

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock

The SEPSIS-ACT Randomized Clinical Trial

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IMPORTANCE Norepinephrine, the first-line vasopressor for septic shock, is not always effective and has important catecholaminergic adverse effects. Selepressin, a selective vasopressin V1a receptor agonist, is a noncatecholaminergic vasopressor that may mitigate sepsis-induced vasodilatation, vascular leakage, and edema, with fewer adverse effects.

OBJECTIVE To test whether selepressin improves outcome in septic shock.

DESIGN, SETTING, AND PARTICIPANTS An adaptive phase 2b/3 randomized clinical trial comprising 2 parts that included adult patients (n = 868) with septic shock requiring more than 5 µg/min of norepinephrine. Part 1 used a Bayesian algorithm to adjust randomization probabilities to alternative selepressin dosing regimens and to trigger transition to part 2, which would compare the best-performing regimen with placebo. The trial was conducted between July 2015 and August 2017 in 63 hospitals in Belgium, Denmark, France, the Netherlands, and the United States, and follow-up was completed by May 2018.

INTERVENTIONS Random assignment to 1 of 3 dosing regimens of selepressin (starting infusion rates of 1.7, 2.5, and 3.5 ng/kg/min; n = 585) or to placebo (n = 283), all administered as continuous infusions titrated according to hemodynamic parameters.

MAIN OUTCOMES AND MEASURES Primary end point was ventilator- and vasopressor-free days within 30 days (deaths assigned zero days) of commencing study drug. Key secondary end points were 90-day mortality, kidney replacement therapy-free days, and ICU-free days.

RESULTS Among 868 randomized patients, 828 received study drug (mean age, 66.3 years; 341 [41.2%] women) and comprised the primary analysis cohort, of whom 562 received 1 of 3 selepressin regimens, 266 received placebo, and 817 (98.7%) completed the trial. The trial was stopped for futility at the end of part 1. Median study drug duration was 37.8 hours (IQR, 17.8-72.4). There were no significant differences in the primary end point (ventilator- and vasopressor-free days: 15.0 vs 14.5 in the selepressin and placebo groups; difference, 0.6 [95% CI, -1.3 to 2.4]; $P = .30$) or key secondary end points (90-day mortality, 40.6% vs 39.4%; difference, 1.1% [95% CI, -6.5% to 8.8%]; $P = .77$; kidney replacement therapy-free days: 18.5 vs 18.2; difference, 0.3 [95% CI, -2.1 to 2.6]; $P = .85$; ICU-free days: 12.6 vs 12.2; difference, 0.5 [95% CI, -1.2 to 2.2]; $P = .41$). Adverse event rates included cardiac arrhythmias (27.9% vs 25.2% of patients), cardiac ischemia (6.6% vs 5.6%), mesenteric ischemia (3.2% vs 2.6%), and peripheral ischemia (2.3% vs 2.3%).

CONCLUSIONS AND RELEVANCE Among patients with septic shock receiving norepinephrine, administration of selepressin, compared with placebo, did not result in improvement in vasopressor- and ventilator-free days within 30 days. Further research would be needed to evaluate the potential role of selepressin for other patient-centered outcomes in septic shock.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT02508649](https://clinicaltrials.gov/ct2/show/study/NCT02508649)

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 [Visual Abstract](#)

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Sepsis is a dysregulated host response to infection that leads to life-threatening acute organ dysfunction. Septic shock is the most severe form, characterized by vasodilatation and increased capillary permeability leading to hypotension and tissue hypoxia.^{1,2} Treatment includes antibiotics and resuscitation with intravenous fluids, vasopressors, and organ support. Even with prompt care, many patients develop multiple organ failure and death.^{1,2} The recommended first-line vasopressor is the catecholamine, norepinephrine.³ Norepinephrine is not always effective at restoring blood pressure and can cause myocardial and peripheral ischemia.⁴ Consequently, there is interest in alternative vasopressors, including noncatecholaminergic agents.

One such agent, vasopressin, induces vasoconstriction via V1 receptor stimulation in vascular smooth muscle. However, vasopressin has pleiotropic effects, not all beneficial in septic shock, because it also stimulates V1b and V2 receptors, resulting in increased procoagulant factors, salt and water retention, nitric oxide release, and corticosteroid stimulation.^{5,6} Selepressin is a selective vasopressin V1a receptor agonist,⁷ potentially mitigating sepsis-induced vasodilatation, vascular leakage, and tissue edema without V1b- or V2-mediated effects.⁸⁻¹³ These effects could be beneficial in septic shock, in which increased capillary permeability may contribute to poor outcomes via pulmonary and other vital-tissue edema, intravascular volume depletion, and impaired oxygen delivery. In a phase 2a trial in patients with septic shock, selepressin reduced norepinephrine requirements, increased the proportion of patients not receiving mechanical ventilation, and appeared to speed resolution of shock.¹⁴ These findings led to the current phase 2b/3 trial of selepressin in adult patients with vasopressor-dependent septic shock.

Methods

Trial Design and Oversight

The trial was conducted under a Special Protocol Assessment agreement with the US Food and Drug Administration and approved by relevant regulatory and ethics authorities, including institutional review boards or equivalent. The study was conducted in accordance with Good Clinical Practice guidelines, local regulations, and the ethical principles described in the Declaration of Helsinki. Written informed consent was obtained for all patients or their surrogates in accordance with local legislation.

The study was a blinded, randomized, placebo-controlled, seamless, phase 2b/3 adaptive clinical trial designed to determine the efficacy of multiple dosing regimens of selepressin and to confirm the efficacy of 1 dosing regimen in the treatment of septic shock (see study protocol and statistical analysis plan in [Supplement 1](#)). The design, published previously, had 2 parts integrated under an overarching Bayesian framework (study protocol, [Supplement 1](#); eFigure 1 in [Supplement 2](#)), with an automatic, or “seamless,” transition from the first to the second part.¹⁵ Like a traditional phase 2b trial, part 1 tested several doses. However, prespecified response-adaptive rules adjusted the number and size of study groups, ensuring adequate power to

Key Points

Question For adults with septic shock treated with norepinephrine, does use of selepressin, a selective vasopressin V1a receptor agonist, compared with placebo, improve patient outcome, defined as an increase in the number of days alive and free of both ventilation and vasopressor use?

Findings In this randomized clinical trial that included 828 patients with septic shock requiring norepinephrine, treatment with selepressin compared with placebo resulted in 15.0 vs 14.4 ventilator- and vasopressor-free days within 30 days, a difference that was not statistically significant.

Meaning Treatment with selepressin was not effective in improving ventilator- and vasopressor-free days.

select the best dosing strategy and transition to part 2.¹⁵ Part 2 would be triggered only if the effect size of the best-performing dosing regimen in part 1 exceeded a prespecified threshold and would consist of 1:1 fixed allocation to the optimal regimen or placebo. Unlike a traditional design, treatment effect would be estimated using all patients from both parts.

The trial was overseen by a blinded trial steering committee (TSC) and an independent, unblinded data and safety monitoring board (DSMB) ([Supplement 2](#)). The TSC oversaw trial conduct and made recommendations to the sponsor regarding all trial-related decisions. The DSMB oversaw safety and performance of the adaptive design.

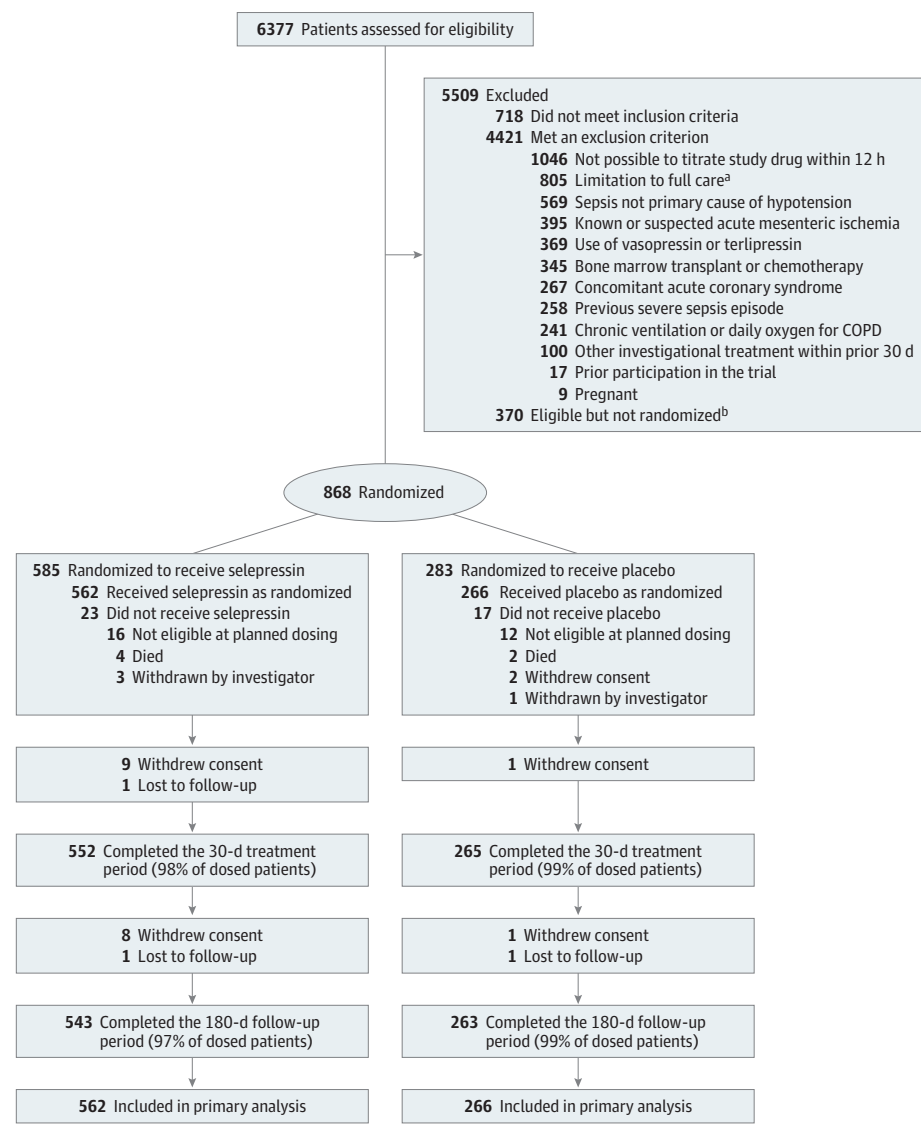
Study Population

Eligible patients were 18 years or older, had proven or suspected infection, and had septic shock defined as hypotension (systolic arterial pressure <90 mm Hg or mean arterial pressure [MAP] <65 mm Hg) requiring more than 5 µg/min of norepinephrine for more than 1 hour despite more than 1 L of intravenous fluid resuscitation. Patients were excluded if they were receiving vasopressin or terlipressin, if it was not possible to start study drug within 12 hours of the onset of any use of vasopressor treatment (discounting use during surgery or other procedures if the vasopressor was completely weaned before use for sepsis-induced hypotension), or if sepsis was not the primary cause of hypotension ([Figure 1](#)) (see [Supplement 2](#) for further entry criteria details). Two coordinating centers (United States and Belgium) reviewed data with sites before each enrollment to confirm eligibility ([Supplement 2](#)).

Study Interventions

Study drug was a continuous intravenous infusion of selepressin or matching placebo started within 12 hours of shock onset. Titration of study drug and other vasopressors was guided by an instruction protocol (study protocol, [Supplement 1](#); eFigure 2, [Supplement 2](#)) based on pharmacokinetic modeling and prior clinical experience.^{14,15} Study drug infusion began at a rate based on patient weight. The protocol instructed the bedside clinician to maintain target MAP while weaning other vasopressors. If target MAP could not be maintained or vasopressors could not be weaned, the study drug infusion rate could be increased by up to 50%.

Figure 1. Screening, Randomization, and Follow-up of a Study of Selepressin for Septic Shock



Patient disposition from screening through day 180 is shown. Efficacy and adverse event analyses are based on all patients who underwent randomization and received selepressin or placebo. Just before dosing, all randomized patients had to fulfill 3 predefined criteria to be eligible for receiving study drug: (1) had received a minimum of 30 mL/kg fluid in total from onset of hypotension (or less if fluid replete/overload); (2) still receiving a continuous infusion of 5 µg/min or more of norepinephrine and having done so for at least 1 hour; and (3) less than 12 hours had passed from start of vasopressor treatment for sepsis. COPD indicates chronic obstructive pulmonary disease.

^a Limitations to full care included any decision to limit care, including lack of commitment to cardiopulmonary resuscitation, blood products, kidney replacement therapy, surgery to ensure source control, or mechanical ventilation if indicated.

^b Reasons for failure to enroll despite meeting eligibility criteria included lack of availability of study personnel or study drug and difficulty communicating with the coordinating center.

Study drug was weaned after all other vasopressors were discontinued and MAP was at or above target but could be restarted for sepsis-induced hypotension. The study began with 3 selepressin dosing regimen groups, defined as starting infusion rates of 1.7, 2.5, and 3.5 ng/kg/min, with the potential to add a fourth group (5 ng/kg/min). Doses were selected based on analysis of the prior feasibility study (<https://clinicaltrials.gov/ct2/show/NCT01612676>). Weight was assessed as per local clinical practice. Data collected on the management of shock included dose of study drug, MAP, vasopressor use, cardiovascular Sequential Organ Failure Assessment (SOFA) score¹⁶ (including study drug as a vasopressor), fluid balance, and initiation of steroids for septic shock. Weaning from mechanical ventilation was based on daily trials of spontaneous breathing, as per best practice guidelines. Other care was at the discretion of the clinical team.

Randomization

Randomization was stratified by study site, need for mechanical ventilation, baseline norepinephrine requirement, and serum creatinine level. Investigators, study personnel, and the clinical team were blinded to allocation. The first 200 patients were randomized in a fixed ratio of one-third to placebo and the remainder allocated evenly among the 3 lowest doses of the 4 possible selepressin groups (eFigure 1 in Supplement 2). Thereafter, the probability of randomization to placebo was held constant while a response-adaptive randomization algorithm determined probabilities of allocation to the selepressin groups. Probability of assignment to each of the 3 lower-dose groups was proportional to the probability that that group was most beneficial based on monthly updates of the accruing data. The fourth selepressin group (5 ng/kg/min) would only be opened if the accruing

Table 1. Demographic and Baseline Disease Characteristics

Characteristic	Selepressin (n = 562)	Placebo (n = 266)
Demographics		
Age, mean (SD), y	66.6 (12.8)	65.7 (14.6)
Sex, No. (%)		
Men	342 (61)	145 (55)
Women	220 (39)	121 (45)
Medical patients, No. (%)	382 (68)	204 (77)
Weight, mean (SD), kg	80.2 (23.6)	78.7 (22.2)
Body mass index, mean (SD) ^a	27.9 (8.4) [n = 559]	27.5 (7.2) [n = 265]
Severity of illness		
Modified SOFA, median (IQR) ^b	9 (8-11) [n = 543]	9 (8-11) [n=258]
APACHE II, mean (SD) ^c	25.7 (7.8) [n = 559]	26.0 (7.7)
Heart rate, mean (SD), /min	102 (23)	101 (23)
Mean arterial pressure, median (IQR), mm Hg	70 (65-76) [n = 561]	69 (64-76)
Norepinephrine, median (IQR), µg/kg/min	0.25 (0.14-0.45) [n = 561]	0.26 (0.15-0.44) [n=265]
Lactate, median (IQR), mmol/L	2.7 (1.6-4.5) [n = 526]	2.6 (1.7-4.2) [n =255]
PaO ₂ :FiO ₂ , mean (SD), mm Hg	221 (118) [n = 514]	230 (141) [n = 248]
Hours of vasopressor therapy ^d	8.2 (2.8)	8.2 (3.0)
Site of infection, No. (%)		
Lower respiratory tract	222 (40)	99 (37)
Intra-abdominal	159 (28)	63 (24)
Urinary tract	82 (15)	51 (19)
Skin or soft tissue	45 (8)	22 (8)
Other	54 (10)	31 (12)
Preexisting conditions, No. (%)		
Cardiovascular	332 (59)	151 (57)
Cancer	182 (32)	70 (26)
Diabetes mellitus	139 (25)	67 (25)
COPD	114 (20)	41 (15)
Kidney disease	93 (17)	41 (15)
Liver cirrhosis	43 (8)	23 (9)
Charlson Comorbidity Index, mean (SD) ^e	2.5 (2.0) [n = 477]	2.5 (2.1) [n=223]

Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; FiO₂, fraction of inspired oxygen; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Denotes the SOFA modified to not include Glasgow Coma Scale (range, 0-16, with higher scores indicating more severe or widespread organ dysfunction). For the purpose of the trial, study drug, vasopressin, terlipressin, and phenylephrine attributed 3 points on the cardiovascular scale, and any dose of the positive inotropes milrinone and levosimendan attributed 2 points on the cardiovascular scale.

^c Scores range from 0 to 71, with higher scores indicating greater severity of illness. A score of approximately 26 for patients with sepsis is typically associated with a short-term mortality rate of 30% to 40%, depending on reason for admission.

^d Duration of vasopressor treatment administered for sepsis when study drug was initiated.

^e Measures the effect of coexisting conditions on mortality, with scores ranging from 0 to 29 and higher scores indicating a greater burden of illness. Age was not included in the calculation.

data demonstrated a 50% or greater probability that the 3.5 ng/kg/min group was superior to the 2.5 ng/kg/min group, with no safety concerns.

The study drug was prepared at the hospital by pharmacy staff not associated with the bedside clinical team. The information for treatment allocation was provided by a password-protected internet-based platform. The study drug, either placebo or selepressin, was diluted in sterile saline in identical syringe or bags blinded to treatment allocation. The label contained only the patient identification and trial name and number. Selepressin is colorless and odorless when dissolved.

End Points

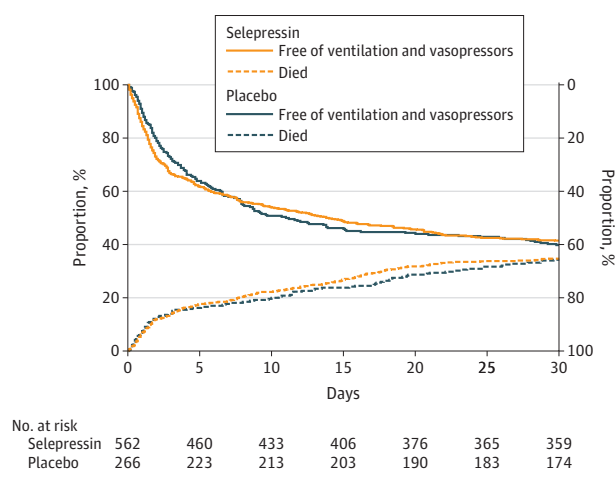
The primary end point was the number of ventilator- and vasopressor-free days up to day 30, defined as days from study drug initiation to 30 days thereafter, during which the patient was alive, free of mechanical ventilation, and free of treatment with intravenous vasopressors including study drug. Any patient who died within 30 days was assigned zero days. After mechanical ventilation and vasopressors were weaned, if either were restarted before day 30 for more than 60 minutes within a 24-hour period, the intervening days

were not counted as being free of ventilator or vasopressor support. Use of mechanical ventilation or vasopressors during and up to 3 hours after surgery or bedside procedure (eg, hemodialysis session) was exempt.

Vasopressor therapy was defined as any intravenous dose of norepinephrine, phenylephrine, dopamine, epinephrine, vasopressin, terlipressin, and study drug (selepressin or placebo). Mechanical ventilation was defined as invasive mechanical ventilation via endotracheal tube (including tracheostomy) or noninvasive ventilation with more than 5 cm H₂O of continuous positive airway pressure and more than 5 cm H₂O of pressure support when deployed to avoid intubation. Other uses of noninvasive ventilation (eg, chronic nighttime use for chronic obstructive pulmonary disease) were not counted.

There were 3 key secondary end points: 90-day all-cause mortality, 30-day kidney replacement therapy-free days, and 30-day intensive care unit (ICU)-free days. Additional prespecified end points are provided in the study protocol (Supplement 1) and Supplement 2 and included organ dysfunction (assessed by the daily SOFA score [excluding the neurologic component] while in the ICU and by need for

Figure 2. Days Alive and Free of Ventilation and Vasopressors



Death and days free of ventilation and vasopressors shown as proportion of patients over time from randomization to day 30. Area above the top 2 curves corresponds to alive and free of ventilation and vasopressors; area between the top 2 curves and bottom 2 curves, alive but still receiving ventilation or vasopressors; area below bottom 2 curves, dead. The combined ventilator- and vasopressor-free days did not differ between groups (15.0 vs 14.4 days; difference, 0.6 days [95% CI, -1.3 to 2.4]; $P = .30$).

vasopressors, mechanical ventilation, or kidney replacement therapy, analyzed as “free days,” duration, and onset of new dysfunction or failure); ICU length of stay; all-cause mortality at 30 and 180 days; daily and cumulative fluid balance and urine output while in the ICU, and health-related quality of life at 180 days using the EuroQol-5D 5-level questionnaire.¹⁷

Safety end points included incidence of adverse events with emphasis on ischemic events, hypotension, and unanticipated changes in vital signs and laboratory values. Additional prespecified end points included hospital-free days and length of stay, patient residence up to 180 days, a health economic evaluation that would be reported separately, and additional measures of the course and management of shock (MAP and vasopressor use). Several substudies of molecular and physiologic end points were planned had the study progressed further (Supplement 2).

All staff collecting outcome data were blinded to treatment allocation.

Statistical Analysis

The statistical analysis plan is detailed in the study protocol (Supplement 1). The design allowed a maximum final sample size of 1800 evaluable patients across parts 1 and 2, which provided 91% power to determine that selepressin yielded a gain of 1.5 ventilator- and vasopressor-free days compared with placebo, with a 1-tailed α error rate of .02.¹⁵ Ventilator- and vasopressor-free days is a new end point, for which a meaningful clinical difference has not been established. We chose a 1.5-day difference because that represented a 7.5% to 15% relative change assuming a control rate of between 10 and 20 ventilator- and vasopressor-free days, based on recent sepsis randomized clinical trials.^{18–21} We assumed smaller effects would not be considered clinically significant.

During part 1, a prespecified Bayesian inference model was used to generate monthly updated probabilities of treatment success for each selepressin group, in which probability of treatment success was the probability that a selepressin group, if tested in part 2, would be statistically superior to the placebo group by the end of the trial. If, after 200 or more patients, all selepressin groups had less than 5% probability of treatment success, the trial would stop for futility. If, with 300 or more patients, any group had more than 90% probability of treatment success, the trial transitioned to part 2. Otherwise, part 1 would continue to 800 patients at which point, if at least 1 selepressin group had more than 25% probability of treatment success, the trial would transition to part 2. Otherwise, the trial would terminate and be reported as a phase 2b trial.

All analyses included all patients who were randomized and received study drug. The primary analysis compared ventilator- and vasopressor-free days between the combined selepressin groups and placebo by the nonparametric van Elteren test,²² stratified by need for mechanical ventilation, time from onset of shock to start of study drug, and baseline norepinephrine requirement, assuming a 2-sided 5% significance level.²³ Missing data during hospitalization for the primary end point were imputed using a worst-case approach. Missing data for patients withdrawn were imputed using last observed status receiving or not receiving vasopressors or mechanical ventilation carried forward to day 30. Prespecified sensitivity analyses using alternative strategies for missingness included exclusion of all patients with missing primary outcome data; use of the ratio of free to nonfree days at last observation instead of last status carried forward; and a tipping-point analysis exploring all possible combinations of “best-case” and “worst-case” scenarios (see statistical analysis plan, version 9.0, section 9.2.2, in Supplement 1). Potential heterogeneity of treatment effect was explored through prespecified subgroup analyses and analysis of treatment effect by risk of death (see statistical analysis plan in Supplement 1).

Secondary outcomes were analyzed as follows: other “free day” end points were analyzed similarly to the primary end point using the van Elteren test, continuous nonrepeated data were analyzed by negative binomial or permutation tests, continuous repeated data by repeated-measures analysis of covariance, binomial data by logistic regression, and survival-type data by Kaplan-Meier log rank. To safeguard against erroneous type I error inflation, the Hochberg procedure for adjustment on multiplicity was applied to the 3 key secondary outcomes. Because of the potential for type I error due to multiple comparisons, findings for analyses of the other secondary end points should be interpreted as exploratory.

All analyses were conducted in SAS Life Science Analytics Framework, version 4.7.1.

Results

Patients

Of 6377 screened patients, 868 were enrolled, 585 were randomly assigned to receive selepressin, and 283 to receive

Table 2. Major End Points^a

End Point	Unadjusted (Observed)				Adjusted (Model)		Difference (95% CI)	P Value
	Selepressin		Placebo		(95% CI)			
	No.	Mean (SD)	No.	Mean (SD)	Selepressin (n = 562)	Placebo (n = 266)		
Primary End Point								
Ventilator- and vasopressor-free days to day 30	562	14.2 (13.1)	266	14.3 (12.9)	15.0 (13.8 to 16.2)	14.5 (12.8 to 16.1)	0.55 (−1.3 to 2.4)	.30
Prespecified Key Secondary End Points								
Day 90 mortality, No. (%)		227 (41.7)		109 (41.1)	40.6	39.4	1.1 [−6.5 to 8.8]	.77
Kidney replacement therapy-free days, day 1 to day 30	550	18.0 (14.3)	261	18.4 (13.9)	18.5 (17.0 to 20.0)	18.2 (16.1 to 20.3)	0.29 (−2.1 to 2.6)	.85
Intensive care unit-free days, day 1 to day 30	562	11.8 (11.9)	266	11.7 (11.6)	12.6 (11.5 to 13.8)	12.2 (10.7 to 13.6)	0.49 (−1.2 to 2.2)	.41
Other Prespecified Secondary End Points								
Components of primary end point								
Days free from ventilator and vasopressors, survivors only ^b	369	21.6 (10.0)	175	21.8 (9.4)	23.2 (22.2 to 24.0)	22.2 (20.7 to 23.4)	0.96 (−0.55 to 2.48)	NA ^c
Days free from vasopressors, survivors only ^b	369	25.1 (7.2)	175	25.9 (5.5)	25.3 (24.6 to 25.9)	25.7 (24.9 to 26.4)	−0.46 (−1.37 to 0.45)	NA ^c
Days free from ventilator ^b , survivors only	369	22.6 (10.1)	175	22.8 (9.7)	24.8 (23.3 to 25.9)	23.4 (20.8 to 25.2)	1.41 (−0.96 to 3.79)	NA ^c
Day 30 mortality, No. (%)		193 (35.0)		91 (34.3)	33.6	32.7	0.9 (−6.4 to 8.2)	.81
Day 180 mortality, No. (%)		241 (44.4)		116 (44.1)	43.8	42.8	1.0 (−6.7 to 8.8)	.79
Other free day-1 end points								
Vasopressor-free days to day 30	562	16.5 (13.3)	266	17.0 (13.1)	16.4 (15.1 to 17.6)	16.8 (15.1 to 18.4)	−0.39 (−2.3 to 1.5)	.39
Ventilator-free days to day 30	562	14.8 (13.5)	266	15.0 (13.8)	16.1 (14.6 to 17.5)	15.2 (13.2 to 17.3)	0.83 (−1.5 to 3.1)	.76
Hospital-free days to day 90	562	29.8 (33.0)	266	29.2 (32.6)	30.1 (26.8 to 33.3)	29.8 (25.4 to 34.1)	0.32 (−4.7 to 5.3)	.67
Duration of therapy, d								
Vasopressor to day 30	562	3.1 (4.2)	266	3.4 (3.7)	3.0 (2.7 to 3.3)	3.3 (2.9 to 3.7)	−0.3 (−0.8 to 0.2)	.21
Mechanical ventilation to day 30	562	5.9 (8.2)	266	6.1 (8.1)	6.4 (5.6 to 7.2)	6.9 (5.7 to 8.0)	−0.48 (−1.8 to 0.8)	.67
Kidney replacement therapy to day 90	550	2.0 (7.6)	261	1.6 (5.5))	1.9 (1.3 to 2.6)	1.6 (1.0 to 2.3)	0.33 (−0.5 to 1.2)	.61
ICU length of stay to day 30	562	9.6 (9.1)	266	10.3 (9.0)	9.6 (8.9 to 10.3)	10.3 (9.3 to 11.4)	−0.63 (−2.1 to 0.3)	.23
Hospital length of stay to day 90	562	25.4 (24.0)	266	26.5 (24.1)	25.4 (23.4 to 27.1)	26.5 (24.0:29.6)	−1.1 (−4.9 to 2.3)	.36
Quality of life at 6 mo								
Visual analog scale ^d	259	69.5 (20.1)	129	72.6 (20.1)	68.9 (66.4 to 71.3)	72.3 (68.9 to 75.7)	−3.5 (−7.7 to 0.7)	.10
EQ-5D 5L index score ^e	264	0.75 (0.21)	130	0.76 (0.22)	0.74 (0.71 to 0.77)	0.76 (0.72 to 0.80)	−0.02 (−0.07 to 0.03)	.48

Abbreviations: EQ-5D 5L, 5-level EuroQol-5D; ICU, intensive care unit; NA, not applicable.

^a The primary analyses for all efficacy end points are generated from statistical models as described in the study protocol in [Supplement 1](#). There were no statistical differences in findings between adjusted and raw observed results. "Free days" reflect the time from end of last use of therapy to end of the period (30 or 90 days), with a higher number indicating a longer period free of therapy. Patients dying in the period are assigned zero free days.

^b "Days liberated from therapy" is similar to "free days" but without a penalty for mortality.

^c Subcomponents of the primary outcome are provided for illustrative purposes and are not accompanied by *P* values.

^d A patient-reported outcome with 100 representing the best thinkable health status and zero representing the worst.

^e Reflects the patient-reported level of physical and mental well-being.

placebo. Forty patients did not receive study drug because of improvement in shock (*n* = 28), withdrawal by investigator because of safety concerns (*n* = 4), death (*n* = 6), or withdrawal of consent (*n* = 2). The remaining 828 comprised the analysis cohort (Figure 1). The study groups had features typical of septic shock and were well-matched at baseline (Table 1; eTable 1 in [Supplement 2](#)). Data were missing for 17 patients (2%), including 11 patients who subsequently withdrew consent or were lost to follow-up before day 30 (Figure 1) and 6 additional patients for whom the last date, but not the time, was recorded for either ventilation or vasopressor use. Overall withdrawal or loss to

follow-up rates did not differ by study group (*P* = .97 by log-rank test). There were 17 response-adaptive randomization updates, during which the fourth selepressin group was never triggered and no study group triggered transition to part 2. Therefore, based on recommendation from the DSMB, the TSC stopped the trial for futility at the end of part 1.

Efficacy End Points

The primary end point of ventilator- and vasopressor-free days did not differ significantly between the combined selepressin and placebo groups (mean, 15.0 vs 14.5 days; difference,

Table 3. Adverse Events

Event	No. (%)	
	Selepressin (n = 562)	Placebo (n = 266)
Adverse events of any grade	2054 (83.8)	1086 (88.3)
Adverse study drug reactions	190 (21.0)	85 (21.4)
Treatment-emergent adverse events ^a	1029 (65.7)	573 (73.7)
Adverse events of special interest ^{b,c}	301 (42.3)	123 (37.2)
Cardiac arrhythmias	209 (27.9)	87 (25.2)
Cardiac ischemia	44 (6.6)	17 (5.6)
Mesenteric ischemia	20 (3.2)	7 (2.6)
Stroke and cerebrovascular events	14 (2.3)	5 (1.5)
Peripheral ischemia	14 (2.3)	7 (2.3)
Serious adverse events ^c	430 (51.2)	200 (53.4)
Adverse events leading to discontinuation of study drug ^c	44 (7.3)	12 (4.5)

^a Denote adverse events with onset during or within 12 hours of stop of study drug.

^b Prespecified event types monitored and collected more systematically. More details on adverse events are presented in eFigures 9 and 10 in Supplement 2.

^c The study was not powered to test for differences in adverse event rates.

0.6 days [95% CI, -1.3 to 2.4]; $P = .30$) (Figure 2, Table 2; and eTable 2 in Supplement 2). Sensitivity analyses excluding missing or imputed data and using the alternative imputation rule were similar ($P = .31$ and $P = .37$), and the tipping-point analysis similarly showed that the results did not change significance under different assumptions about missingness. Subgroup analyses and analysis of treatment effect by deciles of risk of death showed no evidence of heterogeneity of treatment effect (eFigures 3 and 4 in Supplement 2).

There were also no significant differences in the 3 key secondary outcomes (90-day mortality: 40.6% vs 39.4%; difference, 1.1% [95% CI, -6.5% to 8.8%]; $P = .77$; kidney replacement therapy-free days: 18.5 vs 18.2; difference, 0.29 [95% CI, -2.1 to 2.6]; $P = .85$; ICU-free days: 12.6 vs 12.2; difference, 0.49 [95% CI, -1.2 to 2.2]; $P = .41$) (Table 2). There were also no significant differences in the subcomponents of the primary end point (Figure 2 and Table 2). The coagulation SOFA score was significantly higher in the selepressin group on ICU days 3 (mean, 1.73 vs 1.50; difference, 0.23 [95% CI, 0.04 to 0.41]; $P = .02$) and 7 (1.53 vs 1.30; difference, 0.23 [95% CI, 0.04 to 0.43]; $P = .02$), as was the frequency of new-onset coagulation abnormalities in the first week (62.3% vs 53.3%; odds ratio [OR], 1.45 [95% CI, 1.06 to 2.00]; $P = .02$), although there were no significant differences by day 30 (67.3% vs 61.1%; OR, 1.31 [95% CI, 0.95 to 1.80]; $P = .10$). Otherwise, organ failure, organ support, ICU and hospital length of stay, mortality, and quality-of-life end points did not differ significantly (Table 2; eFigures 5-8 and eTable 3 in Supplement 2).

Adverse Events

Adverse events are summarized in Table 3 and in eFigures 9 and 10 in Supplement 2. There were 3140 reported adverse events during the 30-day treatment period, including 275 suspected adverse drug reactions and 630 serious adverse events.

Event rates were similar in both groups, including specific adverse events, such as arrhythmias, hypotension, ischemic events, and laboratory tests required for safety monitoring, including platelet count, serum creatinine level, and serum troponin level.

Administration of Study Drug and Management of Shock

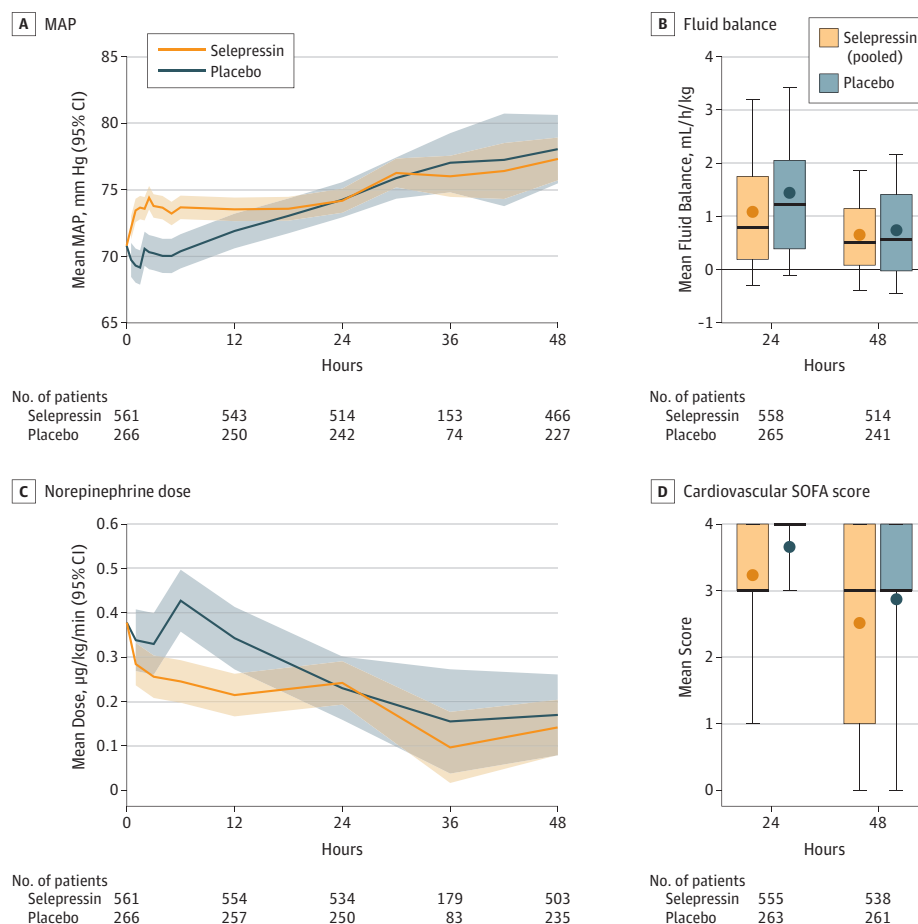
Study drug was administered for a median of 37.8 hours (interquartile range, 17.8-72.4) (eFigure 11 in Supplement 2). During infusion, there were several significant differences in the course of shock and patient care (Figure 3). Over the first 6 hours, the selepressin group had higher MAP (mean, 74 vs 70 mm Hg; difference, 3.3 mm Hg [95% CI, 1.7 to 5.0]; $P < .001$) (Figure 3A) and lower norepinephrine requirement (mean, 0.29 vs 0.48 $\mu\text{g/kg/min}$; absolute difference, -0.19 $\mu\text{g/kg/min}$ [95% CI, -0.29 to -0.10], a 41% reduction vs 8% increase from baseline; $P < .001$) (Figure 3C), with norepinephrine requirements inversely correlated with the selepressin dosing regimen (eFigures 12 and 13 in Supplement 2). Over the first 2 days, the selepressin group had significantly less cardiovascular dysfunction (mean cardiovascular SOFA score, 2.5 vs 2.9; difference, -0.33 [95% CI, -0.55 to -0.11]; $P = .003$) (Figure 3D). Patients receiving selepressin had significantly higher urine output (100 vs 86 mL/h; difference, 14 mL/h [95% CI, 4 to 23]; $P = .006$) and significantly lower net fluid balance (81 vs 107 mL/h; difference, -26 mL/h [95% CI, -38 to -14]; $P < .001$) than those receiving placebo in the first 24 hours, but the groups were similar thereafter (Figure 3B; eFigures 14 and 15 in Supplement 2). The selepressin group was significantly less likely to receive steroids than the placebo group (13.7% vs 22.9%; OR, 0.53 [95% CI, 0.37 to 0.78]; $P = .001$).

Discussion

In this multicenter trial that compared 3 dosing regimens of selepressin, a selective vasopressin V1a receptor agonist, with placebo in the treatment of patients with septic shock, there was no evidence that selepressin offered any benefit on either the primary end point of ventilator- and vasopressor-free days at 30 days or other patient-centered outcomes, including 90-day mortality, kidney replacement therapy-free days, and ICU-free days. These findings were consistent across subgroup and secondary analyses.

Recently, the US Food and Drug Administration approved 2 noncatecholaminergic vasopressors for use in septic or vasodilatory shock: vasopressin and angiotensin II. Vasopressin has strong vasopressor activity, allowing reduction in norepinephrine use but without improvement in patient-centered outcomes, except perhaps in select subgroups.²⁴ Angiotensin II provides short-term improvement in cardiovascular stability without significant improvement in patient-centered outcomes.²⁵ Thus, selepressin, vasopressin, and angiotensin II all appear to have norepinephrine-sparing effects without an increase in adverse events but also without evidence that their use improves patient-centered outcomes compared with a catecholamine-based strategy. However, the

Figure 3. Management of Shock During the First 48 Hours



A, Mean (95% CI) mean arterial pressure (MAP), adjusted for baseline values. B, Mean fluid balance adjusted for body weight and for baseline values. Bottom and top margins of boxes indicate 25th and 75th quartiles, respectively; heavy lines within boxes, median values; dots within boxes, adjusted mean values; whiskers, 10th and 90th quartiles. Fluid balance was defined as intravenous fluid minus urine output, derived by assigning charted data into 24-hour intervals after commencement of study drug and analyzed by repeated-measures analysis of covariance (statistical analysis plan, version 9.0, section 9.3.4, in Supplement 1). The fluid balance differed between groups at 24 hours (81 vs 107 mL/h; difference, -26 mL/h [95% CI, -38 to -14]; $P < .001$) but

not at 48 hours. C, Mean (95% CI) norepinephrine dose, adjusted for baseline values. D, Mean cardiovascular Sequential Organ Failure Assessment (SOFA) score. Bottom and top margins of boxes indicate 25th and 75th quartiles, respectively; heavy lines within boxes, median values; dots within boxes, adjusted mean values; whiskers, 10th and 90th quartiles. The selepressin group had significantly less cardiovascular dysfunction at 24 hours (mean cardiovascular SOFA score, 3.2 vs 3.7; difference, -0.42 [95% CI, -0.65 to -0.19]; $P < .001$) and at 48 hours (mean cardiovascular SOFA score, 2.5 vs 2.9; difference, -0.33 [95% CI, -0.55 to -0.11]; $P = .003$). All comparisons were prespecified secondary analyses.

present trial was designed to compare dosing regimens of selepressin with placebo, rather than with other nonadrenergic vasoactive drugs, and none of these 3 agents have been compared with each other.

To evaluate selepressin, the trial design had several novel features, including the combined organ dysfunction end point with a penalty for death, a dose-ranging strategy with response-adaptive randomization, an integrated 2-part design, pooling of treatment groups to estimate treatment effect and control type I error, a Bayesian inference model to guide interim decision-making, and pretrial simulation of operating characteristics, power, and type I error control. The lack of treatment effect limits the ability to understand the performance of all these design features. However, the trial was able to enroll patients at a rate similar to rates in prior trials, without con-

cern expressed by sites or patients regarding the design, and the combined end point correlated closely with other patient-centered outcomes. During the trial, the monthly updates of efficacy, randomization weights, and study triggers were executed without disruption of enrollment and without corrective action by either the DSMB or any regulatory authority.

Limitations

The study has several limitations. First, patients had received norepinephrine for a median of 8 hours before enrollment, limiting the ability to determine the consequences of avoiding catecholamine-based vasopressor support earlier in septic shock. Second, although selepressin was hypothesized to reduce pulmonary edema, it was only possible to assess the clinical consequences of pulmonary

edema, rather than a more detailed physiologic assessment, in this setting. Third, although the study was well-powered to assess overall effects, septic shock is a heterogeneous condition, and there was limited ability to understand treatment $\times$ subgroup interactions. Fourth, because the primary analysis used a nonparametric test stratified by several patient characteristics, it was not possible to include site as a random effect. Fifth, the study was not powered to detect differences in adverse events.

Conclusions

Among patients with septic shock receiving norepinephrine, administration of selepressin, compared with placebo, did not result in improvement in vasopressor- and ventilator-free days within 30 days. Further research would be needed to evaluate the potential role of selepressin for other patient-centered outcomes in septic shock.

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Supervision: Carlsen, Jacobsen, Opal, Pickkers, Windeløv, Brulé, Decruyenaere, Dugernier, Angus.

Conflict of Interest Disclosures: Dr Laterre reported receiving investigators fees and steering committee fees from St. Luc Hospital during the conduct of the study and receiving personal fees from the St. Luc University Clinical Coordinating Center. Dr Berry reported receiving personal fees from Ferring Pharmaceuticals during the conduct of the study and that he is owner of Berry Consultants, a statistical consulting company that works for a wide range of pharmaceutical and medical device companies. Dr Carlsen reported receiving personal fees from Ferring pharmaceuticals during the conduct of the study. Dr François reported receiving personal fees from Ferring Pharmaceuticals, Inotrem, AM-Pharma, and Asahi Kasei and receiving grants from bioMérieux. Dr Graves reported that he is an employee of Berry Consultants; Berry Consultants was compensated by Ferring Pharmaceuticals for clinical design work. Dr Jacobsen reported receiving personal fees from Ferring Pharmaceuticals during the conduct of the study. Dr Lewis reported that he is an employee of Berry Consultants; Berry Consultants was compensated by Ferring Pharmaceuticals for clinical design work. Dr Opal reported receiving

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Role of the Funder/Sponsor: Ferring Pharmaceuticals had several roles in the study. First, the study was designed by the Trial Steering Committee (TSC), which included 9 academic investigators, 4 Ferring employees, and a nonacademic Ferring consultant (Supplement 1), of whom only the 9 academic investigators had voting power. The design was approved by the sponsor, and the sponsor coordinated all interactions with regulatory authorities before study launch. Second, clinical research coordinators employed by the sponsor were responsible for day-to-day operations during trial conduct, in conjunction with a clinical research organization, local site research and clinical staff, and the TSC. Data were collected by the site research staff, managed by a blinded data management team at the sponsor, monitored by the contract research organization, and overseen by the TSC and the Data and Safety Monitoring Board (DSMB). After study completion and data lock, unblinded data were analyzed by the TSC and the sponsor. The manuscript was prepared by the TSC, and all data interpretation was by the TSC. Under the publications policy (study protocol in Supplement 1, section 13.13.1), the sponsor had the right to a 60-day review of any manuscript to ensure accuracy, request deletion of confidential information, and file for patient applications or intellectual property protection as needed. However, the sponsor had no other editorial rights, including the decision to submit the manuscript for publication.

Disclaimer: Derek Angus is an associate editor of JAMA, and Dr Lewis is a statistical reviewer, but they were not involved in any of the decisions regarding review of the manuscript or its acceptance.

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