A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Safety and Efficacy of Recombinant Human Soluble Thrombomodulin, ART-123, in Patients With Sepsis and Suspected Disseminated Intravascular Coagulation*

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Objectives: To determine the safety and efficacy of recombinant thrombomodulin (ART-123) in patients with suspected sepsis-associated disseminated intravascular coagulation.

Design: Phase 2b, international, multicenter, double-blind, randomized, placebo-controlled, parallel group, screening trial.

Setting: Two hundred and thirty-three ICUs in 17 countries.

Patients: All adult patients admitted with sepsis and suspected disseminated intravascular coagulation as assessed using a modified International Society on Thrombosis and Hemostasis score.

Interventions: Patients were randomized to receive IV ART-123 (0.06 mg/kg/d) for 6 days or placebo, in addition to standard of care. The primary endpoint was reduction in mortality. Secondary endpoints included reversal of overt disseminated intravascular coagulation and reduction in disease severity.

Measurements and Main Results: A total of 750 patients were randomized, nine of whom did not receive the allocated treatment so that 371 patients received ART-123 and 370 received placebo. There were no meaningful differences between the two groups in any of the baseline variables. Twenty-eight-day mortality was 17.8% in the ART-123 group and 21.6% in the placebo group (Cochran–Mantel–Haenszel two-sided *p* value of 0.273 in favor of ART-123, which met the predefined statistical test for evidence suggestive of efficacy). There were no statistically significant differences in event-free and alive days between the two groups. D-dimer, prothrombin fragment F1.2 and TATc concentrations were lower in the ART-123 group than in the placebo group. There were no differences between the two groups in organ function, inflammatory markers, bleeding or thrombotic events or in the development of new infections. In post hoc analyses, greatest benefit from ART-123 was seen in patients with at least one organ system dysfunction and an international normalized ratio greater than 1.4 at baseline.

Conclusions: ART-123 is a safe intervention in critically ill patients with sepsis and suspected disseminated intravascular coagulation. The study provided evidence suggestive of efficacy supporting further development of this drug in sepsis-associated coagulopathy including disseminated intravascular coagulation. Future study should focus on using ART-123 in the subgroup of patients most likely to respond to this agent. (*Crit Care Med* 2013; 41:2070–2079)

Key Words: coagulopathy; organ dysfunction; sepsis

Severe sepsis remains the most common cause of death in critically ill patients (1), and new therapeutic approaches are urgently needed. Disseminated intravascular coagulation (DIC), resulting from widespread intravascular activation of coagulation pathways and diagnosed based on laboratory evidence of consumption of clotting factors and platelets and of fibrin cleavage (2), may occur in a range of medical conditions including trauma, burns, obstetric emergencies, and malignancies. DIC is also a frequent complication of severe sepsis (3), and when present it is associated with increased mortality in these patients (4, 5).

Current management of DIC is primarily focused on treating any associated underlying medical condition, although use of supplemental clotting factors or platelets, or anticoagulant therapy may occasionally be required (6). ART-123 (Artisan Pharma, Waltham, MA) is a soluble recombinant human thrombomodulin that acts by reducing thrombin-mediated clotting and enhancing protein C activation at the site of clotting. ART-123 also has anti-inflammatory properties, including interfering with the activation of complement and inactivating high-mobility group protein B1, a mediator associated with mortality in late sepsis (7–9). IV injection of ART-123 appears to enhance the reversal of DIC in patients with infection or hematologic malignancy (10) and may reduce organ dysfunction and mortality in patients with sepsis-associated DIC (11).

On the basis of a potential benefit of ART-123 in sepsis-induced DIC and in the absence of previous randomized studies in this population, we sought to determine the safety and efficacy of ART-123 when combined with standard care in patients with sepsis-associated DIC.

METHODS

This study was a Phase 2b, multicenter, international double-blind, randomized, placebo-controlled, parallel group trial, conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. Ethical approval was obtained from the Ethics Committees of each participating center, and written informed consent was obtained from all patients or their legal representative.

Adult patients (>18 yr) admitted to one of the 233 study centers in 17 countries (**Appendix 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A674) with sepsis, defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus definition (12), and suspected DIC, identified locally at each center using a score based on platelet count and prothrombin time (PT)-international normalized ratio (INR) derived from the International Society on Thrombosis and Hemostasis (ISTH) DIC score (13), were screened for inclusion. There were four protocol amendments during the study period (v 1.0–1.4); changes from 1.1 to 1.2 and from 1.3 to 1.4 affected the DIC algorithm, the first to expand enrollment and the second to increase the yield of subjects with DIC (**Table 1**). The numbers of patients enrolled in each amendment are shown in **Figure 1**.

Patients were excluded from the study if any of the following criteria were present (full details are provided in **Appendix 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A674): unable to obtain informed consent; presence of any disorder other than sepsis that could alter coagulation; recent history of significant bleeding or increased risk of bleeding (e.g., surgery within 12 hr of screening); presence of a disorder requiring anticoagulation; use of drotrecogin alfa (activated) within the 24 hours prior to enrollment or intended use; use of anticoagulants, antiplatelet agents, antithrombotics, and thrombolytics within the 24 hours prior to study dosing, or intended use, with the exception of heparin locks/flushes or deep-vein thrombosis prophylaxis; platelet count < 20×10^9/L; life expectancy < 90 days or current use of any chemotherapy agent.

After enrollment, patients were randomly assigned in a 1:1 ratio, using a dynamic interactive web response system/interactive voice response system system, with the country ($n = 17$) and the modified disseminated intravascular coagulation (mDIC) algorithm (=2 or >2) as stratification factors, to receive either IV ART-123 (0.06 mg/kg/d) for 6 days or placebo, in addition to standard of care as determined by the treating clinician. ART-123 and placebo were supplied in 1 mL glass ampoules, and patients and staff were blinded to their contents. The dose of ART-123 administered was 0.06 mg/kg (0.01 mL/kg) up to a maximum dose of 6 mg (1 mL) for patients who weighed more than 100 kg. The study drug (ART-123 or placebo) was administered by either IV bolus injection or IV infusion (diluted in 50 mL 0.9% saline) over 15 minutes, via a dedicated IV catheter.

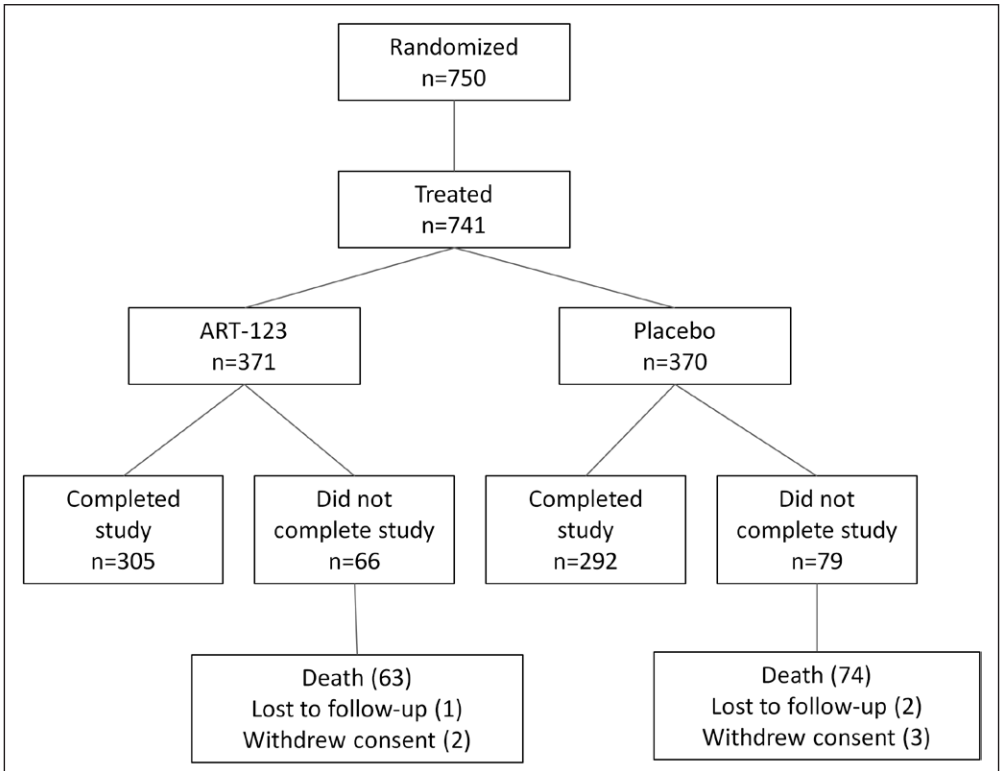
Patients were followed for 28 days after study inclusion. Recorded baseline characteristics included demographic information and information on preexisting conditions and treatments, organ function, and hematologic and other laboratory tests. Central laboratory evaluations for the full ISTH algorithm DIC score (**Table 2**) were performed at randomization (predose), days 1, 3 (predose and postdose), 7, and 14; overt DIC was diagnosed when the ISTH score was ≥ 5. Blood samples were taken for serum chemistry and hematology determinations on days 3, 7, 14, and 28. The presence of ART-123 antibodies was assessed using an enzyme-linked immunosorbent assay method at baseline and on days 7, 14, and 28. All samples determined to be positive for antibody to ART-123 on

TABLE 1. Modified Disseminated Intravascular Coagulation Algorithm

Variable (Units)	Value		Points
	Original and Amendment 1.1	Amendments 1.2, 1.3, and 1.4	
Platelet count ($\times10^9$/L)	>100	≥150	0
	50–100	120 – <150	1
	<50	80 – <120	2
		<80	3
Prothrombin time-international normalized ratio	<1.3	=1.2	0
	1.3 – 1.7	>1.2 – 1.4	1
	>1.7	>1.4 – 1.6	2
		>1.6	3
Total needed for study entry			2 or 3[a]

If the results for a variable were missing, the value for that variable was set to 0. If both variables were missing, the score was unknown. In the first amendment to the modified disseminated intravascular coagulation (mDIC) score (protocol amendment 1.2), the range was increased from 0 to 4 and 0 to 6 to allow enrollment of patients with mild to moderate disseminated intravascular coagulation (DIC; International Society on Thrombosis and Hemostasis score of 5 and 6); in the second amendment to the mDIC score (protocol amendment 1.4), the cut-off for the mDIC score was increased from 2 to 3 to increase enrollment of patients with overt DIC. The numbers of patients enrolled in each amendment are shown in Figure 1.

[a]Amendment 1.4 required ≥ 3 points. All other versions required ≥ 2 points.



	ART-123	Placebo	Total
Enrolled per amendment, n(%)			
v1.0	2 (0.5)	1 (0.3)	3 (0.4)
v1.1	6 (1.6)	6 (1.6)	12 (1.6)
v1.2	90 (24.3)	90 (24.3)	180 (24.3)
v1.3	147(39.7)	151 (40.7)	298 (40.2)
v1.4	125 (33.8)	123 (33.2)	248 (33.5)
Total	**370**	**371**	**741**

Figure 1. Flow of patients through the study and numbers enrolled in each of the protocol amendment groups.

day 28 were tested for the presence of neutralizing antibodies. Patients with antibodies present on day 28 were followed until antibody was no longer detected.

Plasma concentrations of ART-123 (ng/mL) were measured using enzyme-linked immunosorbent assay on day 1 (12 hr postdose), day 3 (predose and 12 ± 3 hr postdose), day 7, and day 14. Blood samples were also obtained at these time points to measure coagulation (TATc, prothrombin fragment F1.2, protein C, protein C inhibitor, plasminogen activator inhibitor-1], antithrombin III) and inflammatory (C5a, interleukin 6, interleukin 10, myeloperoxidase, procalcitonin, high-sensitivity C-reactive protein) markers. Presence of organ dysfunction for four organ systems (renal: creatinine >2 mg/dL; hepatic: bilirubin > 2.0 mg/dL; respiratory: use of mechanical ventilation; cardiovascular: use of a vasopressor) was assessed daily until patients were discharged from hospital. Creatinine clearance was estimated using the Cockcroft-Gault equation (14). Pharmacokinetic variables, including volume of distribution (*V*) and drug clearance (CL), were estimated using a one-compartment model.

Information about serious adverse events (SAEs) was collected prospectively and recorded. An SAE was considered any undesirable sign, symptom, or medical condition that was fatal or life threatening, required prolonged inpatient hospitalization or rehospitalization, resulted in persistent or significant disability/incapacity, was medically significant as determined by a qualified health professional, or was a major bleeding event.

Statistical Analyses

The primary endpoint for this study, based on its clinical relevance, was reduction in mortality. Secondary endpoints included reversal of overt DIC and indicators of reduction in disease severity, including shock-free and alive days, ventilator-free and alive days, and dialysis-free and alive days. Event-free and alive days were calculated based on the number of days a patient was known to be alive and free of the event through day 28.

The study was powered for an endpoint of 28-day all-cause mortality. A sample size of 750 patients was sufficient to provide 90% power at a 5% two-sided alpha level based on an assumption of a placebo mortality rate of 32%, ART-123 mortality rate of 21%, and missing vital status rate of 2.5% (patients with unknown vital status at day 28 were classified as dead for the primary analysis). A prespecified blinded interim analysis conducted after 100 patients had been enrolled showed that the actual prevalence of DIC was insufficient to meet these assumptions. Hence, with the consent of the data-monitoring committee, the study design was changed (protocol amendment 3) to that of a screening trial (15) and decision rules introduced that defined both a "definitive" level of evidence (one-sided p values < 2.5%), indicating definite efficacy, and a "suggestive" level of evidence (one-sided p values < 15%), indicating possible efficacy and warranting further investigation.

TABLE 2. International Society on Thrombosis and Hemostasis Scoring System

Variable	Value	Points
Platelet count ($\times 10^9$/L)	>100	0
	50–100	1
	<50	2
Prothrombin time prolongation (s)	<3	0
	3–6	1
	>6	2
D-dimer (μg/L)	<0.4	0
	0.4–4	2
	>4	3
Fibrinogen (g/L)	1.0	0
	<1.0	1

A score of 5 or more was needed for a diagnosis of overt disseminated intravascular coagulation.

RESULTS

A total of 750 patients were randomized: 371 received ART-123 and 370 received placebo (nine patients [four in the ART-123 group and five in the placebo group] were randomized but did not receive any of the allocated study treatment; Fig. 1). One patient randomized to placebo was incorrectly given ART-123. Under the intent-to-treat principle, this patient was included in the placebo group for the efficacy analyses (full analysis set) but in the ART-123 group for the safety analyses (safety analysis set). A total of 145 patients (19.6%) did not complete the study (66 [17.8%] patients in the ART-123 group; 79 [19.5%] patients in the placebo group), but mortality data were available for all but three patients.

Baseline demographic characteristics are shown in **Table 3**. The mean patient age was 57 years (range, 18–93). There were no meaningful differences between ART-123 and placebo groups in any of the baseline variables. Slightly more patients in the ART-123 group were receiving heparin or low–molecular weight heparin at baseline than in the placebo group (55 [14.9%] vs 45 [12.1%]). The lung was the most common site of infection in both groups (Table 3). Eighty-three percent (n = 587) of patients had microbiological evidence of infection; the most commonly isolated organism was *Escherichia coli* (77 patients [17%] in the ART-123 group and 92 patients [20%] in the placebo group). At baseline, 30% of patients had no organ dysfunction; 134 patients (36.2%) in the ART-123 group and 127 patients (34.2%) in the placebo group had two or more organ dysfunctions at baseline. On day 28, 22 patients (7.8%) in the ART-123 group and 15 patients (5.4%) in the placebo group had some organ dysfunction. Overt DIC (ISTH score ≥ 5) was present at baseline in 98 patients (13.2%): 45 (12.2%) in the ART-123 group and 53 (14.3%) in the placebo group.

Efficacy

Twenty-eight-day mortality was 17.8% (n = 66) in the ART-123 group and 21.6% (n = 80) in the placebo group; Kaplan–Meier survival curves are shown in **Figure 2** and gave a one-sided log-rank p value of 0.17. A Cochran–Mantel–Haenszel test stratified by baseline mDIC and pooled country resulted in a two-sided p value of 0.273 (0.137 one sided) in favor of the ART-123 group, which met the predefined statistical test for evidence suggestive of efficacy (0.15 one-sided alpha level). In the 248 patients admitted after amendment 4 of the protocol, in which the mDIC score required for entry was increased from 2 to 3 and the DIC score needed to be confirmed 4 hours prior to randomization, there was an increase in placebo mortality (24% vs 21%) and in the absolute reduction in mortality with ART-123 (6% vs 3%) compared with patients admitted before this amendment (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A674).

In subgroup analyses for the primary endpoint, the largest treatment effect was seen in patients receiving baseline prophylactic heparin (**Table 4**): 28-day mortality rate 18% (10/55) in the ART-123 group compared with 40% (18/45) in the placebo group (chi-squared p = 0.016 based upon post hoc analysis without multiplicity adjustment). There was no difference in mortality among groups in patients with overt DIC. A series of post hoc analyses were conducted to identify populations that benefited from ART-123 therapy by stratifying subjects according to comorbidities, types of organ dysfunction, and severity of inflammation or coagulopathy based on the biomarker values at baseline. The greatest survival benefit was seen in patients with respiratory or cardiac dysfunction and coagulopathy characterized by PT-INR greater than 1.4 at baseline with a platelet count between 30 and 150×10^9/L: mortality rate of ART-123 was 26.3% (21/80) and placebo was 38.2% (29/76).

There were no statistically significant differences in the event-free and alive days between two groups (**Table 5**). The comparison of resolution of overt DIC between two treatment groups was tested using a stratified Cochran–Mantel–Haenszel test. At day 1, the difference in percentage of patients with resolution of overt DIC (28.9% ART-123 group vs 18.9% placebo group) reached the suggestive level of statistical evidence (p = 0.175).

D-dimer, F1.2, and TAT complex (TATc) concentrations were lower in the ART-123 treatment group than in the placebo group (**Fig. 3**). No differences were seen with regard to platelets or PT. There were no significant differences between the groups in any of the measured inflammatory markers.

Pharmacokinetics

The pharmacokinetics of ART-123 were similar to those reported in previous studies (10, 16, 17) and were not affected by sex, race/nationality, age, or hematocrit. Mean ART-123 concentrations in patients receiving active product increased throughout the study with highest values recorded on day 3 (1031.8 + 430.6 ng/mL). Although ART-123 is mostly excreted by the kidneys, renal dysfunction did not appear to have a major impact on ART-123 volume of distribution or clearance over a large range of creatinine clearances (from 7 to over 400 mL/min).

TABLE 3. Patient Baseline Characteristics

Characteristics	ART-123 (*n* = 370)	Placebo (*n* = 371)	Total (*n* = 741)
Age, yr			
Mean (SD)	57.5 (19.1)	56.9 (17.9)	57.2 (18.5)
Range	18–93	18–93	18–93
Male, *n* (%)	231 (62.4)	224 (60.4)	455 (61.4)
Body mass index (kg/m^2)			
Mean (SD)	25.0 (6.1)	25.3 (6.4)	25.2 (6.3)
Range	13.6–51.9	13.8–59.7	13.6–59.7
Site of infection[a], *n* (%)			
Lung	160 (43)	150 (41)	310 (42)
Gastrointestinal	80 (22)	90 (24)	170 (23)
Urinary tract/kidney	54 (15)	65 (18)	119 (16)
Bacteremia/endocarditis	39 (11)	36 (10)	75 (10)
Skin/soft tissue	11 (3)	13 (4)	24 (3)
Other	45 (12)	39 (11)	84 (11)
Overt disseminated intravascular coagulation score[b], *n* (%)			
<5 (not overt)	257 (69.5)	263 (70.9)	520 (70.2)
≥5 (overt)	45 (12.2)	53 (14.3)	98 (13.2)
Modified disseminated intravascular coagulation score, *n* (%)			
=2	84 (22.7)	83 (22.4)	167 (22.5)
>2	286 (77.3)	288 (77.6)	574 (77.5)
Heparin or low–molecular weight heparin use, *n* (%)	55 (14.9)	45 (12.1)	100 (13.5)
Platelet count, ×10^9/L, mean (SD)[c]	141.0 (114.4)	140.8 (114.2)	140.9 (114.2)
Diabetes, *n* (%)	65 (18)	68 (18)	133 (18)
Organ dysfunction (at least one), *n* (%)	253 (68)	262 (71)	515 (70)
Serum creatinine, *n* (%)			
<1.5 mg/dL	232 (62)	237 (64)	469 (63)
1.5–2 mg/dL	132 (36)	131 (35)	263 (35)
>2 mg/dL	71 (19)	76 (20)	147 (20)

[a]Subjects could have more than one type of infection, hence percentages may be ≥ 100%.
[b]123 missing (68 ART-123 group, 55 in placebo group).
[c]One missing in placebo group.

Safety

Overall, 681 patients (92%) experienced at least one treatment-emergent adverse event (AE): 339 patients (91.4%) in the ART-123 group and 342 patients (92.4%) in the placebo group. The most commonly occurring AEs were hypokalemia, anemia, and pyrexia (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A674). Anemia, thrombocytopenia, and postprocedural hemorrhage were more common in the ART-123-treated patients than in the placebo patients. Overall, 265 patients (35.8%) experienced at least one treatment-emergent SAE: 139 (37.5%) patients in the ART-123 group and 126 patients (34.1%) in the placebo group. Nineteen patients (5.1%) in the ART-123 group and 17 patients (4.6%) in the placebo group experienced an on-treatment serious major bleeding event; four patients (1.1%) in each group had a serious major bleeding event that was fatal. There were no differences between the groups in the prevalence of thromboembolic complications (deep-vein thrombosis, pulmonary embolism, ischemic stroke, acute coronary syndrome). Overall, 71 patients (9.6%) experienced AEs leading to permanent discontinuation of the

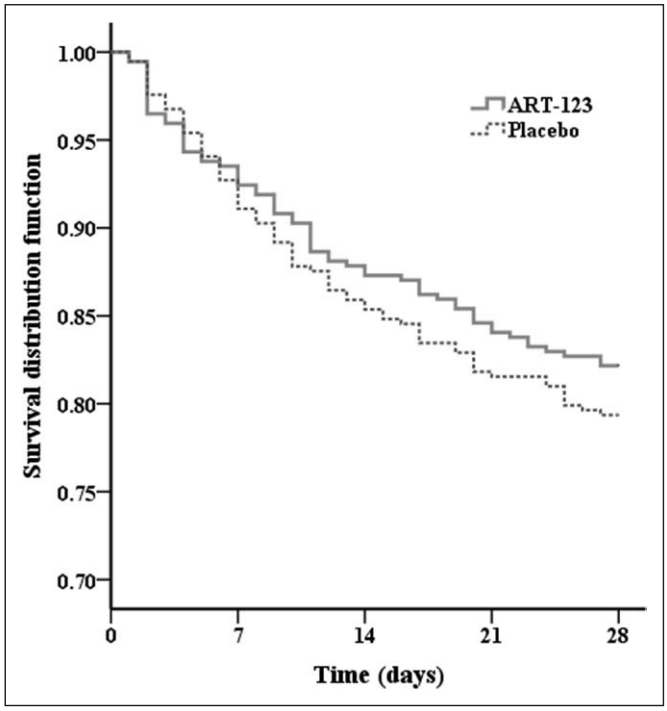


Figure 2. Kaplan–Meier plots of survival time for the two treatment arms: 28-d survival was 82.2% (95% CI, 77.9%, 85.7%) for the ART-123 group and 79.4% (95% CI, 74.9%, 83.2%) for the placebo group (one-sided log-rank *p* value = 0.17). Observations occurring after day 28 were censored at day 28.

study drug: 33 patients (8.9%) in the ART-123 group and 38 patients (10.3%) in the placebo group (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A674). There were no differences between the groups in the development of new infections: 158 patients (43%) in the ART-123 group and 154 patients (42%) in the placebo group. Hematology and biochemistry results were comparable across the study treatments, with no discernible differences between the groups in the number of patients with laboratory results outside of the normal range at any time point.

Eleven patients (six in the ART-123 group and five in the placebo group) had positive results for anti-ART-123 antibody at day 28. No neutralizing antibodies were detected, and no adverse events potentially related to antidrug antibodies were reported.

DISCUSSION

In this phase 2b study, the administration of ART-123 when combined with standard care was associated with lower D-dimer, F1.2, and TATc levels compared with placebo in critically ill patients with sepsis and activation of coagulation as indicated by a modified DIC score. Importantly, the administration of ART-123 was not associated with excess bleeding, thromboembolic events, or increased development of new infections. The difference in 28-day mortality compared with standard care alone met the prespecified level of significance for suggestion of efficacy in this phase 2 trial, although it did

TABLE 4. Summary of 28-Day Mortality Rates by Subgroup

	ART-123 (*n* = 370) (%)	Placebo (*n* = 371) (%)
Creatinine <1.5 mg/dL	31/232 (13)	39/237 (16)
Creatinine ≥1.5 to ≤2.0 mg/dL	15/61 (25)	11/55 (20)
Creatinine >2.0 mg/dL	20/71 (28)	27/76 (36)
Creatinine ≥1.5 mg/dL	35/132 (27)	38/131 (29)
Baseline mDIC score		
=2	13/84 (15)	14/83 (17)
>2	53/286 (19)	66/288 (23)
Baseline overt DIC score		
ISTH DIC <5	39/257 (15)	49/263 (19)
ISTH DIC ≥5	16/45 (36)	18/53 (34)
Baseline heparin or low–molecular weight heparin use		
No	56/315 (18)	62/328 (19)
Yes	10/55 (18)	18/45 (40)
Baseline number of organ dysfunctions		
0	10/117 (9)	11/109 (10)
≥1	56/253 (22)	69/262 (26)

mDIC = modified disseminated intravascular coagulation, ISTH = International Society on Thrombosis and Hemostasis.
Patients without a Yes or No response to mortality status on the "End of Study Status" electronic case-report form (Question: Was patient alive on Day 28?) were assumed to be dead.

TABLE 5. Event-Free and Alive Days

Event-Free and Alive Days, Mean (95% CI)	ART-123 ($n = 370$)	Placebo ($n = 371$)
Ventilator-free	16.8 (15.5, 18.0)	16.3 (15.1, 17.6)
Shock-free	20.5 (19.5, 21.6)	20.1 (19.0, 21.2)
Organ dysfunction-free	20.0 (18.9, 21.2)	19.6 (18.5, 20.7)
Dialysis-free	23.2 (22.2, 24.2)	22.8 (21.8, 23.8)
ICU-free	14.0 (12.8, 15.2)	14.2 (13.0, 15.4)
Hospitalization-free	7.7 (6.6, 8.7)	7.7 (6.7, 8.8)

not meet the target for proof of efficacy. This phase 2b study has, thus, demonstrated that ART-123 is a safe intervention in critically ill patients with coagulopathy due to sepsis; evidence suggestive of efficacy was observed, supporting further development.

Despite improvements in the general management of patients with sepsis over the past 30 years, 28-day mortality rates in sepsis remain unacceptably high, and no targeted therapy is currently available. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study demonstrated a survival benefit in patients with severe sepsis treated with recombinant activated protein C (18), and post hoc analyses of these data suggested that patients with overt DIC (using a different modification of the ISTH score to that used in the present study) may have benefited in particular (19). The recent PROWESS-SHOCK study (20), however, failed to confirm the survival benefit of recombinant activated protein C, possibly in part because of the lower placebo mortality rate compared with the original PROWESS study making it more difficult to demonstrate an effect of the trial agent, and this drug has now been withdrawn.

Thrombomodulin is a thrombin receptor present on the endothelial cell surface that is of key importance in regulating physiological anticoagulation (21, 22). Binding of thrombin to thrombomodulin not only scavenges active thrombin but also creates a complex that activates protein C, thereby effectively converting thrombin from a procoagulant to an anticoagulant. In sepsis, thrombomodulin expression and function are markedly down-regulated, contributing to the procoagulant state. Although serum levels of thrombomodulin increase in patients with sepsis and sepsis-associated DIC or multiple organ failure (23–25), endothelial thrombomodulin expression is decreased, suggesting that the increased serum thrombomodulin levels are the result of shedding from the endothelium following endothelial injury (26). Interestingly, thrombomodulin has been found to have other anti-inflammatory effects not related to its coagulation modulatory activity, including interfering with the activation of complement and inactivating high-mobility group protein B1 (7–9).

ART-123 is a recombinant thrombomodulin currently approved for the treatment of DIC in Japan where more than 28,000 patients have received the drug. In a double-blind

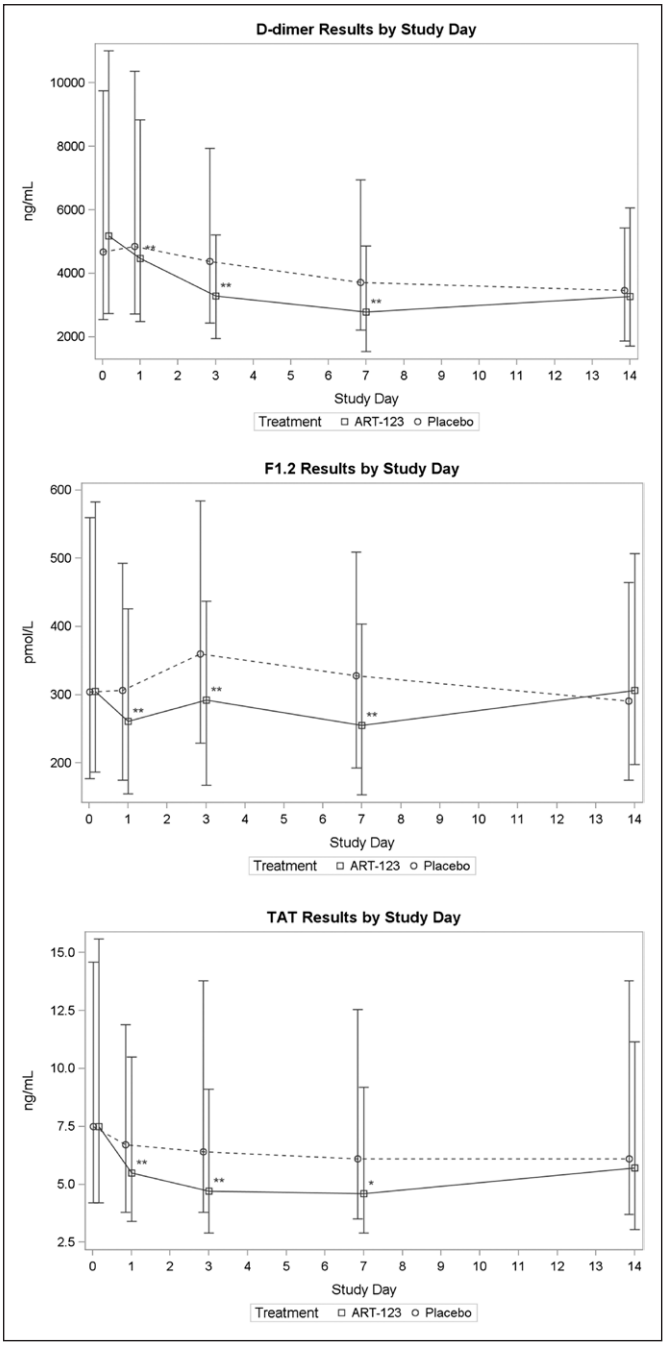


Figure 3. Median D-dimer, F1.2, and TAT complex concentrations over time in the two groups. *$p < 0.05$, $p < 0.001$. p values from Wilcoxon test using change from baseline and imputing a change of zero for subjects who died.

randomized controlled phase 3 study conducted in Japan, patients with DIC and infection or hematological malignancy were randomized to receive treatment with ART-123 (0.06 mg/kg for 30 min, once daily) or heparin sodium (8 U/kg/hr for 24 hr) for 6 days (10). DIC resolved in two thirds of the ART-123 patients compared with one half of the heparin-treated patients. Patients treated with ART-123 had fewer bleeding-related adverse events than those treated with heparin ($p = 0.0487$). There were no differences in 28-day mortality rates, but the study was powered to detect

a difference in the rate of resolution of DIC rather than in mortality. Because the study included patients with DIC caused by hematological malignancy or infection, a retrospective subanalysis was conducted, excluding the patients with malignancy and analyzing the data from the 80 patients with DIC and infection (27). The results indicated a trend to better outcome in the ART-123 group compared with the heparin group (DIC resolution rates 67.5% vs 55.6%; mortality rates 21.4% vs 31.6%). However, patients enrolled in that study appeared more ill than those enrolled in the present study, as indicated by the overall placebo mortality rate of 34.6% versus 21.6% in the current study.

The lack of a mortality benefit in the subgroup population of patients with overt DIC in the present study warrants discussion. Multiple possibilities could explain this finding. First, this subgroup may simply have been too small to see an effect. Second, the drug may truly not be efficacious or have only limited efficacy in DIC. Third, compared with the Japanese Ministry of Health criteria used in the study by Saito et al (10, 27), overt DIC as defined using the ISTH criteria appears to represent a late-stage, far end of the spectrum (28, 29) at which the coagulopathy may be too far advanced to respond to thrombomodulin; patients without overt DIC are also at high risk of death but may be more able to respond to therapy. Fourth, the window for randomization in the current study was up to 36 hours, a period during which supportive care could result in resolution of the coagulopathy prior to treatment with ART-123. Indeed, when a greater degree of coagulopathy was required after protocol amendment 4, with confirmation within just 4 hours of randomization, not only did the placebo mortality increase but so did the absolute reduction in mortality with ART-123, suggesting that ART-123 may be more beneficial for subjects with greater coagulation abnormality. Finally, mechanisms of action other than the anticoagulant activity of ART-123 are likely to be involved.

The population enrolled in the present study had less severe disease (13.2% overt DIC, 30.5% of patients with no organ dysfunction) than anticipated during study design. ART-123 may be efficacious even without organ dysfunction in the presence of coagulopathy; however, the low placebo mortality in the subgroup with no organ dysfunction (10%) makes it difficult to evaluate a treatment benefit of ART-123 on 28-day mortality in these patients. Limiting enrollment to patients with higher ISTH DIC scores (overt DIC) may have resulted in higher rates of death and secondary endpoints, which may have enabled the effects of ART-123 on these endpoints to be better characterized. Alternatively, use of a shorter window for definition of coagulopathy may enable a more responsive population of patients with sepsis and coagulopathy to be selected. Finally, the post hoc analyses raise the possibility of a greater beneficial effect of ART-123 in specific groups of patients, notably patients with a PT-INR > 1.4 and the presence of organ failure, suggesting that presence of organ dysfunction should be included in the target population for further testing of recombinant thrombomodulin.

In conclusion, administration of ART-123 at a dose of 0.06 mg/kg/d for a 6-day treatment period was associated with clear pharmacologic effects (lower D-dimer, F1.2, and TATc levels) and evidence suggestive of efficacy. ART-123 is a safe intervention in critically ill patients with coagulopathy due to sepsis, even in settings where patients are administered prophylactic doses of heparin, with no difference in bleeding complications between ART-123-treated and placebo-treated patients. These findings provide support for undertaking a phase III study, based on the population identified from the post hoc analyses, to extend these observations. Future trials using ART-123 should also be designed to better characterize the complex interactions present within the coagulation cascade in septic patients and to enable a description of the interactions between ART-123 and heparin or low–molecular weight heparins and between ART-123 and the emerging prophylactic/therapeutic anticoagulants (thrombin inhibitors and Xa inhibitors) used in critically ill patients.

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