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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. 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 post-operatively 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 AKI. Supplementing renal function using tissue engineering for AKI has been explored and reviewed

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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

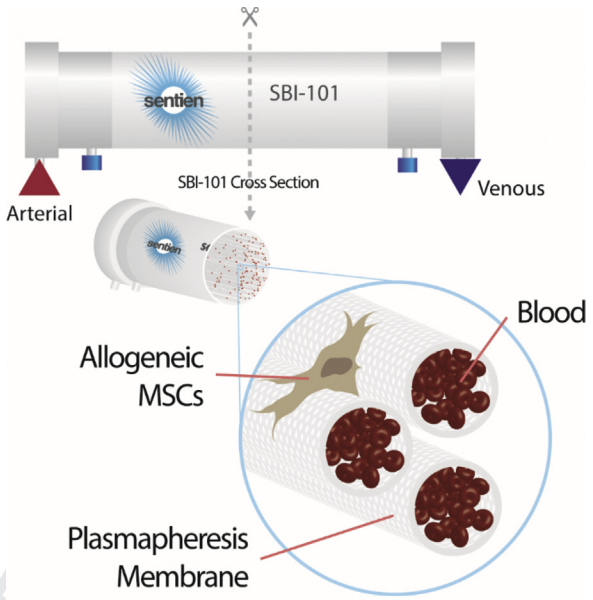

Figure 1. SBI-101: an extracorporeal stromal cell therapeutic. SBI-101 is a combination biologic and device designed to regulate inflammation and promote repair of injured tissue by exposing patient blood ultrafiltrate to allogeneic human mesenchymal stromal cells (MSCs).

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.

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.

Design

This is a randomized, multicenter, sham-controlled, double-blind, dose-escalating phase Ib/IIa study in