supplemental content**

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 end point 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 (AUC_{1-7} ECC). Incidence of fatal and nonfatal (serious) adverse events ([S]AEs) 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; 17.1% 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.

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Acute kidney injury (AKI) occurs in up to 60% of patients in intensive care units (ICUs), and its incidence is increasing.[1,2] Development of AKI in patients with sepsis is associated with increased mortality,[3] and survivors are at risk of developing chronic kidney disease,[4] 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.[5] Currently, no pharmacologic interventions are available to prevent or treat AKI.[6]

Alkaline phosphatase is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of various compounds, including bacterial endotoxins[7] and proinflammatory mediators such as extracellular adenosine triphosphate.[8] In animal sepsis models, treatment with alkaline phosphatase attenuated systemic inflammation and organ dysfunction and improved survival rates.[9] In 2 small clinical trials, administration of bovine alkaline phosphatase significantly improved kidney function in patients with sepsis.[10,11]

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.[12] 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.[12] 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.[13] In rats, renal ischemia-induced and inflammation-induced AKI was attenuated by recombinant alkaline phosphatase.[14] 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

Key Points

Question Does the use of human recombinant alkaline phosphatase improve kidney function in patients who are critically ill with sepsis-associated acute kidney injury?

Findings In this randomized, double-blind, placebo-controlled, dose-finding adaptive phase 2a/2b trial enrolling 301 adults, the optimal therapeutic dose of recombinant alkaline phosphatase was 1.6 mg/kg. Treatment with this dose for 3 days when added to standard care resulted in a median increase in endogenous creatinine clearance of 27.6 mL/min vs 14.7 mL/min for placebo in the first 7 days, a difference that was not statistically significant.

Meaning Among patients who were critically ill with sepsis-associated acute kidney injury, treatment with human recombinant alkaline phosphatase did not improve kidney function in the first week of treatment.

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 serum creatinine increase should be observed from <24 hours to <48 hours) implemented after inclusion of 120 patients, was published previously[15] (Supplement 1 and Supplement 2). Patients admitted to the ICU who were aged 18 to 85 years with a diagnosis of sepsis,[16] a diagnosis of AKI,[17] 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 reconfirmed. 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 1:1:1:1 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

clearance for days 1 through 7, divided by 7 to provide a mean daily creatinine clearance (AUC_{1-7} 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 E_{max} 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 E_{max} dose response correlation.[18] 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[15] 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.[19] 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 (AUC_{1-7} 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.[20] All patients had an indwelling catheter to ensure accurate measurements of urine volume, with a urine collection period of 6 hours (±1 hour) daily.[21,22] 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.[15]

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.[23] 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.[11] 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)
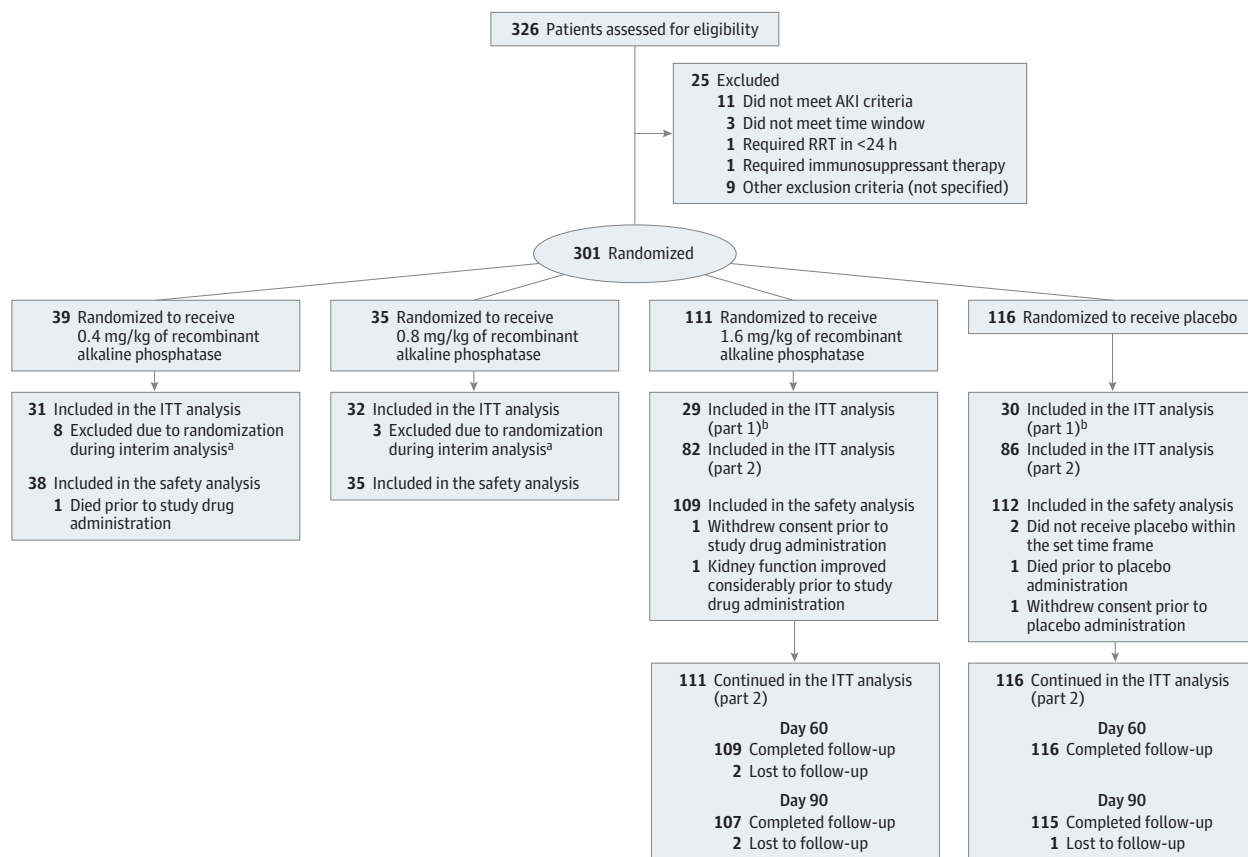
AKI indicates acute kidney injury; ITT, intention-to-treat; RRT, renal replacement therapy; and STOP-AKI, Safety, Tolerability, Efficacy, and Quality of Life Study of Human Recombinant Alkaline Phosphatase in the Treatment of Patients With Sepsis-Associated Acute Kidney Infection. Part 1 of the trial identified the optimal dose of recombinant alkaline phosphatase. Part 2 compared the optimal dose (1.6 mg/kg) with placebo.

[a] 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.

[b] 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.

principle for patients from whom informed consent was obtained and who were randomized to a treatment group.

Patients who were randomized during interim analysis and who were assigned to 1 of the 2 treatment groups that were dropped following interim analysis were not part of the ITT population. The per-protocol analysis supplemented the ITT analysis and compared the intervention groups with the placebo group for patients who received study medication according to the study protocol and had no more than 2 missing ECC values on days 1 through 7, as detailed in the statistical analysis plan.

For the descriptive statistics, continuous variables are presented as least-square means with standard error of mean, or median with interquartile range, depending on their distribution. Normally distributed variables were compared using the t test; Mann-Whitney U tests were used to compare nonnormally distributed variables. Categorical (and binary) variables are presented as numbers with per-

centages and analyzed using χ^2 tests. Survival analyses with Kaplan-Meier curves were used for graphical presentation. Cox proportional hazard regression analyses were used to estimate the hazard ratio for survival and for the number of RRT-free, shock-free, and mechanical ventilation-free days during study days 1 through 28 with the use of recombinant alkaline phosphatase vs placebo. The assumption of proportional hazards was confirmed by visual inspection of those curves.

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.

Table 1. Demographic and Baseline Disease Characteristics of Patients Who Were Critically Ill With Sepsis-Associated Acute Kidney Injury Treated With Recombinant Alkaline Phosphatase vs Placebo, Intention-to-Treat Population

| Characteristics | Recombinant Alkaline Phosphatase Groups, No. (%) | | | Placebo Group (n = 116), No. (%) |
	0.4 mg/kg (n = 31)	0.8 mg/kg (n = 32)	1.6 mg/kg (n = 111)	
Age, median (IQR), y	67.0 (61.0-72.0)	66.5 (62.5-72.0)	65.0 (57.0-73.0)	68.0 (61.0-75.0)
Men	23 (74.2)	16 (50.0)	82 (73.9)	84 (72.4)
Women	8 (25.8)	16 (50.0)	29 (26.1)	32 (27.6)
Race/ethnicity				
White	25 (80.6)	27 (84.4)	95 (85.6)	95 (81.9)
Black	0	0	1 (0.9)	4 (3.4)
Asian	2 (6.5)	0	1 (0.9)	1 (0.9)
Other (specifics not obtained)	0	1 (3.1)	0	0
Not collected	4 (12.9)	4 (12.5)	14 (12.6)	16 (13.8)
Weight, median (IQR), kg	78.0 (70.0-86.0)	79.0 (72.0-90.0)	80.0 (71.8-90.0)	79.2 (70.0-86.5)
Height, median (IQR), cm	172.5 (165.0-184.0) [n=30]	167.0 (160.0-174.0) [n=29]	173.0 (168.0-179.0) [n=110]	174.0 (165.0-178.0) [n=115]
BMI, median (IQR)	25.8 (22.4-28.4) [n=30]	27.4 (25.2 -30.7) [n=29]	26.8 (23.9 -30.2) [n=110]	26.3 (23.9-29.4) [n=115]
Disease severity, median (IQR)				
APACHE II score[a]	30.0 (25.0-35.0)	26.0 (20.0-34.5)	25.0 (19.0-31.0) [n=110]	26.0 (20.0-33.5)
SAPS II[b]	52.0 (42.0-70.0) [n=30]	50.5 (38.0-60.5)	50.0 (42.0-61.0) [n=97]	47.0 (39.0-60.0) [n=97]
SOFA score[c]	10.0 (8.0-13.0) [n=29]	9.0 (8.0-11.0)	10.0 (8.0-12.0) [n=108]	10.0 (8.0-12.0) [n=113]
Mechanical ventilation	23 (74.2)	20 (62.5)	70 (63.1)	68 (58.6)
Vasopressor/inotropic therapy use	28 (90.3)	30 (93.8)	102 (91.9)	103 (88.8)
Vital signs				
Heart rate, median (IQR), beats/min	93.0 (77.0-115.0) [n=31]	90.0 (75.5-107.5)	95.0 (83.0-110.0)	98.0 (85.0-111.0)
Systolic BP, median (IQR), mm Hg	108.0 (100.0-119.0)	118.5 (96.0-131.0)	107.0 (95.0-119.0)	112.0 (101.5-131.5)
Diastolic BP, median (IQR), mm Hg	54.0 (49.0-62.0)	58.0 (54.0-62.0)	55.0 (49.0-62.0) [n=110]	56.5 (51.0-63.5)
Body temperature	31 (100)	32 (100)	108 (100)	114 (100)
<36°C	4 (12.9)	5 (15.6)	11 (9.9)	11 (9.5)
≥36°C-≤38°C	20 (64.5)	22 (68.8)	79 (71.2)	76 (65.5)
>38°C	7 (22.6)	5 (15.6)	18 (16.2)	27 (23.3)
Kidney function				
eGFR, median (IQR), mL/min[d]	27.2 (20.0-42.4) [n=27]	25.6 (20.4-40.7) [n=28]	29.7 (20.5-46.5) [n=98]	37.5 (23.9 -50.8) [n=102]
ECC, median (IQR), mL/min[e]				
Day 0	14.4 (8.8-58.0) [n=10]	26.0 (5.4-30.6) [n=12]	24.1 (10.5-54.9) [n=46]	31.8 (14.7-62.5) [n=49]
Day 1	28.3 (4.3-64.4) [n=30]	25.2 (9.4 -61.0) [n=31]	26.0 (8.8-59.5) [n=102]	35.9 (12.2-82.9) [n=103]
AKI stage[f]	31 (100)	32 (100)	109 (100)	112 (100)
1 (Least affected)	22 (71.0)	23 (71.9)	81 (73.0)	91 (78.4)
2	5 (16.1)	5 (15.6)	17 (15.3)	16 (13.8)
3 (Most affected)	4 (12.9)	4 (12.5)	11 (9.9)	5 (4.3)
Urine output, median (IQR), mL/h	50.0 (21.7-101.7) [n=13]	27.4 (16.4-50.0) [n=14]	39.1 (10.9-85.7) [n=50]	60.0 (21.8-99.3) [n=53]
Serum creatinine, median (IQR), mg/dL	2.3 (1.5-2.8) [n=29]	1.9 (1.5-2.8)	2.0 (1.4-2.8) [n=110]	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.

SI conversion factors: To convert ECC to mL/s, multiply by 0.0167.

[a] 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$_2$ 65 mm Hg (1 point), arterial pH 7.25 (2 points),

serum Na$^+$ 152 mEq/L (1 point), creatinine 140 mg/dL (2 points), hematocrit 47% (1 point), and white blood cell count 29 ×10^9/L (2 points).

[b] SAPS II ranges from 0-163, with higher scores indicating greater severity.

[c] 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.

[d] The eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[24]

[e] Study drug infusion was administrated 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.

[f] AKI stage was stratified according to the AKI-Network definition.[25]

Figure 2. Endogenous Creatinine Clearance (ECC) Among Patients Who Were Critically Ill With Sepsis-Associated Acute Kidney Infection
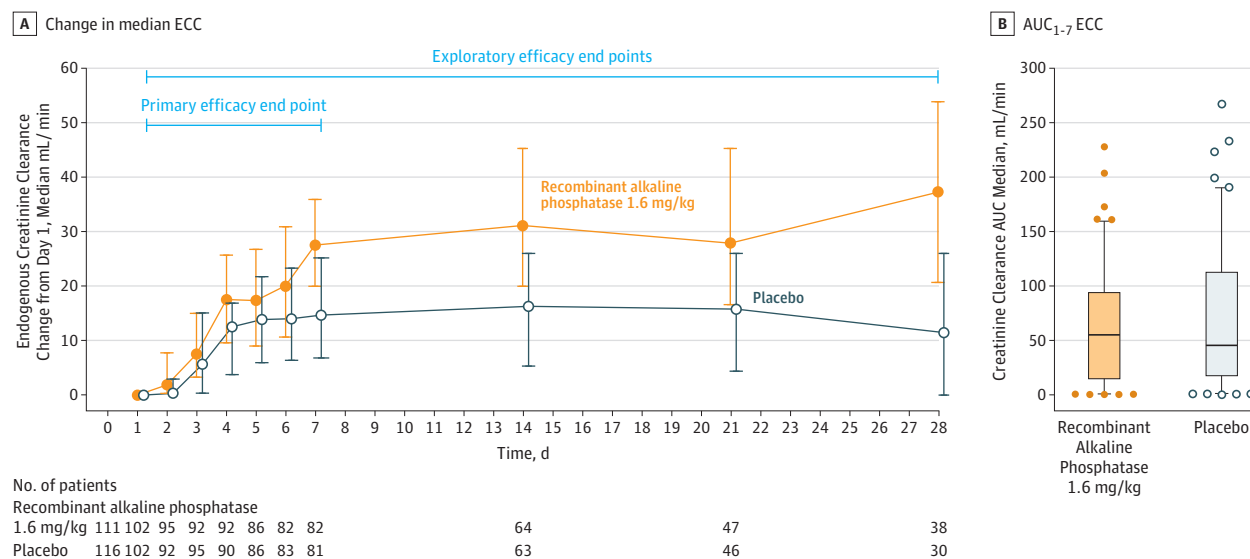
AUC$_{1-7}$ ECC indicates the area under the time-corrected (ie, measured per day) curve (AUC) for ECC from day 1 through 7, divided by 7 to provide a mean daily creatinine clearance. A, Median increase in ECC from baseline to day 28 from part 1 and part 2 (combined data) of the trial. Error bars indicate distribution free intervals. The data points of the 2 treatment groups were slightly staggered to avoid superimposition. B, Median AUC$_{1-7}$ ECC for part 1 and part 2 (combined data) of the trial. The top and bottom of the boxes indicate the IQR, whiskers indicate 95% CI, and the circles indicate the individuals whose values were outside the 5th and 95th percentiles of the AUC$_{1-7}$ ECC.

Four post hoc analyses were performed: First, on the primary end point, a sensitivity analysis using a mixed-effects model with random terms for site was performed. Second, sensitivity analyses were undertaken using a mixed model of repeated measures (MMRM) with time of measurement as a fixed effect and site and patient (nested within site) as random effects. This analysis was initially undertaken on data with imputation to align with the prespecified analysis of the primary end point and additionally without imputation for the data from day 1 through day 28. Third, to determine to what extent kidney function influences its recovery, baseline creatinine clearance was correlated with the primary end point AUC$_{1-7}$ ECC. Fourth, a post hoc, forward stepwise, multivariable analysis was undertaken to assess whether the observed differences in overall survival were related to baseline imbalances in prognostic factors. The following factors were considered; time to treatment, C-reactive protein, sex, weight, age, Acute Kidney Injury Network stage, PaO$_2$/FiO$_2$ ratio, mechanical ventilation status, vasopressor and inotropic therapy, Kidney Injury Molecule-1, ECC, Simplified Acute Physiology Score II (SAPS II), SOFA score, and Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score. Proportional hazards were assumed.

Because these were exploratory analyses, model assumptions were not assessed in any formal way except by confirming a consistent effect in subgroups as indicated by Forest plots. 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 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

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[a]

| | Adverse Events From Day 1-28, No. (%) | | | | Serious Adverse Events From Day 1-28, No. (%) | | | |
| | Recombinant Alkaline Phosphatase Groups | | | Placebo Group (n = 112) | Recombinant Alkaline Phosphatase Groups | | | Placebo Group (n = 112) |
Adverse Event	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)	
Total events	277	252	898	806	34	19	76	89
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 a nonfatal serious adverse event					8 (21.0)	5 (14.3)	28 (25.7)	23 (20.5)
Patients with at least 1 event	35 (92.1)	31 (88.6)	103 (94.5)	111 (99.1)	18 (47.4)	11 (31.4)	47 (43.1)	56 (50.0)
Gastrointestinal disorders	17 (44.7)	16 (45.7)	63 (57.8)	49 (43.8)	3 (7.9)	2 (5.7)	11 (10.1)	6 (5.4)
Infections and infestations	16 (42.1)	16 (45.7)	60 (55.0)	47 (42.0)	5 (13.2)	5 (14.3)	18 (16.5)	18 (16.1)
Metabolism and nutrition disorders	13 (34.2)	13 (37.1)	49 (45.0)	41 (36.6)	0	0	0	1 (0.9)
General disorders and administration site conditions	10 (26.3)	13 (37.1)	44 (40.4)	43 (38.4)	2 (5.3)	0	5 (4.6)	9 (8.0)
Cardiac disorders	11 (28.9)	12 (34.3)	43 (39.4)	44 (39.3)	0	3 (8.6)	9 (8.3)	11 (9.8)
Psychiatric disorders	12 (31.6)	13 (37.1)	42 (38.5)	39 (34.8)	0	0	1 (0.9)	0
Respiratory, thoracic, and mediastinal disorders	14 (36.8)	14 (40.0)	40 (36.7)	52 (46.4)	6 (15.8)	3 (8.6)	9 (8.3)	14 (12.5)
Vascular disorders	12 (31.6)	9 (25.7)	36 (33.0)	40 (35.7)	1 (2.6)	0	5 (4.6)	7 (6.3)
Investigations	8 (21.1)	10 (28.6)	30 (27.5)	30 (26.8)	0	0	1 (0.9)	1 (0.9)
Blood and lymphatic system disorders	10 (26.3)	8 (22.9)	24 (22.0)	22 (19.6)	2 (5.3)	0	2 (1.8)	2 (1.8)
Skin and subcutaneous tissue disorders	7 (18.4)	5 (14.3)	22 (20.2)	17 (15.2)	0	0	1 (0.9)	0
Nervous system disorders	6 (15.8)	10 (28.6)	19 (17.4)	15 (13.4)	4 (10.5)	1 (2.9)	4 (3.7)	1 (0.9)
Kidney and urinary disorders	6 (15.8)	2 (5.7)	16 (14.7)	12 (10.7)	1 (2.6)	0	1 (0.9)	2 (1.8)
Injury, poisoning, and procedural complications	13 (34.2)	7 (20.0)	14 (12.8)	15 (13.4)	3 (7.9)	2 (5.7)	0	3 (2.7)
Musculoskeletal and connective tissue disorders	3 (7.9)	1 (2.9)	13 (11.9)	14 (12.5)	0	0	0	1 (0.9)
Hepatobiliary disorders	1 (2.6)	1 (2.9)	9 (8.3)	9 (8.0)	1 (2.6)	0	0	4 (3.6)
Endocrine disorders	1 (2.6)	1 (2.9)	3 (2.8)	4 (3.6)	0	0	0	0
Eye disorders	3 (7.9)	1 (2.9)	3 (2.8)	2 (1.8)	0	0	0	0
Ear and labyrinth disorders	0	0	2 (1.8)	1 (0.9)	0	0	1 (0.9)	0
Neoplasm benign, malignant, and unspecified (including cyst and polyps)	0	0	1 (0.9)	1 (0.9)	0	0	0	0
Congenital, familial, and genetic disorders	0	0	1 (0.9)	0	0	0	0	0
Reproductive system and breast disorder	0	0	1 (0.9)	0	0	0	0	0

[a] 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.

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 end point, 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

Figure 3. Cumulative Incidence of Fatal Events From Baseline to 90 Days for All Treatment Groups in the Safety Data Population of Patients Who Were Critically Ill With Sepsis-Associated Acute Kidney Infection
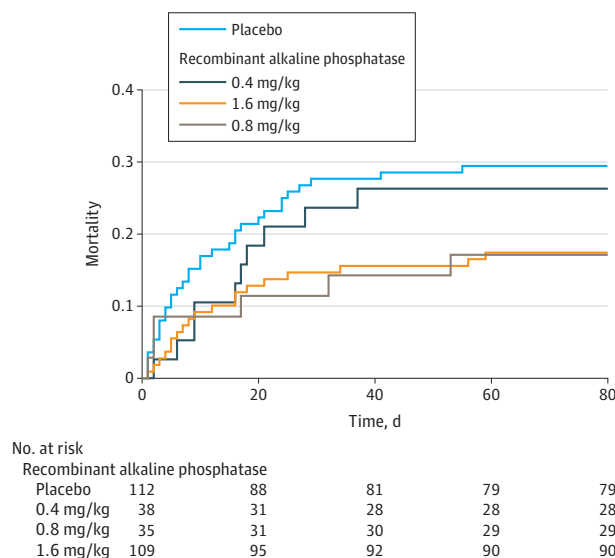
The median observation time (95% CI) was 16.5 days (6-28) for the 0.4-mg/kg recombinant alkaline phosphatase group, 9.5 days (1-53) for the 0.8-mg/kg recombinant alkaline phosphatase group, 9 days (5-21) for the 1.6-mg/kg recombinant alkaline phosphatase group, and 8 days (4-16) for the placebo group. All patients who died were analyzed and classified as a fatal serious adverse event.

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_{1-7} ECC ($r = 0.87$; 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,[26,27] 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,[28] 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.[29] 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.[30,31] 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,[32] 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.[33] 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,[34] and recombinant alkaline phosphatase attenuates the inflammatory response in isolated human proximal tubule cells.[35] However, systemic detoxifying properties may lead to more swift normalization of circulating inflammatory markers[11] indirectly benefiting 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,[36] 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.

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Data Sharing Statement: See Supplement 4.

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