Received: 16 July 2024 | Accepted: 1 September 2024

DOI: 10.1002/prp2.70015

ORIGINAL ARTICLE

A dose-adjusted, open-label, pilot study of the safety, tolerability, and pharmacokinetics of STC3141 in critically ill patients with sepsis

Rinaldo Bellomo[1] | John Patava[2] | Ruth Van Lancker[3] | Nathalie Layios[4] | Marijke Peetermans[5] | Mark Plummer[6] | Rachid Attou[7] | Robert McNamara[8] | Andrew Udy[9,10] | Bradley Wibrow[11] | Adam Deane[12] | Edward Litton[13] | Marcel Tanudji[2] | Fuhong Su[2] | Zhang Zhong[2] | Linda Shi[2] | Li Ning[2]

[1]Austin Hospital, Heidelberg, Victoria, Australia

[2]Grand Medical Pty Ltd, St Leonards, New South Wales, Australia

[3]UZ Brussel, Brussels, Belgium

[4]C.H.U Liège, Sart Tilman, Domaine Universitaire du Sart Tilman—B35, Liège 1, Belgium

[5]UZ Lueven, Leuven, Belgium

[6]Royal Adelaide Hospital, Adelaide, South Australia, Australia

[7]CHU Brugmann, Brussels, Belgium

[8]Royal Perth Hospital, Perth, Western Australia, Australia

[9]Alfred Hospital, Melbourne, Victoria, Australia

[10]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[11]Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

[12]Department of Critical Care, Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia

[13]Fiona Stanley Hospital, Murdoch, Western Australia, Australia

Correspondence
John Patava, Grand Medial Pty Ltd, Shop 6/207 Pacific Highway, St Leonard's, NSW 2065, Australia.
Email: jpatava@innovpharma.com.au

Abstract

Increased circulating histones correlate with sepsis severity and are a potential therapeutic target. Pre-clinical studies showed benefit with a histone-neutralizing polyanion molecule (STC3141). We aimed to investigate the safety, tolerability, and pharmacokinetics of STC3141 in critically ill patients with sepsis. We studied 26 patients with sepsis divided into four cohorts of one, five, ten, and ten subjects, respectively. We conducted a dose-adjusted, open-label study to determine the safety, tolerability, and pharmacokinetics of STC3141 administered as an IV infusion for up to 72 h, with rate adjusted to estimated creatinine clearance. Four steady-state concentrations were targeted. Twenty of the 26 subjects (77%) in the study experienced at least one adverse event (AE). The most frequently reported study drug-related AE was a mildly prolonged aPTT (four events). Only one AE (pulmonary hemorrhage) led to discontinuation of the drug. After excluding patients receiving renal replacement therapy (RRT) patients, clearance ranged from 3.3 to 4.2 L/h across cohorts and was essentially completely renal in nature. Half-life values ranged from 5 to 7 h. The mean (±SD) terminal half-life for non-RRT subjects and for whom it was possible to calculate was approximately 9 (±4.77) h but increased to 19 (±7.94) h for subjects on RRT. Overall, 18 (69.2%) patients completed the study to day eight in the ICU, and 22 (84.6%) survived to 28 days. STC3141 administration appeared to have an acceptable degree of safety and tolerability and expected pharmacokinetics. Cautious, larger randomized efficacy trials in sepsis appear justified.

KEYWORDS
histones, inflammatory response, NETs, sepsis, small molecule polyanion

Abbreviations: aPTT, activated pro-thrombin time; AUC, area under the curve; Cmax, maximum plasma concentration; CrCl, creatinine clearance; Css, plasma concentration as steady state; CTCAE, common terminology criteria for adverse events; DAMPs, damage associated molecular pattern molecules; ICU, intensive care unit; IDMC, Independent Data Monitoring Committee; mCBS, β-O-methyl, cellobioside hepta sulfate; NETs, neutrophil extracellular traps; PK, pharmacokinetic; PT, preferred term; SAE, serious adverse event; SOC, system organ class; SSMC, Study Safety Management Committee; TEAE, treatment emergent adverse event; tmax, Time to maximum plasma concentration.

1 | INTRODUCTION

Sepsis is a highly morbid condition with significant variation in individual disease progress and outcomes.[1] Its progression results from a generalized dysregulated inflammatory response to infection mediated by, among other mechanisms, a variety of Damage Associated Molecular Pattern molecules (DAMPs).[2] Histones are a group of highly ionic DAMP molecules and act as powerful drivers of inflammation and lead to significant tissue damage and death in animals.[3–6] They are released into the extracellular milieu in association with DNA due to tissue damage or by neutrophils in the form of Neutrophil Extracellular Traps (NETS) that contain chromatin DNA to wall off sites of infection. Histones, released into the local tissue with chromatin, can diffuse into the circulation, along with other NET components when the DNA is broken down by bacterial DNases.

Extracellular histones are toxic to endothelial cells, cause aggregation of platelets and erythrocytes, increase erythrocyte fragility, and directly affect coagulation.[7] Given these observations, a program was initiated to develop a histone-neutralizing therapy based on small-molecule polyanions.[7] The lead candidate from the development program was a highly sulphated disaccharide of glucose (β 1,4 linkage) with a methylated group at the terminal reducing end at the β anomeric position, that is, β-*O*-methyl, cellobioside hepta sulfate (mCBS), which is highly anionic in an aqueous environment. mCBS attenuated the pathogenic effects of extracellular histones in several preclinical models.[7–11]

mCBS was evaluated in healthy volunteers to characterize its pharmacokinetics and safety. In this study of infusions of up to 72 h, mCBS reached a steady state concentration of 23 μg/mL, had a favorable safety profile, a short plasma half-life of 3–4 h, and almost exclusive renal clearance (unpublished data). These characteristics made it suitable for administration by continuous infusion with a target steady-state concentration in sepsis.

Accordingly, mCBS was administered for the first time to patients presenting with sepsis in Intensive Care Units in Australia and Belgium. We aimed to assess its safety, tolerability, and pharmacokinetics in sepsis patients with normal or impaired renal function.

2 | METHODS

The REFINE study (ACTRN12620000716965) was a single-arm, dose-adjusted, open-label, multi-center study to determine the safety, tolerability, and pharmacokinetics of STC3141 administered as an IV infusion of up to 72 h in patients admitted to ICU with sepsis, where the rate of infusion was adjusted according to estimated creatinine clearance. Four target steady state plasma concentrations were planned: 5, 10, 20, and 25 μg/mL, and 26 subjects were enrolled into four corresponding cohorts (Cohort 1, Cohort 2, Cohort 3, and Cohort 4) with one, five, ten, and ten subjects in each cohort, respectively.

2.1 | Description of study drug

For clinical use, the active pharmaceutical agent was manufactured as the sodium salt of β-*O*-methyl-cellobioside-hepta sulfate (mCBS.Na). Each molecule consists of seven sodium counterions, which rapidly dissociate and form the anionic β-*O*-Methyl-cellobioside-hepta sulfate (mCBS) molecule.

STC3141 is a sterile solution for IV infusion consisting of 70 mg/mL of mCBS.Na manufactured in compliance with current Good Manufacturing Practice (cGMP) by Sypharma Pty Ltd, Dandenong, Victoria. This preparation has been shown to be stable for 36 months when stored at 2°C to 8°C.

At the trial site, the appropriate amount of STC3141 was dispensed to each study subject in accordance with the dosing schedule (see Tables S1 and S2).

2.2 | Subject enrolment

Subjects between 18 and 85 years of age, admitted to ICU with confirmed or suspected infection and receiving antibiotics, a SOFA sore of ≥2, underwent screening over a 48-hour period starting no later than 24 h after admission. Subjects, or their legal representative, signed an Informed Consent Form (ICF) before any study-specific procedures or assessments. Subjects who met all inclusion and none of the exclusion criteria were enrolled in the study.

The key exclusion criteria applied during the study are set out in the Supplementary Appendix.

After all screening and baseline assessments on Day 0 and Day 1 were performed, eligible subjects were administered an IV infusion of STC3141 for up to 72 h, subject to the stopping rules set out below. A schematic of the study design is provided in Figure 1, and a schematic of the study phases is provided in Figure S1.

2.3 | Treatment of subjects

We enrolled 26 eligible subjects into four sequential treatment cohorts. They received an infusion of STC3141 with the objective of achieving a steady-state plasma concentration of 5, 10, 20, and 25 μg/mL of mCBS with 1, 5, 10, and 10 patients in each cohort, respectively.

A review by SSMC and subsequently IDMC of the biochemical and coagulation parameters at the completion of each cohort was carried out to determine the safety of the infusion prior to the decision to escalate to the next cohort.

As shown in Figure 1, the study drug was administered as a continuous IV infusion for up to 72 h using 3 × 100 mL bags. Each 100-mL bag was administered over 24 h at a rate of 4.1 mL/h via a dedicated infusion line and was prepared daily prior to use.

The dose of the study drug infusion required for each subject was adjusted based on their estimated creatinine clearance using the "Cockcroft-Gault" formula. The infusion rate of STC3141 (in mg/h)

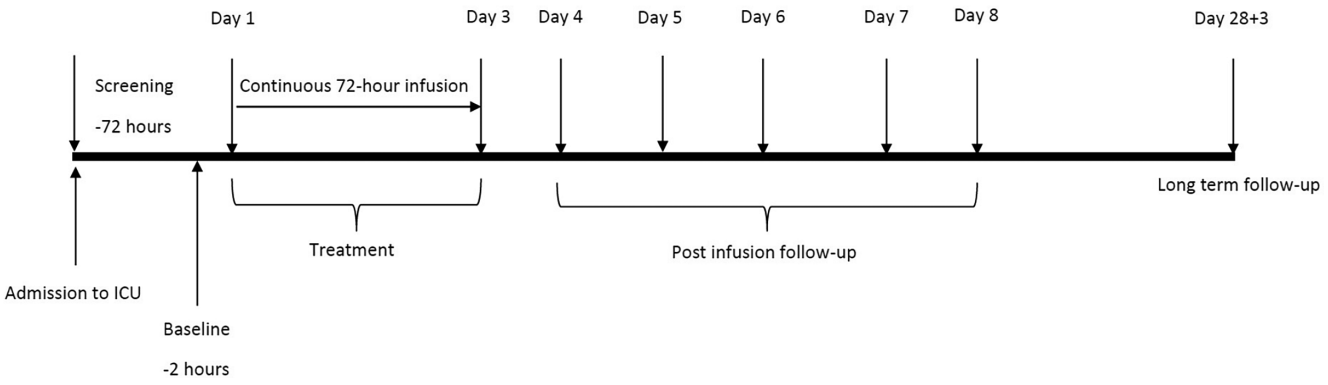

FIGURE 1 Diagram showing the process of patient identification, infusion administration and follow-up.

required to reach the target plasma concentration steady state (Css) in subjects with varying creatinine clearance (CrCL) was calculated in accordance with the formulae presented in Table S1. Simulation-based modeling indicated a strict linear relationship (R = 1) between the estimated renal function and the dose of STC3141 required for each target *C*ss (see Figure S2). The infusion rate for each target *C*ss was calculated using the regression line equation from each curve and the CrCL for each subject (determined prior to infusion) as per Table S2. The dose rate calculated above was then used daily to prepare the STC3141 IV infusion solution.

The STC3141 infusion was interrupted when the activated prothrombin time (aPTT) exceeded 55 s and recommenced after 4 h at a rate no greater than 80% of the original rate. In addition, the medication was permanently stopped if:

- Any AE occurred that required stopping the STC3141 infusion
- The condition of the subject deteriorated such that active treatment was withdrawn
- The treating clinician determined not to continue with the infusion in the subject's best interest
- The subject or relatives withdrew consent
- Death occurred

2.3.1 | Prior/concomitant medications

The use of any investigational drug or investigational medical device within 90 days prior to screening was prohibited, as was the use of therapeutic doses of heparin or oral antithrombotic anticoagulants, although subjects could receive thromboprophylaxis doses. All concomitant medications administered as part of the standard care of the patients in the ICU during the course of the study were recorded.

2.3.2 | Study drug treatment compliance

All doses were administered in the ICU in the presence of the Investigator or their designee and reviewed by the study sponsor. Pauses in drug infusion in accordance with the above-listed stopping rules were recorded. Compliance was determined to be achieved if the subject had received between 80% and 120% of their planned dose.

2.3.3 | Safety monitoring

Safety was assessed and monitored during the infusion period and follow-up period of up to 8 days after the start of study drug infusion as long as the subject remained in the ICU. Safety monitoring included physical examination, vital signs, laboratory testing [hematology, coagulation, biochemistry, and urinalysis], 12-lead ECG, occurrence of AEs, and changes in concomitant medications/therapies.

Summaries of the clinical and biochemical parameters that were measured at the different timepoints in the study are presented in Table S3.

Adverse events were classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The severity of AEs was determined by the investigators at each site and graded by Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The treatment-emergent AEs (TEAEs) were summarized by severity and by relationship to treatment.

Biomarker—samples and analyses

Where possible, additional blood samples were collected prior to the start of the infusion and at 12, 24, 48, and 72 h post-infusion to carry out the analyses of the following exploratory endpoints: circulating DNA, myeloperoxidase (MPO), IL-6, and pro-calcitonin (see Appendix for details).

Pharmacokinetics (PK) analyses

Blood and urine/dialysate samples were obtained for the determination of the PK of IV-administered STC3141 in subjects with sepsis at these time points: pre-infusion, 12, 24, 48, 72, 74, 78, 84, and 96 h post-infusion of the study drug using K_2 EDTA as the anticoagulant.

All PK analyses were based on the PK population, defined as all subjects who received any amount of drug and had a quantifiable C_{max} and AUCt profile. The PK parameters were estimated using

non-compartmental methods by statistical software R Version 4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria) and verified by R Version 4.2.3 and Phoenix® WinNonlin® Version 8.3.4. The NPK1 PK population was used for all data presentation and summaries. Actual elapsed time from dosing was used for the final PK parameter calculations. The details of PK analysis are presented in the Appendix.

Global clinical measures. Global clinical measures, including time alive to Day 28 and free of ICU, time alive to Day 28 and free of Hospital, time alive to Day 28 and free of mechanical ventilation and time alive to Day 28 and free of vasopressors were assessed from medical records. All exploratory efficacy endpoints were analyzed on the ITT population based on the observed data, using descriptive summary statistics.

3 | RESULTS

As shown in Table 1, we studied 26 subjects aged between 41 and 84 years of age with equally distributed sex. The most frequent underlying site of infection was respiratory, followed by gastrointestinal, urinary, and other sources (Table 1). The median baseline estimated creatinine clearance was 63.0 mL/min. At baseline, 10 subjects were on mechanical ventilation, 20 on vasopressors, and three on continuous renal replacement therapy (CRRT).

3.1 | Disposition of subjects

A summary of subject disposition is presented in Table S4 of the Appendix. Overall, 29 consenting subjects were screened, with 26 eligible patients identified and 20 (76.9%) included in the PK analysis. Overall, 22 subjects (84.6%) survived to 28 days. The investigators did not attribute any of the 4 deaths to the study medication. Overall, 18 of 26 (69.2%) subjects completed the full protocol to day eight in the ICU. The remaining subjects were not able to complete the full protocol to day eight due to death (1), SAE (1), early discharge from the ICU (4), premature discharge from the ICU (1) or requiring other treatments (1). Overall, 22 (84.6%) subjects achieved a treatment compliance of >80%. More details of subject disposition are given in the text of Table S4.

3.1.1 | Safety

Adverse events and serious adverse events are summarized in Table 2. Overall, 77% of the 26 subjects in the study experienced an AE. Most of the AEs were of CTCAE (Common Terminology Criteria for Adverse Events) Grade 1 and 2 categories. Most were considered unrelated to the study drug ($n = 108$ of 124). The most frequent related AE was a prolonged aPTT (four events).

There was only one serious AE, of pulmonary hemorrhage in a subject from Cohort 3, that was deemed by the study investigator to be related to the study drug, which led to study drug withdrawal.

3.1.2 | Biochemistry and APTT

There were no effects on urea, electrolytes, liver function tests, or troponin. C-reactive protein (Figure S3), decreased from a median baseline level of 240 to 106.3 mg/L at Day 3 and further to 84.1 mg/L at Day 8/ET. This trend was observed across all four cohorts.

Average creatinine concentrations decreased from baseline to Day 8 in all cohorts (see Table S5 and Figure S3) from a median of 107 μmol/L at baseline to 82.2 μmol/L after 72 h and 70 μmol/L at Day 8. APTT changes are summarized in Table S6 and Figure S4.

3.2 | STC3141 pharmacokinetic parameters—plasma

The mean (±SE) concentration-time profiles by cohort are presented in Figure 2 on the linear scale. For all cohorts, PK profiles showed a rise in concentrations during the first 24 h of the infusion period, followed by a plateau. At the end of infusion, concentrations declined in a multi-exponential manner.

Drug exposure increased with increasing dose at each target C_{ss} as the study progressed through the cohorts from 1 to 4. However, the C_{ss} of STC3141 in all cohorts was lower than the target plasma concentrations of 5, 10, 20, and 25 μg/mL, respectively. Clearance and drug plasma half-life were similar for all cohorts. When subjects receiving RRT were excluded, mean values of clearance ranged from 3.3 to 4.2 L/h across cohorts, while median half-life values ranged from approximately 5 to 7 h. The calculated terminal elimination half-life was different between cohorts, mainly due to the PK profile of STC3141 (three compartmental PK model) and the low concentrations at the terminal phase in Cohorts 1 and 2. The data suggests that the PK of STC3141 was linear in this population. Across cohorts, the time to reach C_{max} (t_{max}) varied greatly, and was explained by differences in drug administration rates between subjects. The subjects' exposures in Cohort 3 appeared to be higher than in other cohorts, and the terminal elimination half-life of STC3141 in these subjects was longer than in other cohorts. Three of the 10 subjects in this cohort received RRT. The mean (±SD) terminal half-life for non-RRT subjects for whom it was possible to calculate (4 subjects) was approximately 9 (±4.77) h but increased to 19 (±7.94) h in the 3 subjects on RRT.

3.3 | STC3141 pharmacokinetic parameters—urine

The mean (±SE) cumulative amount of STC3141 excreted over time for the PK population is presented by cohort in Figure 3. Such amounts increased until approximately 96 h post-dose once a plateau was reached. The fraction of dose excreted in urine was

TABLE 1 Baseline characteristics of study population.

Characteristic	Cohort 1 (*N* = 1)	Cohort 2 (*N* = 5)	Cohort 3 (*N* = 10)	Cohort 4 (*N* = 10)	Overall (*N* = 26)
Age (years)					
n	1	5	10	10	26
Median (Min, Max)	75.0 (75, 75)	60.0 (45, 64)	62.0 (41, 84)	65.5 (41, 84)	61.5 (41, 84)
Sex, *n* (%)					
Male	0	3 (60.0)	5 (50.0)	5 (50.0)	13 (50.0)
Female	1 (100)	2 (40.0)	5 (50.0)	5 (50.0)	13 (50.0)
Race, *n* (%)					
White	1 (100)	5 (100)	10 (100)	9 (90.0)	25 (96.2)
Black or African American	0	0	0	0	0
Asian	0	0	0	0	0
Aboriginal	0	0	0	0	0
Other	0	0	0	1 (10.0)	1 (3.8)
Female subjects of childbearing potential, *n* (%)					
Yes	0	0	2 (40.0)	2 (40.0)	4 (30.8)
No	1 (100)	2 (100)	3 (60.0)	3 (60.0)	9 (69.2)
Height (cm)					
n	1	5	10	10	26
Median (Min, Max)	160.00 (160.0, 160.0)	172.00 (147.0, 177.0)	176.50 (155.0, 185.0)	169.50 (152.0, 186.0)	172.50 (147.0, 186.0)
Estimated/Actual weight (kg)					
n	1	5	10	10	26
Median (Min, Max)	63.90 (63.9, 63.9)	91.00 (55.8, 120.6)	83.00 (58.0, 128.0)	81.75 (66.0, 120.0)	82.75 (55.8, 128.0)
BMI (kg/m^2)					
n	1	5	10	10	26
Median (Min, Max)	24.960 (24.96, 24.96)	36.450 (18.64, 38.49)	27.395 (18.31, 37.40)	30.540 (19.58, 51.94)	29.335 (18.31, 51.94)
Primary infection site, *n* (%)					
Lung	0	2 (40.0)	2 (20.0)	7 (70.0)	11 (42.3)
Gastrointestinal	1 (100)	1 (20.0)	4 (40.0)	2 (20.0)	8 (30.8)
Heart	0	0	0	0	0
Skin	0	0	0	1 (10.0)	1 (3.8)
Soft tissue	0	0	1 (10.0)	0	1 (3.8)
Unknown	0	0	0	0	0
Other	0	2 (40.0)	3 (30.0)	0	5 (19.2)
Hickmann line	0	0	1 (10.0)	0	1 (3.8)
Left hip	0	0	1 (10.0)	0	1 (3.8)
Urinary sepsis	0	0	1 (10.0)	0	1 (3.8)
Urine	0	2 (40.0)	0	0	2 (7.7)
Total SOFA score					
n	1	5	10	10	26
Median (min, max)	10.0 (10, 10)	8.0 (6, 14)	6.5 (3, 14)	7.5 (5, 10)	7.5 (3, 14)
APACHE II score					
n	1	5	10	10	26
Median (min, max)	17.0 (17, 17)	18.0 (11, 21)	21.0 (14, 25)	21.5 (10, 29)	20.5 (10, 29)
Baseline lactate					
n	1	5	10	10	26
Median (min, max)	2.600 (2.600, 2.600)	1.100 (0.900, 4.000)	1.250 (0.700, 3.600)	1.050 (0.500, 5.000)	1.150 (0.500, 5.000)

(Continues)

TABLE 1 (Continued)

Characteristic	Cohort 1 (*N* = 1)	Cohort 2 (*N* = 5)	Cohort 3 (*N* = 10)	Cohort 4 (*N* = 10)	Overall (*N* = 26)
Creatinine clearance (mL/min)					
n	1	5	7	10	23
Median (min, max)	59.0 (59, 59)	69.0 (26, 165)	57.0 (30, 128)	65.0 (30, 140)	63.0 (26, 165)
Mechanical ventilation n (%)					
Yes	1 (100)	2 (40.0)	3 (30.0)	4 (40.0)	10 (38.5)
CRRT *n* (%)					
Yes	0	0	3 (30.0)	0	3 (11.5)
Vasopressor n (%)					
Yes	1 (100)	5 (100)	7 (70.0)	7 (70.0)	20 (76.9)

Abbreviations: APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CRRT, continuous renal replacement therapy; SOFA, sequential organ failure assessment.

TABLE 2 Adverse events (AE) and serious adverse events.

	Cohort 1 *N* = 1 *n* (%)	Cohort 2 *N* = 5 *n* (%)	Cohort 3 *N* = 10 *n* (%)	Cohort 4 *N* = 10 *n* (%)	Overall *N* = 26 *n* (%)
Number of subjects with AE	1 (100)	4 (80.0)	8 (80.0)	7 (70.0)	20 (76.9)
Number of subjects with serious AE	1 (100)	3 (60.0)	1 (10.0)	0	5 (19.2)
Number of subjects with worst severity of AE[a,b]					
Grade 1 and 2 (mild to moderate)	0	1 (20.0)	4 (40.0)	4 (40.0)	9 (34.6)
Grade 3 and 4 (severe, life threatening)	1 (100)	2 (40.0)	4 (40.0)	3 (30.0)	10 (38.5)
Grade 5 (Death)	0	1 (20.0)	0	0	1 (3.8)
Number of worst relationship to study drug					
Related	0	1 (20.0)	5 (50.0)	2 (20.0)	8 (30.8)
Not related	1 (100)	3 (60.0)	3 (30.0)	5 (50.0)	12 (46.2)

Note: One (3.8%) subject from Cohort 2 experienced a Grade 5 event of disease progression on Day 5, which was considered as AE, leading to death and study discontinuation. Cohort 1: STC3141 (Target C_{ss} 5 μg/mL), Cohort 2: STC3141 (Target C_{ss} 10 μg/mL), Cohort 3: STC3141 (Target C_{ss} 20 μg/mL), Cohort 4: STC3141 (Target C_{ss} 25 μg/mL). N, The total number of subjects in each Cohort under the stated population. n, Number of subjects with non-missing data within the specific category. Percentages were based on N. The AEs that started from the first dose of study drug followed until the 30-day follow-up period in this study or were already present prior to the first dose of study drug in this study regardless of causality and increased in severity following administration of study drug regardless of causality. Relationship was considered as related, if it was definitely related, probably related, possibly related, and unlikely related. Adverse events were coded using MedDRA, Version 23.0.

Abbreviation: AE, adverse event; C_{ss}, average concentrations at steady state; MedDRA, medical dictionary for regulatory activities.

[a]Subjects with multiple severity were counted only once under worst grade.

[b]Subjects with more than one relationship were counted only once under worst relationship.

approximately 80% across all cohorts. It was lower in Cohort 3 due to the use of RRT in 3 subjects. The subsequent decrease in Cohort 4 was due to the difference in the number of data points between the last 2 collection intervals and the earlier ones ($n = 7$ vs. $n = 8$ at 96 h and $n = 10$ before 96 h). The mean drug renal clearance ranged from approximately 1.9 L/h to 3.6 L/h; the lowest mean value was associated with Cohort 3.

3.4 | Assessment of the dose adjustment criteria

The adjustments made to the rate of infusion ensured that the C_{ss} did not exceed the target C_{ss}. Only in 3 cases was the rate of infusion modified due to the aPTT exceeding the target of 55 s, and, at a cohort level, C_{ss} was well within the predetermined safety margin. The general condition was that C_{ss} was 60 to 70% of target.

3.5 | Biomarkers

The concentrations of potential biomarkers of disease progression and pharmacodynamic activity, including circulating DNA, myeloperoxidase, and procalcitonin, are presented in Appendix—Figure S5.

3.5.1 | Clinical outcomes

The key clinical outcomes are summarized in Appendix—Table S7.

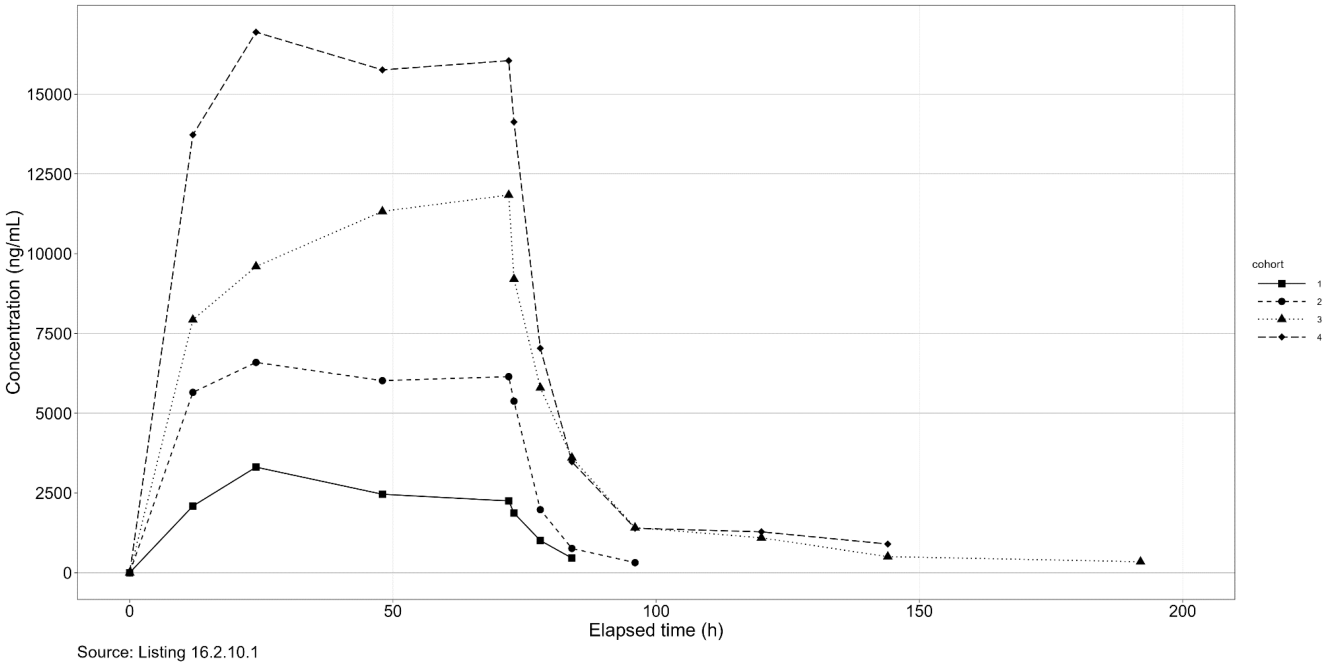

FIGURE 2 Mean (±SE) STC3141 Plasma Concentrations by Cohort (Linear Scale) over time in patients receiving full PK assessment. Plasma PK parameters were computed from the individual data using a Non-Compartmental Analysis (NCA) approach. The PK parameters included maximum observed plasma concentration (C_{max}), time at which C_{max} was observed (T_{max}), apparent terminal rate constant was the slope of the ln-linear terminal phase (Kel), area under the plasma concentration time curve from zero until the last detectable time point (AUC0-t), Area Under the Curve from time 0 to time infinity (AUC0-inf), apparent terminal half-life (t1/2), total body clearance (CL), area under the moment curve from time zero to the last observed concentration (AUMC0-t), area under the moment curve from zero to infinity (AUMC0-inf), mean residence time (MRT), concentration at steady state (Css), total volume of distribution V_{ss}. Cohort 1: STC3141 (Target C_{ss} 5 µg/mL); Cohort 2: STC3141 (Target C_{ss} 10 µg/mL), Cohort 3: STC3141 (Target C_{ss} 20 µg/mL), Cohort 4: STC3141 (Target C_{ss} 25 µg/mL).

4 | DISCUSSION

4.1 | Key findings

This is the first report of the administration of STC3141 in critically ill patients with sepsis. STC3141 had an acceptable safety and tolerability profile in this highly morbid patient population. Protocol compliance was satisfactory, with 84.6% of subjects receiving between 80% and 120% of the planned study drug dose. There was no relationship between dose, safety, and tolerability, and no dose-related increase in AEs, SAEs, and deaths. PK analysis showed that C_{max} and C_{ss} increased in accordance with the planned target C_{ss}. However, the calculated C_{max} and C_{ss} for each cohort were lower than the target plasma concentration, likely related to improvements in renal function over time. In addition, there were required adjustments to dose, based on protocol, when aPTT exceeded the predetermined value of 55 s. Approximately 80% of STC3141 was eliminated in urine over the duration of the study, and mean renal clearance was very similar to total clearance.

4.2 | Relationship to previous studies

The implication of extracellular histones as mediators of inflammatory pathogenesis in sepsis has been evaluated for well over a decade. O'Meara et al.[7] demonstrated that SCT3141 can neutralize many of the toxic effects of extracellular histones in vitro and in animal models of disease. mCBS is a highly negatively charged molecule that was developed to counter the highly positively charged extracellular histone molecules. This is the first study of a therapy that aims at neutralizing extracellular histones in septic patients and was developed on the basis of such research.

4.3 | Implications of study findings

Our findings suggest that a continuous infusion of mCBS in critically ill septic patients is feasibly and reasonably safe. Moreover, they imply that renal function and its dynamic changes are the major determinants of clearance and plasma drug levels. In addition, they suggest that the

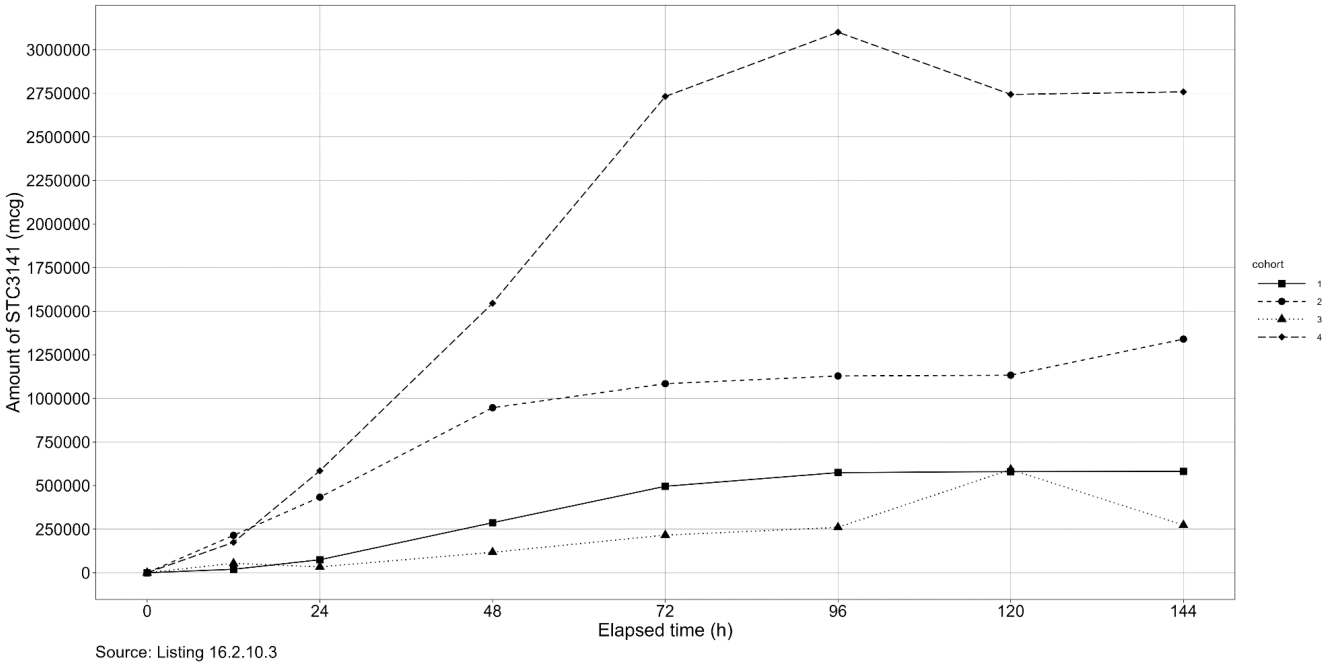

FIGURE 3 Mean (±SE) Cumulative Amount of STC3141 Excreted by Elapsed Time by cohort over time in patients receiving full PK assessment. Urine PK parameters were computed from the individual data using a Non-Compartmental Analysis (NCA) approach. The total amount of STC3141 excreted unchanged in the urine from zero until the last detectable time point (Ae0 t), fraction of STC3141 excreted unchanged in the urine (fe), and renal clearance of STC3141 (CLr). Cohort 1: STC3141 (Target C_{ss} 5 µg/mL); Cohort 2: STC3141 (Target C_{ss} 10 µg/mL), Cohort 3: STC3141 (Target C_{ss} 20 µg/mL), Cohort 4: STC3141 (Target C_{ss} 25 µg/mL). For Cohort 4, the number of datapoints at the 120 h and 144 h collection intervals was $n = 7$ compared to previous collection intervals where there were more datapoints ($n = 8$ at 96 h and $n = 10$ when time was <96 h).

study drug does not have specific adverse biochemical effects but that it prolongs aPTT. Thus, coagulation parameters should be monitored during mCBS infusion. Finally, the observed patient outcomes and the changes in circulating DNA, neutrophil extracellular traps (NETs) (measured by MPO levels), interleukin-6 (IL-6), procalcitonin, and other parameters suggest no harmful trends in the relevant biology and clinical states targeted with this intervention.

4.3.1 | Study strengths

The strengths of this study are that it describes for the first time a novel approach for the treatment of a proposed mechanism of sepsis (extracellular histones), which is considered a driver of disease morbidity and mortality. In addition, it found that STC3141 has an acceptable safety profile in this population. Moreover, the biological markers studied provide a basis for further controlled investigations of STC3141. Finally, the demonstrated tolerability, ability to deliver the product with high compliance, and PK information can help guide dosing in future studies.

4.4 | Study limitations

We acknowledge several limitations. This is not a randomized controlled trial. Thus, no inferences can be made regarding efficacy. However, understanding of the feasibility, safety, and PK of this drug is necessary prior to interventional trials. The sample size was small. However, the range of conditions was wide and the spread of renal function similarly wide, enabling an assessment of PK that is relevant to sepsis. The assessment of safety was limited to a small cohort. Thus, side effects may emerge with more patients or higher doses or both. However, this first study in critically ill humans with sepsis provides the rationale and preliminary safety data for continued cautious investigations of this agent.

5 | CONCLUSIONS

This study provides first insights into the safety, tolerability, and pharmacokinetics of STC3141 in septic patients when administered as a continuous intravenous infusion for up to 72 h in an intensive

care unit setting. Its findings provide justification and rationale for its continued investigation in future controlled trials.

AUTHOR CONTRIBITIONS

Rinaldo Bellomo was responsible for conceptualization and design, writing review and editing, and conduct of the clinical study; John Patava was responsible for conceptualization and design, writing the original draft, and project oversight; Li Ning was responsible for study conceptualization and design data analysis and manuscript writing and editing. Ruth Van Lancker, Nathalie Layios, Marijke Peetermans, Mark Plummer, Rachid Attou, Robert McNamara, Andrew Udy, Bradley Wibrow, Adam Deane, and Edward Litton were responsible for the conduct of the clinical studies and review and editing of the manuscript. Marcel Tanudji was responsible for project management and manuscript writing and editing. Fuhong Su, Zhang Zhong, and Linda Shi contributed to study oversight, data curation and review, and editing of the manuscript.

ACKNOWLEDGMENTS

The study was sponsored and fully funded by Grand Medical Pty Ltd. JP, MT, and LN were employees of Grand Medical Pty Ltd.

CONFLICT OF INTEREST STATEMENT

The Authors declare no conflict of interest.

ETHICS STATEMENT

The study received ethical approval in all study sites and was monitored by a Study Safety Monitoring Committee (SSMC) with independent review of all aspects of patient safety being reviewed by an Independent Data Monitoring Committee (IDMC) (see Appendix for member lists).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

John Patava https://orcid.org/0009-0003-1886-5424

REFERENCES

1. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(21):2063. doi:10.1056/NEJMc1312359 PMID: 24256390.
2. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest*. 1997;112:235-243.
3. Xu J, Zhang X, Pelayo R, et al. Extracellular histones are major mediators of death in sepsis. *Nat Med*. 2009;15(11):1318-1321. doi:10.1038/nm.2053
4. Chaaban H, Keshari RS, Silasi-Mansat R, et al. Inter-α inhibitor protein and its associated glycosaminoglycans protect against histone-induced injury. *Blood*. 2015;125(14):2286-2296. doi:10.1182/blood-2014-06-582759 Epub 2015 Jan 28. PMID: 25631771; PMCID: PMC4383802.
5. Zhang H, Wang Y, Qu M, et al. Neutrophil, neutrophil extracellular traps and endothelial cell dysfunction in sepsis. *Clin Transl Med*. 2023;13(1):e1170. doi:10.1002/ctm2.1170
6. Li X, Ye Y, Peng K, Zeng Z, Chen L, Zeng Y. Histones: the critical players in innate immunity. *Front Immunol*. 2022;21(13):1030610. doi:10.3389/fimmu.2022.1030610
7. O'Meara CH, Coupland LA, Kordbacheh F, et al. Neutralizing the pathological effects of extracellular histones with small polyanions. *Nat Commun*. 2020;11(1):6408. doi:10.1038/s41467-020-20231-y
8. Ge Y, Wang C, Yao C, et al. STC3141 improves acute lung injury through neutralizing circulating histone in rat with experimentally-induced acute respiratory distress syndrome. *Front Pharmacol*. 2023;22(14):1166814. doi:10.3389/fphar.2023.1166814
9. Kordbacheh F, O'Meara CH, Coupland LA, Lelliott PM, Parish CR. Extracellular histones induce erythrocyte fragility and anemia. *Blood*. 2017;130(26):2884. doi:10.1182/blood-2017-06-790519 Epub 2017 Nov 13. PMID: 29133350; PMCID: PMC5774183.
10. Shah M, He Z, Rauf A, et al. Extracellular histones are a target in myocardial ischaemia-reperfusion injury. *Cardiovasc Res*. 2022;118(4):1115-1125. doi:10.1093/cvr/cvab139
11. Popp SK, Vecchio F, Brown DJ, et al. Circulating platelet-neutrophil aggregates characterize the development of type 1 diabetes in humans and NOD mice. *JCI Insight*. 2022;7(2):e153993. doi:10.1172/jci.insight.153993

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bellomo R, Patava J, Van Lancker R, et al. A dose-adjusted, open-label, pilot study of the safety, tolerability, and pharmacokinetics of STC3141 in critically ill patients with sepsis. *Pharmacol Res Perspect*. 2024;12:e70015. doi:10.1002/prp2.70015