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CLINICAL RESEARCH

Extracorporeal Stromal Cell Therapy for Subjects With Dialysis-Dependent Acute Kidney Injury

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Introduction: The pathophysiology of acute kidney injury (AKI) involves damage to renal epithelial cells, podocytes, and vascular beds that manifests into a deranged, self-perpetuating immune response and peripheral organ dysfunction. Such an injury pattern requires a multifaceted therapeutic to alter the wound healing response systemically. Mesenchymal stromal cells (MSCs) are a unique source of secreted factors that can modulate an inflammatory response to acute organ injury and enhance the repair of injured tissue at the parenchymal and endothelial levels. This phase Ib/IIa clinical trial evaluates SBI-101, a combination product that administers MSCs extracorporeally to overcome pharmacokinetic barriers of MSC transplantation. SBI-101 contains allogeneic human MSCs inoculated into a hollow-fiber hemofilter for the treatment of patients with severe AKI who are receiving continuous renal replacement therapy (CRRT). SBI-101 therapy is designed to reprogram the molecular and cellular components of blood in patients with severe organ injury.

Methods: This study is a prospective, multicenter, randomized, double-blind, sham-controlled, study of subjects with a clinical diagnosis of AKI who are receiving CRRT. Up to 32 subjects may be enrolled to provide 24 evaluable subjects (as a per protocol population). Subjects will receive CRRT in tandem with a sham control (0 MSCs), or the low- (250×10^6 MSCs) or high-dose (750×10^6 MSCs) SBI-101 therapeutic.

Results: The study will measure dose-dependent safety, renal efficacy, and exploratory biomarkers to characterize the pharmacokinetics and pharmacodynamics of SBI-101 in treated subjects.

Conclusion: This first-in-human clinical trial will evaluate the safety and tolerability of SBI-101 in patients with AKI who require CRRT.

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AKI is a devastating syndrome that accounts for nearly 200,000 deaths annually in the United States. Approximately 1% of patients admitted to hospitals in the United States have AKI at the time of admission. AKI develops within 30 days postoperatively in approximately 1% of general surgery cases[1] and is present in up to 67% of patients in an intensive care unit (ICU).[2] The mortality associated with dialysis-dependent AKI is reported to be as high as 70%,[3,4] even with current treatment. The current standard-of-care for severe AKI includes CRRT for hemodynamically unstable patients. This offers renal support, but fails to address the underlying inflammatory processes of the disease. Single factor medications have also failed to show efficacy for AKI, perhaps due to the complex nature of the disease. Therefore, there is an urgent need for a therapy that can address the multiple pathophysiologies present in AKI and to reduce the significant morbidity and mortality associated with the disease.

Cell and tissue therapies represent a potential approach to provide the breadth of treatment that may be required to restore physiological balance during

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AKI. Supplementing renal function using tissue engineering for AKI has been explored and reviewed extensively.[5,6] Several preclinical studies have been reported using biomaterials combined with various adult or progenitor cell types to act as a bioartificial kidney graft, but reproducibly fabricating large-sized functional renal constructs at scale remains a major obstacle for clinical translation. A renal assist device (RAD) that consisted of primary human kidney cells seeded in the intraluminal space of standard dialyzers was used in conjunction with conventional CRRT. Validation studies did not show dramatic differences between the RAD and an acellular control device in changing the extent of kidney injury or survival in uremic dogs.[7] The use of the RAD was terminated during the phase IIb trial because no demonstrable survival benefit in larger patient cohorts was observed in a controlled study. It remains unclear if the hypothesis of supplementing renal function will resolve the systemic inflammation and peripheral organ dysfunction caused by AKI after the injury process has reached clinical symptomatology.

As an alternative form of regenerative medicine, MSCs have shown significant therapeutic potential to stimulate an endogenous wound healing response due primarily to an anti-inflammatory mechanism of action.[8,9] The successful use of MSCs in preclinical studies has been reported in models of injury to gastrointestinal,[10–14] skin,[15] heart,[16,17] lung,[18–21] liver,[22,23] and kidney[24] tissue, as well as in settings of immunomodulation for solid organ[25] and hematopoietic cell transplantation[26–28] in humans. These studies have revealed that the immunomodulatory activity of MSCs is primarily due to secreted factors.[29,30]

I.v. infusion of allogeneic MSCs to treat AKI has been reported in human patients,[31] and nonclinical studies have provided evidence of mouse MSCs reversing AKI by providing angiogenic and anti-inflammatory support.[24,32,33] However, clinical outcomes of i.v. MSC therapy in human AKI failed in phase IIb studies,[34] and this may be due, in part, to a lack of controlled and sustained exposure to MSCs and their secretome. Evidence suggests that dosing may be a limiting factor; i.v. injection of MSCs, although clinically practical to broadly resolve systemic inflammation, is hindered by the short-circulating half-life of MSCs,[35] limited long-term engraftment,[36] and a maximum i.v. dose that can be tolerated safely without lung toxicity.

SBI-101 is a combination product that is designed to overcome these dosing constraints by integrating allogeneic MSCs within an extracorporeal blood-contacting device (Figure 1) to fundamentally change the administration route. As opposed to i.v. MSCs that are diluted throughout the body and rapidly degraded, SBI-101 allows delivery of a stable and more durable dose of cells by exposing the blood ultrafiltrate of a subject to MSCs that are immobilized on the extraluminal side of membranes within a hollow fiber hemofiltration device that is incorporated into a CRRT circuit. The conditioned ultrafiltrate is then delivered back to the subject, which allows for controlled, sustained exposure of the MSCs to patient blood for the duration of CRRT treatment (Figure 2). SBI-101 enables MSCs to regulate inflammation and promote repair of injured tissue while keeping the MSCs confined in a device outside of the body, thereby overcoming the MSC dosage limits and duration of therapy seen during i.v. infusion. Moreover, in contrast to MSC transplantation, in which the endocrine MSC effect is temporary once cells are localized within a tissue bed and can influence only nearest-neighbor tissue cells via paracrine signaling, SBI-101 concentrates and hones this endocrine therapeutic mechanism by assuring continuous MSC–blood interactions. This paper describes the methodology for a first-in-human study of SBI-101 in subjects with dialysis-dependent AKI.

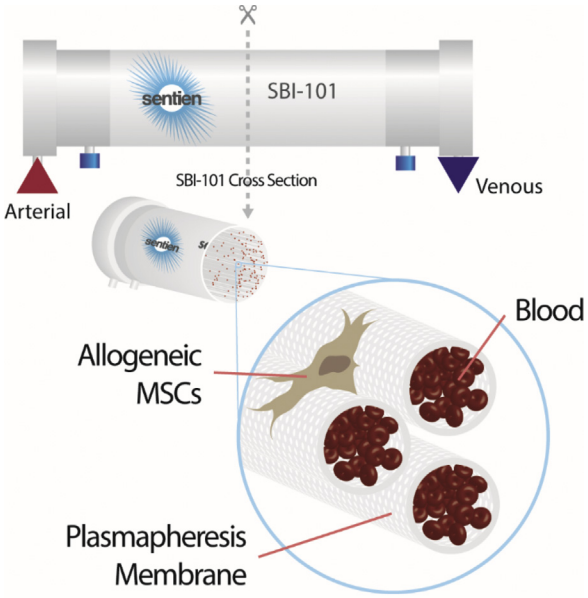

Figure 1. SBI-101: an extracorporeal stromal cell therapeutic. SBI-101 is a combination biologic and device designed to regulate inflammation and promote repair of injured tissue by exposing patient blood ultrafiltrate to allogeneic human mesenchymal stromal cells (MSCs).

METHODS AND DESIGN

Hypothesis

The tandem administration of CRRT and SBI-101 to subjects with AKI is feasible, safe, and biologically active compared with sham controls.

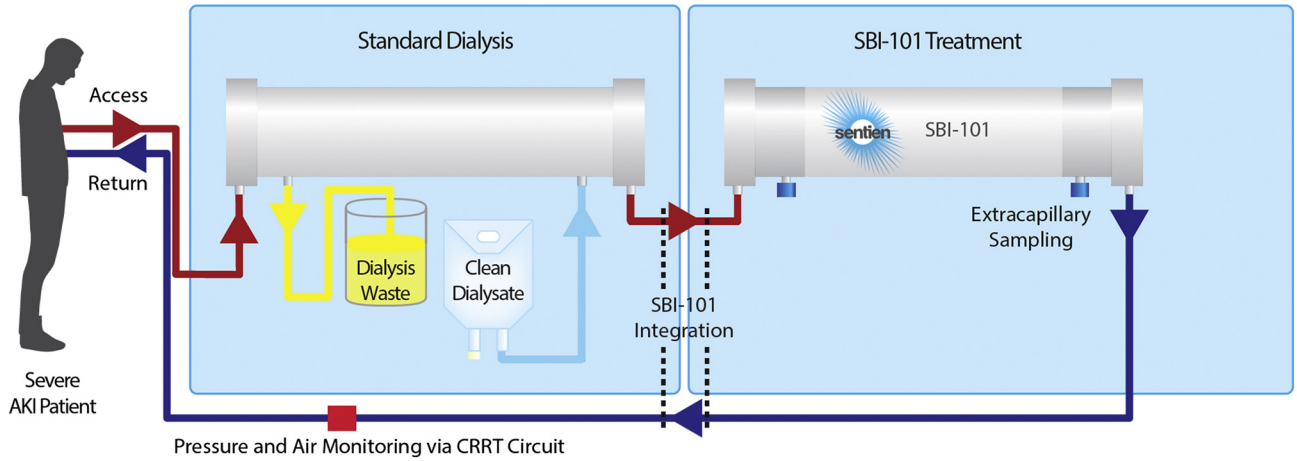

Figure 2. Integration of SBI-101 with a dialysis circuit. SBI-101 is integrated in a series after a standard continuous renal replacement therapy dialyzer to provide acute kidney injury (AKI) patients with both standard-of-care hemofiltration as well as mesenchymal stromal cell–mediated blood conditioning in a single session.

Design

This is a randomized, multicenter, sham-controlled, double-blind, dose-escalating phase Ib/IIa study in patients with AKI who are receiving CRRT. The primary objective of the study is to assess the safety and tolerability of SBI-101 in these patients. Secondary endpoints will assess efficacy as measured by overall survival, renal function, time to cessation of CRRT, and length of stay in the ICU. Exploratory analyses will characterize the effect of SBI-101 on changes in circulating inflammatory biomarkers.

Patients will be randomized to receive 1 of 3 treatments: low-dose SBI-101, high-dose SBI-101, or sham control. SBI-101 or sham control will be prepared on an as-needed basis with labeling that blinds the contents. Once prepared, it will be placed in a shipping container and transported under controlled conditions to the clinical site. SBI-101 or sham control will be integrated into the CRRT circuit (the integration of SBI-101 and sham is identical), and patients will be treated for up to 24 hours.

Up to 32 patients may be enrolled at up to 10 sites to provide 24 evaluable subjects as a per-protocol population, which is defined as those who receive at least 12 hours of SBI-101 or sham device therapy.

Day Numbering in Relation to Treatment Day

Day 0 will be the SBI-101 or sham treatment day, with the start of i.p. administration defined as time zero ($t = 0$). Treatment will last for at least 12 hours and up to 24 hours (for the per-protocol population). The start of day 1 is then defined to be 24 hours after completion of treatment.

Setting

The study will be conducted in the ICU at up to 10 hospitals in the United States.

Population

Eligible patients will be those with established AKI who require CRRT. Consent will be obtained via either the patient or a legally authorized representative.

Eligibility Criteria

Inclusion criteria are designed to identify critically ill adults with AKI who are being treated with CRRT and are likely to require CRRT during the full duration of i.p. administration to allow for product manufacture and delivery. All 6 criteria must be fulfilled.

Inclusion Criteria

1. AKI as determined by the investigator based on his/her clinical judgment
2. Able to tolerate indwelling intravascular access
3. ≥18 years of age
4. Has tolerated CRRT for at least 12 hours before treatment
5. Likely to require CRRT for at least an additional 48 hours
6. Ability to give informed consent or have a legally acceptable representative do so for them

Exclusion Criteria

Patients are excluded if they meet any of the following criteria:

1. Pregnant, planning to become pregnant, or lactating
2. Known end-stage liver disease
3. Hepatorenal syndrome
4. Acute glomerulonephritis (e.g., rapidly progressive glomerulonephritis membranoproliferative glomerulonephritis; post-streptococcal glomerulonephritis); acute interstitial nephritis (e.g., toxin- or drug- induced interstitial nephritis), or

hereditary renal disease (e.g. Alport's syndrome; polycystic kidney disease)
5. AKI due to postrenal outflow obstruction
6. Acute or chronic vasculitis of any etiology
7. Clinical evidence (e.g., febrile) suggestive of an uncontrolled or inadequately treated systemic infection at the time of randomization
8. History of a chronic systemic infection of any etiology, regardless of therapy
9. Active malignancy(ies) and/or receiving active treatment for a malignancy(ies), with the exception of nonmelanoma skin cancer
10. Subjects who, in the opinion of the investigator, are likely to require escalating doses of vasopressors to attain and/or maintain hemodynamic stability
11. History of measured estimated glomerular filtration rate $\leq$20 ml/min per 1.73 m^2 before onset of AKI
12. Imminent death expected in $<$24 hours
13. Concurrent enrollment in another interventional trial
14. Use of any investigational drug or device within the previous 30 days
15. History of solid organ or bone marrow transplantation
16. Systemic immunosuppressive therapy that has not been stabilized for $>$4 months and/or long-term corticosteroid therapy of $>$15 mg/d of prednisone or the equivalent within the past 30 days
17. Organ failure affecting $>$2 nonrenal organs
18. Platelet count $<$25,000/μl or other serious hematological abnormalities that would place subject in imminent danger of death
19. Any previous medical condition that, in the judgment of the investigator, would prevent the subject from safely participating in and/or completing all study requirements.

Screening Process

Research coordinators or physicians will screen patients for eligibility in the ICU each day. Because some of the inclusion criteria are dynamic, patients who are not initially eligible for the study may continue to be re-screened for eligibility on subsequent days. Those patients who meet all inclusion criteria and who have no exclusion criteria will be enrolled into the study.

This study has a 2-part screening process: (i) screen A: to identify patients who are diagnosed with AKI and are prescribed, but have not yet started, CRRT; and (ii) screen B: to identify AKI patients who have been initiated on CRRT. These patients will be evaluated for all other eligibility criteria, and those who are deemed eligible will be randomized into the study.

Randomization and Blinding

A total of 24 subjects will be randomized into 1 of 2 cohorts, each of which will consist of approximately 12 subjects. The low-dose cohort will consist of 8 subjects who will receive 250 $\times$ 10^6 MSCs per hollow fiber unit and 4 subjects who will receive the sham control, which is a hollow fiber unit without MSCs. The high-dose cohort will consist of 8 subjects who receive 750 $\times$ 10^6 MSCs per hollow fiber unit and 4 subjects who will receive the sham control. The low-dose cohort will be enrolled first.

The first 3 patients enrolled into each cohort will be part of a safety run-in group. These three subjects will be enrolled sequentially with a minimum 48-hour enrollment hold from completion of treatment for safety evaluation. After this safety window, the Safety Committee and, as applicable, the Data Safety and Monitoring Board, will evaluate reported safety issues and determine whether to continue enrollment or modify the protocol.

Once preliminary safety has been established, enrollment can continue at will until the cohort is completed. Select individuals designated to oversee manufacturing and patient safety will be unblinded to treatment allocation throughout the study. After completion of the low-dose cohort, a data safety monitoring board will assess safety before escalation to the high-dose cohort.

Initiation of SBI-101/Sham Therapy (Day 0, t = 0)

I.p. administration will be initiated by the insertion of SBI-101 or sham control into the CRRT circuit. Adverse event (AE), serious adverse event (SAE), and unanticipated adverse device effect (UADE) collection will begin at the time the hemofiltration circuit is taken offline for the integration of SBI-101 or sham control.

During SBI-101/Sham Therapy (Day 0, 0 $<$ t $<$ 24 Hours)

SBI-101 or sham will be administered continuously for up to 24 hours with the investigational product being sampled during the treatment period to verify MSC activity. Subjects will be continuously monitored for vitals during initiation of treatment. SBI-101 can be operated with different modalities of CRRT, in conjunction with other extracorporeal support, such as extracorporeal membrane oxygenation, and with anticoagulation per the physician's and institution's standard of practice for best care of the subject.

Cessation of SBI-101 Treatment

I.p. administration will be initiated by the insertion of SBI-101 or sham control into the CRRT circuit, and subjects may or may not continue on CRRT, at the discretion of the investigator.

Monitoring and Follow-up

The schedule of events for this study is shown in Table 1. Subjects will be evaluated for the frequency and severity of AEs, SAEs, and UADEs, as well as for efficacy and exploratory endpoints. Efficacy and exploratory endpoints will be evaluated during and up to 28 days following completion of SBI-101 and/or sham treatment. The follow-up period for safety will be 180 days. In-home nurses can be sent to facilitate follow-up visits of patients to better assure long-term follow-up compliance.

Study Endpoints

Safety and Tolerability

- Incidence and severity of AEs, SAEs, and UADEs
- Vital signs
- Physical examination
- Electrocardiograms
- Clinical chemistries, hematology, and urinalysis

Efficacy

- All-cause mortality at day 28 posttreatment with SBI-101 or sham
- Change in estimated glomerular filtration rate from baseline (start of treatment with SBI-101 or sham control) to day 28
- Change in serum creatinine and blood urea nitrogen concentration from baseline to day 28
- Use of medical services:
  - Time to cessation of CRRT
  - Length of ICU stay posttreatment with SBI-101 and sham devices
  - Number and percent of subjects who require ongoing renal replacement therapy of any type at day 28.

Exploratory

- Measures of immune cell populations, kidney injury biomarkers, and biomarkers of inflammation (blood or urine) at predose, conclusion of treatment, day 1, day 3, day 7, day 14, day 21, and day 28 posttreatment with SBI-101 or sham control.

Exploratory biomarkers will also be measured to characterize the pharmacodynamic effects of SBI-101 in treated subjects.

Sample Size

This is a first-in-human phase Ib/IIa study, and no formal calculation of sample size was performed.

Data Analysis Plan

Dose groups will be compared against the control group using unpaired *t* tests for continuous endpoints, a Wilcoxon rank sum test for ordinal outcomes, and by a Fisher's exact test for binary outcomes. Within-dose comparisons (using the subject as his/her own control) will be evaluated using a paired *t* test for continuous endpoints and using a McNemar paired comparison test for changes from baseline. An exact binomial test will be used to compute overall rates for safety, tolerability, and 28-day survival outcomes relative to a predetermined acceptability standard.

Ethical Conduct of the Study

The study will be performed in accordance with ethical principles defined by the International Council for Harmonization/Good Clinical Practice and in accordance with applicable Food and Drug Administration and institutional regulatory requirements. The trial has been registered under ClinicalTrials.gov Identifier: NCT03015623. Local institutional review board approval will be obtained at each site, and informed consent will be obtained from all participants.

DISCUSSION

This study is designed to evaluate a novel cell therapy product for AKI to address a significant unmet medical need for therapies that address the high mortality rates in dialysis-dependent AKI. MSCs are a powerful therapeutic with unrealized potential. MSCs can resolve an inflammatory reaction *in vitro* by dynamically secreting proteins,[22,37,38] lipids,[10,39] and extracellular vesicles[40] in response to activated immune cells.

This mechanism has spurred the use of MSCs as an i.v. treatment for systemic inflammatory conditions (e.g., AKI). In a phase II study that administered allogeneic MSCs as an i.v. injection, 156 patients with prerenal AKI secondary to cardiovascular surgery were enrolled before the study was terminated due to futility. No safety or tolerability issues were attributed to the MSC treatment.[34] It is likely the natural constraints of administering MSCs via direct injection have impacted translation into an effective therapy. First, MSCs have been shown to have a short half-life *in vivo*. In a phase I clinical study in which autologous MSCs were infused i.v., 52% of patients with injected cells were found to have undetectable levels of MSCs in the peripheral blood after 15 minutes, creating a limited and uncontrolled exposure of the patient to the MSC-secreted factors.[41] Second, due to potential concerns regarding pulmonary toxicity, greater exposure to the factors could not be achieved by simply increasing the number of cells infused. Therefore, i.v. MSC therapy is severely limited by initial dose constraints and a short duration of blood bioavailability. This pharmacological profile does not provide the durable, dynamic MSC–immune cell interaction that has been modeled effectively *in vitro*.[42–46] New approaches to control MSC–immune cell interactions in a stable manner may help finally unlock the true potential of MSCs by leading to

Table 1. SBI-101-01 SCHEDULE OF Events

	Screen A	Screen B		Day										
	Post-AKI diagnosis, before initiation of CRRT	After starting on CRRT	Predose baseline	Day 0 time 0−24 h (or before removal)	Day 0 time 24 h or removal of SBI-101	Day 1 + 1 post-treatment	Day 3 + 1	Day 7 ± 1	Day 14 ± 2	Day 21 ± 3	Day 28 ± 3	D/C	Day 90 ± 14	Day 180 ± 14 or WD
Module/visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed consent[a]	X	X												
Inclusion/exclusion[b]	X	X	X											
Randomization[c]		X												
Demographics		X												
Medical history	X	X												
PE or limited PA[d]		X	X		X	X	X	X	X	X	X	X	X	X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies[f]		X	X	X	X	X	X	X	X	X	X	X	X	
Clinical labs[g,r]	X	X	X	X		X	X	X	X	X	X	X	X	X
Urine tests[h]	X	X	X		X	X	X	X	X	X	X	X	X	X
Fluid input and output monitoring[i]			X	X	X	X	X	X						
ECG[j]			X		X									
SBI-101 Administration[k]				X Initiation	X Complete									
Research sampling[l]	X	X	X	X	X	X	X	X	X			X	X	X
Adverse events[m]		X	X	X	X	X	X	X	X	X	X	X*		
UADEs[n]				X	X	X								
Discharge[o]												X		
SAEs[p]				X	X	X	X	X	X	X	X	X	X	X
Outcomes[q]						X	X	X	X	X	X	X		X

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECG, electrocardiogram; HEENT, head, eyes, ears, nose, and throat; PA, limited physical assessment; PE, physical examination; SAE, serious adverse event; UADE, unanticipated adverse device effect; WD, withdrawal.

[a]Informed consent will be obtained before the conduct of any study procedures. For subjects undergoing screen A (in which subjects are identified following an AKI diagnosis but before the initiation of CRRT), and for subjects undergoing screen B, consent may be obtained directly from the study subject or from their legally authorized representative. The institutional review board will dictate which individuals shall be considered legally authorized to render consent for a subject.

[b]Eligibility will be assessed for all subjects by the investigator before randomization of a subject into the study.

[c]Subjects will be randomized 2:1 (8 low-dose cohort + 4 sham), and 2:1 (8 high-dose cohort + 4 sham).

[d]Full physical examinations will be conducted at screening and at required visits through day 7 (module 8). Thereafter, physical examinations may be limited but should include cardiac, respiratory, HEENT, and gastrointestinal systems.

[e]Vital signs include measurement of respiration, pulse, and blood pressure collected before start of treatment, then after start of SBI-101 or sham therapy at 1, 5, 10, 15, 30, and 60 minutes, then at 2, 4, 6, 8, 12, 16, 20, and 24 hours, until completion of SBI-101 or sham therapy. In addition, vitals will be collected at the time of removal from SBI-101 or sham therapy, and at 4, 6, and 12 hours postremoval. Temperature will be collected at 30 minutes and at 2, 4, 6, 8, 12, 16, 20, and 24 hours.

[f]Concomitant therapies will be collected for 3 days before investigational product administration through day 28. Concomitant medications will be collected at the discharge day if it occurs within 28 days of completion of SBI-101 or sham therapy.

[g]Clinical laboratory assessments will include chemistry panel, hematology panel (coagulation tests), and pregnancy testing for women of child-bearing potential at screen B.

[h]Urine tests will include urinalysis (urine tests).

[i]Fluid input/output monitoring: ins and outs will be collected for 12 hours before initiation of SBI-101 or sham therapy, out to a maximum of 7 days as long as the subject has an indwelling catheter and data are available.

[j]A 12-lead ECG will be recorded at predose baseline, within 1 hour of completion of SBI-101 or sham therapy. Additional ECGs should be collected for study purposes if subject has chest pain, palpitations and/or syncope, or other symptoms or arrhythmia or signs of cardiac malfunction.

[k]I.p. administration will be initiated by the insertion of SBI-101 or sham control into the CRRT circuit.

[l]Research sampling will occur at the following timepoints: screen A (as applicable) and screen B; predose baseline (venous sampling and urine collection, and a sample from the device ultrafiltrate compartment after integration with i.p. but before subject hookup); and during SBI-101 or sham administration at 30 minutes, and at 6, 12, 18, and 24 hours (or before removal); for these timepoints, only plasma will be collected and will come directly from the device. Additional research samples will be collected from venous sampling at timepoints outlined in the table, following completion of treatment. Urine collection for research will also be collected at screen A (as applicable), screen B, and at least once during SBI-101 and/or sham administration. Additional urine research samples will be collected at conclusion of treatment, and at days 1, 3, 7, 14, 21, and 28 posttreatment.

[m]Adverse events (AEs) will be collected from before SBI-101 and/or sham administration (predose baseline) through day 28 follow-up. AEs will be collected at the discharge day if it occurs within 28 days of completion of SBI-101 or sham therapy.

[n]UADEs will be collected from the time of SBI-101 and/or sham administration through 12 hours postremoval.

[o]Hospital discharge; this visit may come at any time in the time course of study visits (may be before day 28 or after); if discharge happens on the same date as an already defined study visit, then only the study visit module should be completed.

[p]SAEs will be collected from the time of SBI-101 and/or sham administration (predose baseline) through day 180.

[q]Outcomes including survival, time to cessation of CRRT, intensive care unit length of stay, and need for on-going renal replacement therapy will be assessed at all postdose study visits out to day 28.

[r]Antibodies against allogeneic mesenchymal stromal cells only at baseline, 3, and 6 months.

reproducible pharmacodynamic responses, and, ultimately, clinical benefits.

This study evaluates a new drug delivery approach to using allogeneic MSCs for the treatment of AKI. The underlying hypothesis of this study is that controlled exposure of the factors secreted by MSCs can elicit a therapeutic response that has thus far been largely unrealized in human patients. SBI-101 is designed to overcome i.v. dosing limits of MSCs by immobilizing them in an extracorporeal device to both concentrate and control the dose and duration of interaction between MSCs and blood through a semipermeable membrane. Because there is no direct physical contact of the blood or the patient to MSCs, allosensitization to MSCs or their culture media components may be eliminated; this will be evaluated in trial subjects. This platform allows highly viable MSCs to act durably outside the body, and, in response to blood inflammatory signals, delivers a potent mixture of secreted proteins and extracellular vesicles that have the capacity to target numerous pathways of regeneration, cytoprotection, and anti-inflammation concurrently.[3,4] We and others have observed in rodent models of AKI that extracorporeal MSC therapy can reduce inflammatory cascades and resolve disease after onset.[47,48] Furthermore, in a canine model of AKI, a 1-week survival advantage of SBI-101 therapy (91%; N = 11) was observed compared with untreated (50%; n = 6) or dialysis controls (70%, N = 10; Jai Radhakrishnan, Columbia University, personal communication, August 22, 2016). Importantly, due to the localization of MSCs in SBI-101 and the inclusion of sampling ports in the device design, the MSC compartment can be sampled and measured as a way to evaluate MSC activity and pharmacokinetics.

There are a few aspects of the study design that warrant specific mention. AKI patients who require CRRT are severely ill, and the decision of when to initiate CRRT in these patients can itself be a complex process.[49] In selecting the patient population for our study, we seek to better assure feasibility and to minimize heterogeneity by including only those patients who have reached a level of hemodynamic stability, which we have defined as at least 12 hours of CRRT. Further criteria will be important to better select a homogeneous population of responding patients. AKI arises from several etiologies, and although we have excluded certain forms, we generally are accepting all-comers. Clinical biomarkers for AKI can potentially aid in patient selection; however, current diagnostics (e.g., creatinine) are inadequate for accurately diagnosing AKI and determining its severity and prognosis. It was recently reported that AKI recovery rates differ among patients who have had 1 or >1 episode of AKI during a single hospitalization.[50] This is another source of patient heterogeneity of which we should be mindful as we analyze the data from this study and plan for subsequent studies.

A key strength in the design of our study is that there is minimal disruption to the existing AKI CRRT infrastructure; SBI-101 integrates as an add-on to the CRRT circuit to supplement the standard of care. Therefore, ICU staff require only minimal training to administer the product. In this study, we have included a sham control to allow for double blinding and to isolate clinical responses between MSCs and the addition of a tandem extracorporeal device.

Trial Status

Recruitment is currently active and will continue into 2018.

DISCLOSURE

BLKM, PG, BB, EL, HL, AWT, and BP are either employees or consultants of Sentien Biotechnologies, Inc. (Lexington, Massachusetts). The other author declared no competing interests.

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