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The safety and efficacy of stem cells for the treatment of severe community-acquired bacterial pneumonia: A randomized clinical trial

Pierre-François Laterre [a,1,*], Miguel Sánchez García [b], Tom van der Poll [c], Xavier Wittebole [l], Fernando Martínez-Sagasti [b], Gonzalo Hernandez [d], Ricard Ferrer [e,f], Jesus Caballero [g,h], Kathy-Ann Cadogan [i,1], Adam Sullivan [i,1], Barbara Zhang [i], Olga de la Rosa [j], Eleuterio Lombardo [j], Bruno François [k,**], on behalf of the SEPCELL Study Group [2]

[a] Department of Intensive Care Medicine, CHR Mons-Hainaut, Mons, Belgium
[b] Critical Care Department, Hospital Clínico San Carlos, Madrid, Spain
[c] Amsterdam University Medical Centers, University of Amsterdam, Center of Experimental and Molecular Medicine and Division of Infectious Diseases, Amsterdam, Netherlands
[d] Intensive Care Department, Toledo University Hospital, Toledo, Spain
[e] Intensive Care Department, Vall d'Hebron University Hospital, Barcelona, Spain
[f] Shock, Organ Dysfunction and Resuscitation (SODIR) Research Group, Vall d'Hebron Institut de Recerca, Barcelona, Spain
[g] Intensive Care Department, Arnau de Vilanova University Hospital, Lleida, Spain
[h] Grup de Recerca Medicina Intensiva, Institut de Recerca Biomèdica de Lleida Fundació Dr Pifarré, IRB Lleida, Lleida, Spain
[i] Takeda Pharmaceuticals, Cambridge, MA, USA
[j] Takeda Madrid, Cell Therapy Technology Center, Tres Cantos, Spain
[k] Intensive care unit and Inserm CIC 1435 & UMR 1092, Limoges University Hospital, Limoges, France
[l] Department of Intensive Care Medicine, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, UCLouvain, Brussels, Belgium

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ABSTRACT

Purpose: Evaluate the safety profile of expanded allogeneic adipose-derived mesenchymal stem cell (eASC) for the treatment of severe community-acquired bacterial pneumonia (CABP).
Materials and methods: Randomized, multicenter, double-blind, placebo-controlled, phase 1b/2a trial. Patients with severe CABP were enrolled to receive intravenous infusions of Cx611 or placebo. The primary objective was safety including hypersensitivity reactions, thromboembolic events, and immunological responses to Cx611. The secondary endpoints included the clinical cure rate, ventilation-free days, and overall survival (Day 90).
Results: Eighty-three patients were randomized and received infusions (Cx611: $n = 42$]; placebo: $n = 41$]. The mean age was similar (Cx611: 61.1 [11.2] years; placebo: 63.4 [10.4] years). The number of AEs and treatment-emergent AEs were similar (243; 184 and 2; 1) in Cx611 and placebo respectively. Hypersensitivity reactions or thromboembolic events were similar (Cx611: $n = 9$; placebo: $n = 12$). Each study arm had similar anti-HLA antibody/DSA levels at Day 90. The clinical cure rate (Cx611: 86.7%; placebo: 93.8%), mean number of ventilator-free days (Cx611: 12.2 [10.29] days; placebo: 15.4 [10.75] days), and overall survival (Cx611: 71.5%; placebo: 77.0%) did not differ between study arms.
Conclusion: Cx611 was well tolerated in severe CABP. These data provide insights for future stem cell clinical study designs, endpoints and sample size calculation.
Trial registration: NCT03158727 (retrospectively registered: May 09, 2017).
Full study protocol: https://clinicaltrials.gov/ProvidedDocs/27/NCT03158727/Prot_000.pdf

Abbreviations: AEs, adverse events; DSAs, donor-specific antibodies; eASCs, expanded allogeneic adipose-derived stem cells; HLA, human leukocyte antigen; ICU, intensive care unit; IMP, investigational medicinal product; MSCs, mesenchymal stem cells; SD, standard deviation; CABP, community-acquired bacterial pneumonia; TEAEs, treatment-emergent adverse events; TESAEs, treatment-emergent serious adverse events..

* Corresponding author at: Department of Intensive Care Medicine, CHR Mons-Hainaut, Mons, Belgium.
** Corresponding author at: Intensive care unit, Limoges University Hospital, Limoges, France.
E-mail addresses: pierrefrancoislaterre@gmail.com (P.-F. Laterre), bruno.francois@chu-limoges.fr (B. François).

[1] At the time of the study.

[2] **SEPCELL Study Group:** Dr. Thierry Boulain, Dr. Ana Rosa Ochagavía Calvo, Dr. Sulamita Caarvalho-Brugger, Dr. Raúl de Pablo, Dr. Thierry Dugernier, Dr. Enrique Piacentini Gómez, Dr. Silvia Iglesias-Moles, Dr. Armelle Mathonnet, Dr. Ferhat Meziani, Dr. Miguel Ferrer Monreal, Dr. Alejandro Hugo Rodriguez Oviedo, Dr. Gaëtan Plantefeve, Dr. Paula Ramírez, Dr. Jean Reignier, Dr. Silvia Rodríguez-Ruiz, Dr. Herbert Spapen, Dr. Aihem Yehia, Dr. Marius Zolubas.

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1. Background

Bacteria are the most common causative agent of community-acquired pneumonia, which has an annual incidence of 1.07–1.2 per 1000 person-years in European adults, rising to 14 per 1000 person-years in those older than

65 years [1,2]. Severe community-acquired bacterial pneumonia (CABP) is a life-threatening condition characterized by respiratory failure or symptoms of sepsis or septic shock [3]. Patients require supportive therapy (e.g. vasopressors and/or mechanical ventilation) within an intensive care environment, in which 28-day mortality is up to 29% [4]. Current treatment options include antibiotics, systemic corticosteroids, and hemodynamic and respiratory support [5-7]. However, prognosis remains poor [8] and other treatments are urgently required.

Sepsis is characterized by a dysregulated host response to infection [9]. Mesenchymal stem cells (MSCs) are multipotent, non-hematopoietic stem cells with immunomodulatory and anti-microbial effects [10-12] that have been investigated for therapeutic use in multiple inflammatory diseases [13-19]. In animal models of severe CABP, administration of MSCs improved bacterial clearance from the lungs and overall survival when compared with controls [20,21]; moreover, reductions in acute lung injury, organ dysfunction, and pro-inflammatory cytokine levels have been reported [12,20]. Furthermore, in phase 1 and 2 clinical trials, MSCs were well tolerated in patients with acute respiratory distress syndrome [15,16], which is frequently associated with pneumonia [22]. Taken together, these studies suggest that MSCs may have therapeutic potential in patients with severe CABP.

MSCs can be isolated from multiple adult tissues, including bone marrow and adipose tissue. Compared with those derived from bone marrow, adipose-derived MSCs are about 500-fold more abundant and, because they lack natural killer cell-activation receptors, are less susceptible to natural killer cell-mediated lysis [23,24]. This potentially prolongs their presence in tissues and allows them to exert immunosuppressive effects [23,25]. Therefore, the use of expanded allogeneic adipose-derived mesenchymal stem cells (eASCs) in patients with severe CABP-related sepsis may offer a novel mechanism of action to address the underlying immune dysregulation.

Cx611 is an intravenously administered product comprising eASCs. Non-clinical studies have shown Cx611 to have anti-inflammatory effects in vitro and in vivo, limited biodistribution, and low toxicity [26-28]. From an allogeneic viewpoint, Cx611 has a low capacity to trigger host immune responses [27,29-31]. In a human model of endotoxemia, Cx611 was well tolerated and elicited pro- and anti-inflammatory responses, enhanced coagulation, and reduced the fibrinolytic response [32].

Here we describe the safety outcomes of SEPCELL, a phase 1b/2a study designed to evaluate the safety and efficacy of Cx611 in patients with severe CABP. This is the first study to report the use of eASCs in CABP-related sepsis. The data generated from this study will advance our understanding of Cx611 with respect to mode of action, safety, and efficacy and will be critical for the design of future confirmatory clinical investigations.

2. Methods

SEPCELL (NCT03158727) was a randomized, multicenter, double-blind, placebo-controlled, phase 1b/2a study designed to assess the safety of intravenous Cx611 as adjunctive therapy in patients with severe CABP. The study was conducted in 20 sites across Belgium, France, Lithuania, and Spain from January 30, 2017 to July 7, 2020.

2.1. Objectives

The primary objective was to evaluate the safety of intravenous Cx611, including adverse events (AEs) and host immune responses against the administered cells, during the first 90 days after 2 infusions of Cx611 (one infusion on Day 1 and one infusion on Day 3). The secondary objective was to explore the efficacy of Cx611 in patients with severe CABP.

2.2. Study design

The study comprised a screening period (up to 18 h), a 3-day treatment period, and two follow-up periods (up to Day 90 and Day 730; Additional file 1: Fig. S1). Patients were randomized 1:1 to receive two central line infusions of Cx611 (1.6×10^8 cells per infusion) or placebo (CryoStor CS10 and Ringer's lactate) administered within 18 h of CABP severity criteria onset and repeated on day 3. The end of the study was defined as the patient's last scheduled visit (Day 90) or study discontinuation before Day 90 ($\pm$ 4 days). Safety data were collected by a phone call up to Day 730 as requested by the regulator. When primary endpoint data were available, a blinded adjudication committee of experts assessed patient evaluability and agreed the clinical response assessments and the patient assignment process. A detailed study design has been published previously [33]. Additional details on study design, pathogen identification and diagnostic tests, and selection of study doses can be found in Additional file 1: eMethods.

2.2.1. Randomization and blinding

Patients were randomized using a pre-established randomization list that was stratified to balance for shock and/or invasive mechanical ventilation between the investigational medicinal products (IMP; Cx611 or placebo). After screening and verification of patient eligibility, investigators requested a randomization authorization number from the Saint Luc University Clinical Coordinating Centre. The investigator (or delegate) then contacted the interactive response technology and a randomization number was allocated to each patient. This number was linked to a treatment arm and a specified unique medication number for the package of IMP to be dispensed to the patient at each administration.

Participants, care providers, investigators, and outcome assessors were blinded to treatments, which were prepared by unblinded personnel in a blinded location. When reconstituted, Cx611 and placebo formulations were masked to maintain blinding.

2.2.2. Protocol amendments and rationale

A list of protocol amendments has been previously published [33] and is presented in Additional file 1: Table S1.

2.3. Participants

Adults (aged 18–80 years) admitted to the intensive care unit (ICU) with a clinical diagnosis of severe CABP were included. Full inclusion/exclusion criteria are available in Additional file 1: eMethods.

2.3.1. Safety

Treatment-emergent AEs (TEAEs) and AEs were measured throughout the study. To monitor for thromboembolic events, a lower limb ultrasonography was scheduled for Days 5 or 6. Blood samples were collected to assess the presence of anti-HLA antibodies and donor-specific antibodies (DSAs) on Days 1 (pre-dose), 14, and 90 or study discontinuation. Changes from baseline in vital signs, electrocardiograms, and laboratory assessments (hematology and coagulation, biochemistry, and urine analysis) were assessed at various timepoints during the study. An independent data monitoring committee reviewed safety data throughout the study. Details of safety assessments are presented in Additional file 1: Table S2.

2.3.2. Clinical outcomes

Clinical outcomes included severe CABP clinical response (including clinical cure) at predefined time points (Days 8–10, Days 14 $\pm$ 2, Day 29 $\pm$ 2, and at early termination [where applicable]), invasive mechanical ventilation-free and vasopressor-free days over 28 days, and survival

(overall survival [Day 90 or early discontinuation date if before Day 90], 28-day severe CABP-associated mortality, and 28-day all-cause mortality). Details of clinical outcomes are presented in Additional file 1: Table S3.

2.4. Statistical analysis

To fulfil the objectives of this study, recruitment of 180 patients (i.e. 90 patients per group) was deemed sufficient. For safety endpoints (between-group difference in percentage of patients with at least one adverse experience), the precision of the estimate (1/2 width of the 95% confidence interval [CI]) is equal to 15%. The calculation assumes a percentage of patients with at least one adverse experience approximately equal to 50%. For the efficacy endpoint "Between-group difference in number of ventilator-free days", the precision of the estimate (1/2 width of the 95% CI) is equal to 3, assuming a standard deviation equal to 10 for the variable number of ventilator-free days. Owing to ongoing recruitment challenges throughout the study, enrollment was closed early; 92 patients were enrolled in total, (Additional file 1: Table S1) which was too low to detect differences in efficacy signals. The safety population comprised all randomized patients who received at least 1 dose of the IMPs (Cx611 or placebo) and was used for safety and clinical outcome analyses. All data were presented as summary statistics and analyses were performed using SAS version 9.3 or later (SAS, USA).

3. Results

3.1. Patient disposition, baseline demographics, disease characteristics

In total, 92 patients were screened, of which 84 were randomized, and 83 received the IMP (Cx611: $n = 42$; placebo: $n = 41$) and comprised the safety population. Overall, 78 patients (94%) received their two scheduled infusions (n = 39 in each study arms), and 48 patients (57.8%) completed the study according to the protocol (Cx611: $n = 23$ [54.8%]; placebo: $n = 25$ [61%]). The primary reason for study discontinuation was death (total $n = 23$; Cx611: $n = 12$ [28.6%]; placebo: $n = 11$ [26.8%]; Fig. 1).

Demographic and disease characteristics were well balanced between the study arms (Table 1). At baseline, Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II scores were comparable between the study arms. Microbiology findings were confirmed in 35 patients in the Cx611 arm and 34 patients in the placebo arm. Of these, *S. pneumoniae* was confirmed in 52 patients using a pneumococcal urine antigen test and in 4 patients by Gram staining and culture after bronchoalveolar lavage, mini-bronchoalveolar lavage/protected specimen brush and/or endotracheal aspiration, and sputum

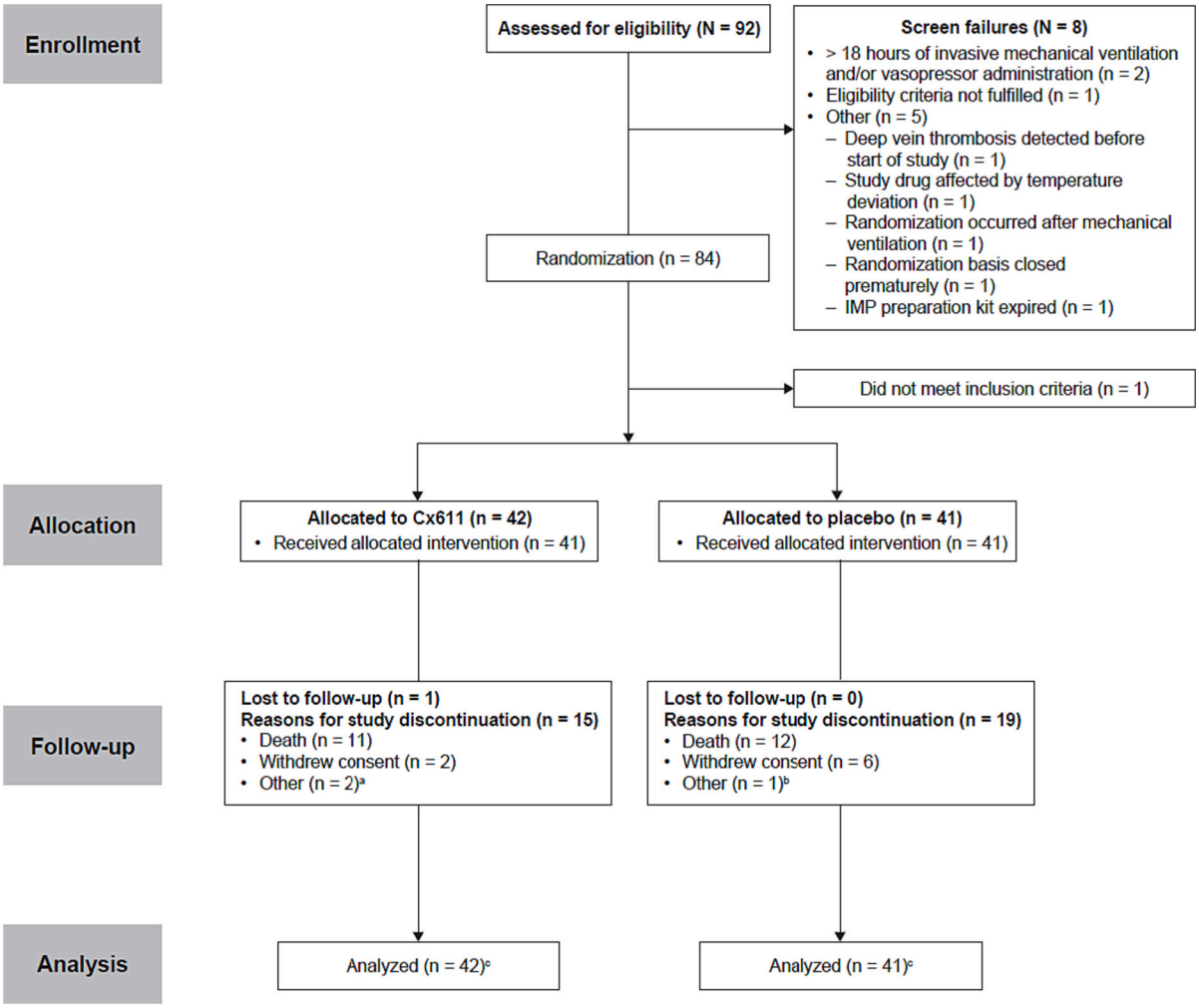

Fig. 1. CONSORT flow diagram.
[a]One patient did not have a Day 90 (± 4 days) visit by mistake.
[b]Two patients did not want to return to the hospital for their study visit.
[c]All patients who received at least one dose of the IMP were included in the safety and clinical outcome analyses.
IMP = investigational medicinal product.

production for nonventilated patients. In total, 77 patients (Cx611: n = 38 [90.5%]; placebo: n = 39 [95.1%]) reported the use of concomitant medications for severe CABP. The most frequently reported medications included β-lactam antibacterials (69.9%), macrolides, lincosamides, and streptogramins (total: 48.2%), quinolone (41.0%), and systemic corticosteroids (37.3%; Additional file 1: Table S4).

3.2. Safety

Overall, 427 TEAEs were recorded: 243 in the Cx611 arm and 184 in the placebo arm (Table 2). Most TEAEs were considered mild in severity and 27 were considered related to the IMP (Cx611: n = 18; placebo: n = 9). The most frequently reported TEAEs by patient were anemia (n = 17), atrial fibrillation (n = 10), constipation, diarrhea, and hypokalemia (n = 9 each). Only hypernatremia was less frequently reported in the Cx611 arm than the placebo arm (n = 1 vs n = 6, respectively; Additional file 1: Table S5).

In total, 78 treatment-emergent serious adverse events (TESAEs) were reported during the study (Cx611: n = 43; placebo: n = 35). Most TESAEs (n = 75) were considered moderate or severe. The most frequently reported TESAEs were multiple organ dysfunction syndrome (Cx611: n = 1; placebo: n = 4), hypoxia (Cx611: n = 2; placebo: n = 2), and worsening respiratory conditions (Cx611: n = 1; placebo: n = 3; Additional file 1: Table S6). Overall, the number of reported TEAEs and TESAEs were similar between the study arms (Additional file 1: Tables S5 and S6). Importantly, there was no imbalance in reports of AEs of special interest (thromboembolic events or hypersensitivity reactions) between the study arms (Table 3). There were 25 deaths during the study (Cx611: n = 13; placebo: n = 12).

For anti-HLA antibody/DSA assessments, patients were considered pre-sensitized (i.e. pre-existing anti-HLA class I and class II antibodies at Day 1) or naïve (i.e. no detectable levels of preexisting anti-HLA class I and class II antibodies at Day 1) and were evenly distributed between study arms (Cx611: n = 7 and n = 35; placebo: n = 9 and n = 33, respectively).

In the pre-sensitized population, five patients in each treatment group had detectable anti-HLA antibody levels at Day 14. Owing to missing samples, it was not possible to establish anti-HLA antibody titer stability at Day 90 (± 4 days) in the Cx611 arm; however, four patients in the placebo group maintained anti-HLA antibody titers. A similar number of naïve patients in each study arm had anti-HLA antibodies/DSAs by Day 14 (Cx611: n = 3; placebo: n = 1), of which most (Cx611: n = 2 [1 sample was unavailable]; placebo: n = 1) had cleared by Day 90. Overall, titers of anti-HLA antibodies/DSAs were similar across treatment arms throughout the study (Table 4).

There were no identifiable patterns observed regarding vital signs (blood pressure, respiratory rate, core temperature heart, and

Table 1
Patient demographics and baseline characteristics.

	Cx611 (n = 42)	Placebo arm (n = 41)
Age, years, mean (SD)	61.1 (11.2)	63.4 (10.4)
Female, n (%)	14 (33.3)	15 (36.6)
Race, n (%)		
Caucasian	28 (66.7)	31 (75.6)
Other	2 (4.8)	4 (9.8)
Missing	12 (28.6)	6 (14.6)
APACHE II score[a]		
n	41	40
Mean (SD)	20.0 (7.8)	18.9 (6.2)
95% CI	17.5–22.4	16.9–20.9
CURB-65		
n	41	41
Mean (SD)	2.8 (1.0)	2.9 (1.0)
95% CI	2.5–3.2	2.6–3.2
Total SOFA score[a]		
n	42	41
Mean (SD)	8.5 (3.0)	7.9 (2.4)
95% CI	7.6–9.5	7.1–8.6
Microbiology findings		
n	35	34
Pneumococcal urine antigen test		
n	40	39
Positive, n (%)	27 (67.5)	25 (64.1)
Negative, n (%)	13 (32.5)	14 (35.9)
Reasons for a pneumococcal urine antigen test not being completed		
n	2	2
Blood culture positive, n (%)	0 (0.0)	1 (50.0)
Mistake, n (%)	1 (50.0)	0 (0.0)
Not collected, n (%)	1 (50.0)	0 (0.0)
Not done, n (%)	0 (0.0)	1 (50.0)

APACHE II = Acute Physiology and Chronic Health Evaluation II, CI = confidence interval, CURB-65 = confusion, urea, respiratory rate, blood pressure, and 65 years of age or older, SD = standard deviation, SOFA = Sequential Organ Failure Assessment.

Table 2
Summary of TEAEs.

	Cx611 (n = 42)	Placebo arm (n = 41)
Patients with TEAEs, n (%)	40 (95.2)	37 (90.2)
Patients with immediately reportable events, n (%)[a]	26 (61.9)	24 (58.5)
Patients with any TESAE, n (%)	24 (57.1)	20 (48.8)
Patients with TEAEs leading to death, n (%)	11 (26.2)	9 (22.0)
Patients with any TEAE related to treatment, n (%)	9 (21.4)	8 (19.5)
Adverse events of special interest, n (%)	9 (21.4)	12 (29.3)
Patients with any adverse event of special interest, n (%)	7 (16.7)	9 (22.0)
Patients with any TEAE leading to investigational medicinal product discontinuation, n (%)	2 (4.8)	1 (2.4)

No differences were observed between groups.
IMP = investigational medicinal product, TEAE = treatment-emergent adverse event, TESAE = treatment-emergent serious adverse event.
[a] Immediately reportable events were defined as those subject to immediate notification (within 24 h) and included but were not limited to serious adverse events, pregnancy of study patient (or female partner of a study patient), medication errors (namely overdose) leading to a suspected adverse reaction, accidental exposure, adverse event which leads to IMP discontinuation, and an adverse event of special interest.

Table 3
Adverse events of special interest (thromboembolic events and hypersensitivity reactions).

Preferred term	Cx611 arm (n = 42)		Placebo arm (n = 41)	
	AEs, n	Patients, n (%)	AEs, n	Patients, n (%)
Deep vein thrombosis	3	3 (7.1)	5	5 (12.2)
Cerebrovascular accident	2	2 (4.8)	0	0 (0.0)
Atrial thrombosis	1	1 (2.4)	0	0 (0.0)
Cerebral artery embolism	1	1 (2.4)	0	0 (0.0)
Device-related thrombosis	1	1 (2.4)	0	0 (0.0)
Pulmonary embolism	1	1 (2.4)	2	2 (4.9)
Anaphylactic shock	0	0 (0.0)	1	1 (2.4)
Jugular vein thrombosis	0	0 (0.0)	1	1 (2.4)
Rash macular	0	0 (0.0)	1	1 (2.4)
Venous thrombosis	0	0 (0.0)	1	1 (2.4)
Venous thrombosis limb	0	0 (0.0)	1	1 (2.4)

AEs were counted by Preferred Term once for each patient. Codification was done with MedDRA version 19.1.
AE = adverse event.

respiratory rate) or electrocardiogram data (data not shown). No identifiable differences in laboratory assessments (hematology and coagulation, biochemistry, and urine analysis) were observed between the study arms.

3.3. Clinical outcomes

In total, 39 patients with severe CABP had a clinical response classified as cure at Days 8–10, 48 patients at Day 14 ± 2, and 56 patients at Day 29 ± 2 (Additional file 1: Table S7). Conversely, there were 14 patients with clinical response failures not leading to death at Days 8–10, 9 patients at Day 14 ± 2, and 2 patients at Day 29 ± 2. No difference in time to clinical cure was observed between the study arms.

The mean (SD) number of invasive mechanical ventilation-free days over 28 days was similar between the study arms (Cx611: 12.2 [10.29] days; placebo: 15.4 [10.75] days), and a similar result was observed for vasopressor-free days over 28 days (Cx611: 18.5 [10.73] days; placebo: 19.2 [9.99] days). Additionally, 28-day all-cause mortality (Additional file 1: Fig. S2), overall survival (Additional file 1: Fig. S3), and 28-day severe CABP-associated mortality (i.e. death due to index pneumonia; data not shown) were similar between study arms.

The mean (SD) duration of antibiotic treatment was similar between the Cx611 and placebo arms (10.6 [7.72] days and 9.6 [5.82] days, respectively). Similarly, the study arms had equivalent lengths of stay in the ICU (mean [SD]: 21.7 [25.90] days vs 16.1 [14.32] days) and in hospital (33.2 [36.72] days vs 24.9 [17.19] days). The number of ICU-free days over 28 days (mean [SD]) was also similar between the study arms (8.5 [9.01] days vs 12.1 [9.74] days, respectively). In addition, no differences were observed between Cx611 and placebo with respect to the time to recurrence/reinfection of pneumonia after clinical cure, discharge from ICU, or discharge from hospital (data not shown).

4. Discussion

Severe CABP is characterized by local and systemic inflammation and is associated with high mortality and significant morbidity [4,34]. Dysregulated host immune responses can lead to organ dysfunction (e.g. renal failure), septic shock, and death [34]; therefore, therapeutic interventions that modulate immunological responses in this patient population are of interest [35]. Current immunomodulatory interventions include macrolide antibiotics, corticosteroids, and intravenous immunoglobulins [36], but new therapies are urgently required to improve patient outcomes. Novel immunomodulatory interventions under investigation include toll-like receptor agonists [37], protease-activated receptor antagonists [38], neutrophil elastase inhibitors [39], anti-toxin agents [40], and MSCs [12].

Table 4
Titers of anti-human leukocyte antigen antibodies and donor-specific antibodies by visit.

Assessment	Cx611 arm (n = 42)	Placebo arm (n = 41)
Donor eASCs		
Visit 1 (Day 1), number of positive samples	7	8
MFI (antibody titer), mean (SD)	1.1 (1.21)	2.3 (2.25)
Donor-specific antibodies		
Visit 1 (Day 1), n	4	6
MFI (antibody titer), mean (SD)	5736.8 (3394.4)	14,758 (12730)
Visit 9 (Day 14 ± 2 days), n	5	4
MFI (antibody titer), mean (SD)	9765.0 (7323.9)	10,018 (3897.5)
Visit 11 (Day 90 ± 4 days), n	4	4
MFI (antibody titer), mean (SD)	19,262 (10834)	24,722 (31579)
Anti-HLA antibodies		
Visit 1 (Day 1), n	7	8
MFI (antibody titer), mean (SD)	52,806 (89833)	119,961 (143482)
Visit 9 (Day 14 ± 2 days), n	9	6
MFI (antibody titer), mean (SD)	28,672 (47862)	83,520 (67512)
Visit 11 (Day 90 ± 4 days), n	6	7
MFI (antibody titer), mean (SD)	130,747 (197754)	173,302 (273403)

eASCs = expanded allogeneic adipose-derived stem cells, HLA = human leukocyte antigen, MFI = median fluorescence intensity, SD = standard deviation.

Mesenchymal stem cells have both immunomodulatory and antibacterial properties and can enhance bacterial clearance and survival in animal models when compared with controls; therefore, they are of interest for the treatment of severe CABP [20]. In this study, we reported the results of SEPCELL, the first placebo-controlled trial to assess the safety and efficacy of eASCs in severe CABP. This study demonstrated that Cx611 is well tolerated in patients with severe CABP. Overall, the number of reported TEAEs, TESAEs, and AEs of special interest were similar between the study arms.

Allogeneic MSCs can elicit anti-donor immune responses in recipients, such as the production of DSAs [41,42], which may lead to stem cell rejection and subsequent treatment failure [43]. In this study, we observed an increasing titer of DSAs over the study period in patients treated with Cx611 compared with those who received placebo. However, owing to the number of patients in this study, statistical significance could not be determined. There is a need for larger studies assessing the potential impact of the generation of DSAs on patient outcomes after treatment with eASCs.

MSCs administered intravenously have been associated with procoagulant activity and therefore an increased risk of thrombogenic events [44]. Importantly, no differences in thromboembolic events between the Cx611 and placebo arms were observed in this study. Additionally, no changes from baseline in vital signs or laboratory safety evaluations were observed.

Owing to early closure of enrollment, the number of patients recruited into the study was too low to detect differences in clinical outcomes; therefore, it was not possible to draw inferences from this study regarding the effect of Cx611 on clinical outcomes. Exploratory biological analyses from blood samples collected during the study, including cell response assessments (e.g. analysis of cell proliferation, activation status, and secretion of peripheral blood mononuclear cells in response to stimulation), RNA expression profiles of leukocytes and protein biomarker levels (e.g. tumor necrosis factor-α and interleukin [IL]-1β, IL-6, IL-8, IL-10, soluble triggering receptor expressed on myeloid cells-1, and C-reactive protein) in leukocytes are ongoing and will be published separately.

This study has several limitations. Firstly, the use of a fixed dose in this study may have limited the observable therapeutic benefit of eASCs and the dose could have been adjusted to the optimal body weight. Future studies may consider altering the timing between interventions, administering >2 doses and earlier in the clinical course of severe CABP, or using a dose-escalation strategy to assess clinical outcomes. Additionally, no data are available for the number of patients undergoing continuous renal replacement therapy, which can be used to treat sepsis-related renal failure via the removal of inflammatory mediators and stabilization of the circulation [45]. Lower limb compression ultrasonography assessments were scheduled as part of the study design, but upper limb ultrasound, computerized tomography, and cardiac ultrasound were conducted at the discretion of the treating physician, meaning that some thromboembolic events may have been missed. Finally, in this multicenter study, patients may be subject to heterogeneous clinical practices. This is particularly relevant to ICU treatment where a uniform approach to care may not be observed across sites, potentially confounding results. However, owing to the strict inclusion criteria and the use of study sites able to conduct studies in critically ill patients and employ a similar standard of care for patients with severe CABP, the risk of treatment heterogeneity was minimized.

5. Conclusions

In conclusion, this study shows that intravenous infusion of Cx611

was well tolerated in patients admitted to ICU with severe CABP. Overall, there were no significant outcome benefits seen, although the limited number of patients recruited makes it difficult to draw definite conclusions on the potential benefit of MSCs in CABP and requires further investigation. Importantly, these data provide crucial insights that will inform the design of future clinical studies that utilize stem cells with respect to endpoints and sample size.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (E6 version 4.8) and all applicable local regulations. Independent ethics committees reviewed and approved the study protocol, protocol amendments, and other study-related documents. Written consent was sought from all patients, their legal representative, or next of kin. If a legal representative or relative provided consent on the patient's behalf owing to poor health, informed consent to continue participation or withdraw from the study was sought from the patient as soon as they were conscious and able to consent.

Consent for publication

Not applicable.

Author contributions

Kathy-Ann Cadogan, Olga de la Rosa, Bruno François, Miguel Sánchez García, Pierre-François Laterre, Eleuterio Lombardo and Tom van der Poll: conceptualization. Jesus Caballero, Olga de la Rosa, Ricard Ferrer, Bruno François, Miguel Sánchez García, Gonzalo Hernandez, Pierre-François Laterre, Fernando Martínez-Sagasti, and Xavier Wittebole: investigation. Kathy-Ann Cadogan, Olga de la Rosa, Bruno François, Miguel Sánchez García, Gonzalo Hernandez, Pierre-François Laterre, Adam Sullivan, Xavier Wittebole and Barbara Zhang: formal analysis. All authors: Writing original draft, review and editing. All authors approved the final version of the manuscript for publication.

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Authors statement

I certify that all authors have participated to the study design, data collection, analysis, interpratation of the data and have reviewed and approved the writing of the manuscript.

Declaration of Competing Interest

PFL has received honorarium from Takeda for blinded adjudication activities related to the SEPCELL trial and received consulting fees with Inotrem and Adrenomed.

MSG has received honorarium from Takeda for blinded adjudication activities related to the SEPCELL trial.

TvDP has received honorarium from Takeda for blinded adjudication activities related to the SEPCELL trial and received consulting fees from Pluristem outside the trial (both paid to Amsterdam UMC).

XW was part of the clinical coordinating center located at Cliniques universitaires Saint-Luc, which assessed all patients' eligibility.

FMS declares no conflict of interest.

GH has received speaking fees and travel expenses from Fisher & Paykel Healthcare.

RF has received consulting fees with Grifols, MSD, Pfizer, Shionogi, Gilead, Baxter, GSK, Menarini, and Boehringer outside the trial.

JC has no conflict of interest.

KAC and **AS** were salaried employees of Takeda Pharmaceuticals, Cambridge, MA, USA at the time of the study.

BZ is a salaried employee of Takeda Pharmaceuticals, Cambridge, MA, USA.

EL and OdlR are salaried employees of Takeda Madrid, Cell Therapy Technology Center, Tres Cantos, Spain.

BF has received honorarium from Takeda for blinded adjudication activities related to the SEPCELL trial and consulting fees with Aridis, Enlivex, Inotrem, AM-Pharma, and GSK outside the trial.

Data availability

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual patient data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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The authors would like to acknowledge the valued contribution of the following investigators to the SEPCELL study:

Investigator	Address
Dr Christine Colienne, Dr. Diego Castanares Zapatero, Dr. Ludovic Gerard, Dr. Philippe Hantson, and Dr. Virginie Montiel	Clinique Universitaire Saint-Luc, 10 avenue Hippocrate, 1200 Bruxelles
Dr Jean-Pierre Pelgrim, Dr. Marco Vinetti, Dr. Nicolas De Schryver, and Dr. Sophie Terneu	Clinique Saint-Pierre Avenue Reine Fabiola, 9, 1340 Ottignies
Dr Bernard Lambermont and Dr. Philippe Morimont	CHU Sart Tilman Avenue de l'hopital, n°1, 4000 Liège
Dr Elisabeth De Waele, Dr. Joris Bart Troubleyn, Dr. Jouke De Regt and Dr. Patrick Honore	Address: UZ Brussel, Laarbeeklaan 101, 1090 Brussels
Dr Manuel Álvarez González, Dr. Mercedes Nieto Cabrera, and Dr. Mª José Jiménez	Hospital Clínico, San Carlos, UCI 2a planta Norte, C/Prof Martín Lagos, s/n, 28040 Madrid
Dr Antoni-Jordi Betbesé Roig, Dr. Maria Torrents Sonet, Dr. Mario Antonio Alfaro Farias, Dr. Miguel Ovejero Gordillo, Dr. Mireia Cuartero Sala, Dr. Nuria Rodriguez Farre, and Dr. Jaume Baldirà Martinez	Hospital de la Santa Creu i Sant Pau, Secreataría Área de críticos (UCI o Cures Intensives), Planta −1, letra B., Avda San Quintín, 89, 08041 Barcelona
Dr Cristina Pinilla, Dr. Mª Asunción Romero, Dr. Noemí Paredes and Dr. Rosario Cuadra	Hospital Universitario Ramón y Cajal UVI MÉDICA, planta 1 - derecha Carretera de Colmenar, km 9,100, 28034 (Madrid)
Dr Adrian Ceccato, Dr. Antoni Torres Marti, Dr. Catia Cilloniz, Dr. Cristina Dominedò, and Dr. Gianluigi Li Bass	Hospital Clínic I Provincial de Barcelona, Department of Pulmonary and Critical Care Medicine, Villaroel, 170, 08036, Barcelona

(*continued on next page*)

(*continued*)

Dr Adolfo Ruiz Sanmartín, Dr. Alejandro Cortes Herrera, Dr. Jaume Baldirà Martinez, Dr. Juan Carlos Ruiz Rodriguez and Dr. Sofía Contreras Medina	Hospital Universitari Vall d'Hebron, UCI 3a planta, Passeig Vall d'Hebron, 119–129, 08035 Barcelona
Dr Juan Carlos Montejo, Dr. Helena Marín, Dr. Ignacio Saez, Dr. Silvia Chacón, and Dr. Zaida Molina	Hospital Universitario 12 de Octubre, Servicio de Medicina Intensiva., Secretaría, 2a planta. Residencia General. Glorieta de Málaga s/n, 28041 Madrid
Dr Rafael Máñez Mendiluce, Dr. Gabriel Moreno González, and Dr. Juan Carlos López Delgado	Hospital Universitari Bellvitge Feixa Llarga s/n 08907, Hospitalet de Llobregat (Barcelona)
Dr Jordi Codina Calero, Dr. Maria Begoña Balsera Garrido, Dr. Mar Miralbés Torner, Dr. Mercedes Palomar Martínez, and Dr. Montserrat Vallverdú Vidal	Hospital Universitari, Arnau de Vilanova de Lleida, Intensive Care Department (6th Floor) Avda. Alcalde Rovira Roure, 80, 25198, Lleida
Dr Baltasar Sánchez González, Dr. Carles Ferrer i Peretó and Dr. Josep Trenado Álvarez	Hospital Universitari Mútua de Terrassa, Planta 4. UCI.Pl. Dr. Robert 5 08221 Terrassa Barcelona
Dr Gerard Moreno Muñoz, Dr. Gonzalo Sirgo Rodríguez, Dr. Maria A. Bodí, and Dr. Mònica Marget Iglesias	Hospital Universitari de Tarragona Joan XXIII, Dr. Mallafrè Guasch, 4 43005, Tarrragona
Dr Borja Suberviola Cañas, Dr. Alejandro Gonzalez-Castro, Dr. Andrés Jiménez, and Dr. Maite Arlabán Carpintero	Hospital Marqués de Valdecilla Avda Valdecilla s/n, 39008, Santander
Dr José Manuel Añón, Dr. Alexander Agrifoglio, Dr. Lucía Cachafeiro, and Dr. Manuel Quintana	Hospital Universitario La Paz-Carlos III, Servicio de Medicina Intensiva-Planta 1ª, Paseo de la Castellana 261, 28046 Madrid
Dr Gadea Alonso, Dr. Mª Concepción García and Dr. Mª Luisa Rodríguez	Hospital Virgen de la Salud, Servicio de Medicina Intensiva, 1ª planta, Ave. de Barber 30, 45071. Toledo
Dr Esther Villareal and Dr. Mónica Gordon	Hospital Universitario y Politécnico La Fe, Unidad de Medicina Intensiva torre G 1ª planta, Avda. Fernando Abril Martorell n°106, 46026, Valencia
Dr Ana Maria Navas Pérez, Dr. Emilio Diaz Santos and Dr. Jordi Vallés Daunis	Hospital de Sabadell – Parc Taulí, Parc Taulí, 1,08208, Sabadell, Barcelona
Dr Diana Noreikiene, Dr. Sandra Mazeikiene and Dr. Vitalija Nausediene	Public Institution, Klaipėda Republican Hospital, S. Nėries st. 3, 92231 Klaipeda
Dr Pål Klepstad, Dr. Hege-Merete Krabseth and Dr. Johan-Arnt Hegvik	St. Olavs Hospital, Clinical Immunology and Infectious Disease, Prinsesse Kristinas gate 3, 7030 Trondheim
Dr Roberto Alberto De Blasi, Dr. Livia Errico and Dr. Maria Teresa Cirasa	Azienda Ospedaliera Sant'Andrea, Anesthesiology and Intensive Care, Via di Grottarossa, 1035/1039, 00189 Roma
Dr Anne Laure Fedou, Dr. Arnaud Desachy, Dr. Bruno Evrard, Dr. Guillaume Gilbert, Dr. Julien Vaidie, Dr. Marine Goudelin, Dr. Philippe Vignon and Dr. Thomas Daix	CHU de Limoges - CHU Dupuytren, Anesthésie Réanimation, 2 Avenue Martin Luther King, Limoges, 87000 Cedex, France
Dr David Schnell, Dr. Charles Lafon, Dr. Christophe Cracco, Dr. Gilles Lardillon, Dr. Olivier Longuet, Dr. Olivier Thierry Baudin, Dr. Stephane Rouleau, and Dr. Sylvie Nicole Calvat	CH d'Angoulême, Service de réanimation polyvalente, Rond point de Girac, Angoulême, 16959, France
Dr Brian Emonet, Dr. Caroline Pouplet, Dr. Christine Lebert, Dr. Gwenhael Colin, Dr. Isabelle Vinatier, Dr. Jean-Claude Lacherade, and Dr. Konstantinos Bachoumas, Dr. Laurent Camous, Dr. Laurent Martin-Lefevre, Dr. Marie-Ange Azais, Dr. Matthieu Henry-Lagarrigue, and Dr. Maud Fiancette	CHD Vendee, Service de réanimation polyvalente, Boulevard Stéphane Moreau, La Roche sur Yon Cedex 9, 85925, France
Dr Anne Bretagnol, Dr. Armelle Mathonnet, Dr. Dalila Benzekri Lefèvre, Dr. François Barbier, Dr. Grégoire Muller, Dr. Isabelle Runge, Dr. Marie Skarzynski, and Dr. Sophie Jacquier	CH Régional d'Orléans Médecine Intensive Réanimation, 14 Avenue de l'hôpital, Orléans, 45067, France
Prof. Bertrand Souweine, Dr. Armelle Gilard, Dr. Claire Bachelier, Dr.	CHU de Clermont Ferrand, Réanimation médicale, 58 rue Montalembert,

(*continued on next column*)

(*continued*)

Elisabeth Coupez, Dr. François Thouy, Dr. Jean Mathias Liteaudon, Dr. Marjolaine Borel, and Dr. Laure Calvet	Clermont-Ferrand Cedex 1, 63003, France
Dr Charlotte Garret, Dr. Jean-Baptiste Lascarrou, Dr. Maëlle Martin, Dr. Noëlle Brulé and Dr. Laura Crosby	CHU de Nantes, Service de Réanimation Médicale, Bd Jean-Monnet, Nantes Cedex 1, 44093, France
Dr Emmanuelle Mercier, Dr. Annick Legras, Dr. Antoine Guillon, Dr. Charlotte Salmon-Gandonniere, Dr. Denis Garrot, Dr. Laetitia Bodet-Contentin, Dr. Marlène Morisseau, Dr. Pierre-François Dequin, Dr. Stephan Ehrmann, and Dr. Yonatan Perez	CHRU Bretonneau, Médicine Intensive Réanimation, 2 Boulevard Tonnellé Tours, 37000, France
Dr Alexandra Monnier, Dr. Christine Kummerlen, Dr. Hamid Merdji Dr. Hassene Rahmani, Dr. Julie Helms, Dr. Laure Stiel, Dr. Raphael Clere-Jehl and Dr. Yannick Rabouel	CHRU de Strasbourg, Nouvel Hopital Civil 1 place de l'hopital, Strasbourg, 67091, France
Dr Jean-Pierre Quenot, Dr. Audrey Large, Dr. Auguste Dargent and Dr. Pascal Andreu	CHU de Dijon-Bourgogne, 14 rue Gaffarel, Dijon, 21000, France
Dr Damien Contou, Dr. Elsa Logre, Dr. Hervé Mentec, Dr. Jean-Pierre Laforet, Dr. Olivier Pajot and Dr. Radj Cally	CH Victor Dupouy, 69 rue du Lieutenant Colonel Prud'hon, Bâtiment Roger Viguié - 2ème étage, Argenteuil, 95107, France
Dr Saadalla Nseir, Dr. Anne Sophie Moreau Dr. Geoffrey Ledoux, Dr. Julien Poissy, Dr. Laurent Robriquet Dr. Marion Houard Dr. Olivier Pouly, Dr. Raphael Favory Dr. Sophie Six and Dr. Thibault Duburcq	CHU de Lille, Rue E. Laine Pôle Réanimation Lille, 59037, France

Appendix A. Supplementary data

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