Title: A phase Ib/IIa, randomised, double blind, parallel group, placebo controlled, multicentre study to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the intravenous treatment of adult patients with severe community-acquired bacterial pneumonia and admitted to the intensive care unit

NCT Number: NCT03158727

Protocol Approve Date: 19 December 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

A protocol clarification letter for the final protocol, dated 19-December-2019, explaining the discrepancies within the protocol is appended to the back of the protocol.

CLINICAL STUDY PROTOCOL

A phase Ib/IIa, randomised, double blind, parallel group, placebo controlled, multicentre study to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the intravenous treatment of adult patients with severe community-acquired bacterial pneumonia and admitted to the intensive care unit

SEPCELL Study

Study Code:	Cx611-0204
EudraCT Number:	2015-002994-39
Version:	Final, Version 7 incorporating Amendment 5
Date:	19 December 2019
Coordinating Investigators:	**Overall Study Coordinator:** PPD **Clinical Project Coordinators:** PPD **Coordinator Host Biomarkers:** PPD
Sponsor:	TIGENIX, S.A.U. *A Wholly Owned Subsidiary of Takeda Pharmaceutical Company Limited* C/ Marconi, 1 Parque Tecnológico de Madrid 28760, Tres Cantos, Madrid ***Please Note:*** *TIGENIX S.A.U., is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and may be referred to in this protocol as 'TiGenix,' 'sponsor,' or 'Takeda.'*
Sponsor Signatory:	PPD

PROTOCOL AMENDMENT 05 SUMMARY OF CHANGES

Rationale for Amendment 05

This document describes the changes to the protocol incorporating Amendment 05. The primary reason for this amendment is the early closure of enrolment. This decision was the result of persistent enrolment challenges throughout the study and the high risk of not meeting study enrolment goals in a sufficient period of time. Of note, TiGenix has not observed any new safety concerns related to Cx611 in this study.

Changes in Amendment 05

1. Study enrolment will be closed early, at which time the projected enrolment will be approximately 85 subjects.
    a. The number of study centres across Europe was updated to reflect the revised enrolment, and a statement was added regarding distribution of subjects across sites.
2. The secondary objective of identifying pro-inflammatory and anti-inflammatory pathways through which Cx611 may affect the underlying processes of sepsis was made into an exploratory objective. Data analysis with the reduced number of subjects will not be powered to detect a statistical difference but may provide useful information on trends.
3. Unblinding of the study will occur after the Day 90 data have been collected and analysed for all subjects (including the primary safety and secondary efficacy variables). The Day 180 (Visit 12) and Day 365 (Visit 13) visits will be replaced with follow-up safety phone calls for reporting of serious adverse events (SAEs), similar to the Month 18 and Month 24 safety phone calls. No additional efficacy data will be collected beyond Day 90 (Visit 11).
    a. Removal of the secondary objective: Follow-up safety (only SAEs) at Months 6 and 12 after the first investigational medicinal product (IMP) dose administration (Day 1).
    b. Removal of the secondary safety endpoints from Day 180 and Day 365, including collection of anti-human leukocyte antigen complex/donor antibodies, treatment emergent SAEs, and changes in haematology and coagulation, clinical chemistry, and urine analysis.

- Removal of blood volume estimates for Day 180 (Visit 12) and Day 365 (Visit 13).
- Removal of Day 180 and Day 365 planned analyses for collected samples (e.g. shift tables for each assessed laboratory parameter).

c. End of Study redefined to the date of the subject's last scheduled visit (Day 90 ±4 days) or early withdrawal from study prior to Day 90 ±4 days.

d. Premature discontinuation redefined to patients who withdraw from the study before Day 90. These subjects will complete the Early Termination (ET) visit assessments.

4. All safety and efficacy data will be summarized using descriptive statistics only, without any statistical inference or sensitivity analyses based on different patient populations. Due to the early closure of enrolment, the total number of enrolled subjects will be too low to detect any safety and efficacy signals; therefore any statistical inference including 95% confidence intervals and p-values may be misleading, and any sensitivity analyses based on different patient populations will be unnecessary.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only. Updates to the Schedule of Study Assessments and the Study Design have been implemented to reflect the changes outlined above.

1 SYNOPSIS

Name of the Sponsor/Company: TiGenix S.A.U	**Study Code:** Cx611-0204
Name of Investigational Product: Cx611 (eASCs)	**EudraCT No.:** 2015-002994-39
Development Phase of the Study: Ib/IIa	**Trial under an IND:** Not applicable

TITLE OF THE STUDY:

A phase Ib/IIa, randomised, double blind, parallel group, placebo controlled, multicentre study to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the intravenous treatment of adult patients with a severe community-acquired bacterial pneumonia and admitted to the intensive care unit. SEPCELL study.

OBJECTIVES:

The purpose of this randomised, multicentre, double blind, placebo controlled, phase Ib/IIa study is to assess the safety, tolerability and efficacy of eASCs (Cx611) administered intravenously as adjunctive therapy, therefore in addition to standard of care (SoC) therapy, to patients with severe community-acquired bacterial pneumonia (sCABP).

The key objectives of this study are to:

Primary objective:

Investigate the safety profile of two allogeneic Cx611 80 mL infusions administered through a central line within 3 days (on Days 1 and 3) at a dose of 160 million cells each (320 million cells total). To monitor any adverse event and potential immunological host responses against the administered cells during 90 days of follow-up after the first infusion.

Secondary objective:

Explore the clinical efficacy of Cx611 in terms of a reduction of the duration of mechanical ventilation and/or need for vasopressors and/or improved survival, and/or clinical cure of the sCABP, and other efficacy-related endpoints.

Exploratory objectives:

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[redacted]

The completion of this study will contribute to the basic knowledge on mesenchymal stem cells and their mode-of-action, and has a large translational character, i.e. to document the safety and explore the efficacy of Cx611 in patients with sCABP. The study results will be informative for the potential design of further confirmatory clinical trials in terms of definition of endpoints, key biomarkers and sample size determination.

OVERALL STUDY DESIGN:

Phase Ib/IIa, randomised, double blind, parallel groups, placebo controlled, and multicentre trial.

Subjects treated in an intensive care unit (ICU) for sCABP, but that may be screened at the emergency department, will receive SoC therapy according to local guidelines plus two 80 mL intravenous (IV) central line infusions (on Days 1 and 3) at 240 mL/h of Cx611 at a fixed dose of 160 million cells per infusion (total 320 million cells), or placebo. The administration of the first infusion of Cx611 or placebo will be performed as early as possible in the ICU within the first 18 hours of patients fulfilling at least one of the two major criteria of severity for community-acquired pneumonia (CAP) (i.e. from the initiation of invasive mechanical ventilation or vasopressors, whichever comes first), after patient's eligibility is confirmed. The calendar day of administration of the first dose of Cx611 will be considered Day 1 of the study. From Day 1 onwards study days will be considered as calendar days.

This study will enrol approximately 85 male and female subjects, who will be treated with Cx611 or placebo in a 1:1 ratio. Each subject will receive two 80 ml IV central line infusions (active or placebo) in 20-30 minutes on Day 1 and Day 3 respectively according to a pre-defined randomisation list.

The Screening duration will be about 18 hours, treatment duration will be three days and the total study duration per subject will be two years. There will be a total of 12 visits per subject: Screening visit and on Days 1, 2, 3, 4, 5, 6, 7, 8-10, 14, 29 and 90. Four safety follow-up phone calls will be made to the patient, or otherwise to the patient's General Practitioner (GP) or family doctor, at Months 6 (Day 180), 12 (Day 365), 18 (Day 545) and 24 (Day 730) to collect spontaneous report of health status, and eventually to investigate any SAE with the GP.

The double blind design will be maintained by a specific blinding of study treatments, which will be described in the study operations manual and site blinding plan to ensure an unbiased safety and efficacy evaluation. The double blind design will be maintained until the primary safety and secondary efficacy endpoints have been assessed (i.e. at Day 90). The study participants (Sponsor, investigators and site team members) will be unblinded after all Day 90 data have been collected.

The study will permit concomitant SoC treatment of the sCABP including antibiotic and standard therapy in the ICU, in an add-on design.

Stratification will be considered based on CABP severity criteria at inclusion:

- shock requiring vasopressors, or
- respiratory failure requiring invasive mechanical ventilation, or
- both.

In each stratum, patients will be randomised 1:1 to Cx611 or placebo.

INVESTIGATIONAL PRODUCT:

Cx611, two 80 mL Ringer lactate dilutions of adult eASCs at one fixed dose of 160 million cells each (total 320 million cells per patient) and excipient, provided at 240 mL/h via IV central line on Days 1 and 3 or placebo as two 80 mL IV central lines infusions of excipient and Ringer lactate solution alone (on Days 1 and 3).

Subjects will also receive SoC therapy as per local guidelines, with IV and/or oral antibiotics or other drugs, either alone or in combination. Details for dose and frequency of administration of SoC therapy (as well as warnings, precautions, and contraindications) can be found in the referenced summaries of product characteristics for the specific drugs selected by the investigator as SoC. Investigators will be instructed to select only country-approved therapies.

NUMBER OF PATIENTS:

This study will enrol approximately 85 subjects in total.

NUMBER OF STUDY CENTRES:

The study will be conducted in approximately 20 centres across Belgium, France, Lithuania, and Spain.

DISEASE UNDER STUDY

sCABP requiring mechanical ventilation and/or vasopressors.

Due to the short time window (up to 18 hours) between fulfilment of severity criteria (i.e. initiation of invasive mechanical ventilation or vasopressors, whichever comes first) and start of administration of the first dose of study treatment, patients with a sCABP, either suspected and/or later confirmed of bacterial origin by any established standard diagnostic method routinely applied at the study site (please refer to section 7.2.2.1), can be entered into the study.

PATHOGEN IDENTIFICATION AND SUSCEPTIBILITY TESTING

For the confirmation of the causative pathogen of the bacterial pneumonia, pulmonary, pleural, blood and urine samples will be collected and analysed by any established standard diagnostic method routinely applied at the study site including classical microbiology and/or any other methods.

Pulmonary samples can be obtained by bronchoalveolar lavage (BAL) and/or mini-BAL/protected specimen brush (PSB) and/or by endotracheal aspiration (ETA) for intubated patients, and sputum production for non-ventilated patients. Samples will be rapidly proccessed for Gram stain and culture and/or other established standard rapid diagnostic system, e.g. peptide nucleic acid fluorescent in situ hybridization (PNA FISH) or Cepheid GeneXpert for *S. aureus*, urinary antigen test for *S. pneumoniae* or *Legionella*, or real-time polymerase chain reaction (rt-PCR). Should a bacterial pathogen grow in culture, susceptibility testing against the standard local antibiotic panel for the pathogen will be performed according to the site´s practice. Pathogen identification and susceptibility testing will be collected from follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well. Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence.

INCLUSION AND EXCLUSION CRITERIA

The reference population will consist of adult patients with a sCABP, admitted to the ICU.

A patient will be included in the study if he/she meets ALL the following criteria:

Inclusion criteria

1. Adult subjects of either gender (aged ≥18 years and ≤80 years old).
2. Body weight between 50 kg and 100 kg.
3. Clinical diagnosis of acute (developed within ≤21 past days) community-acquired bacterial pneumonia based on the presence of two relevant signs (fever, tachypnoea, leukocytosis, or hypoxemia) and radiographic findings of new pulmonary infiltrate/s.
4. Subjects with pneumonia of sufficient severity requiring ICU management and with at least one of the two following major criteria of severity present for less than 18 hours:
   a) Requiring invasive mechanical ventilation for respiratory failure due to pneumonia, or
   b) Requiring treatment with vasopressors (i.e., dopamine >5 µg/kg/min or any dose of epinephrine, norepinephrine, phenylephrine or vasopressin) for at least 2 hours to maintain or attempt to maintain systolic blood pressure (SBP) >90 mm Hg (or mean arterial pressure [MAP] ≥70 mm Hg) after adequate fluid resuscitation (i.e. for shock).

   NOTE: Patients that are for 18 hours or more under high flow nasal cannula (HFNC) at ≥50 litres per minute and FiO2 ≥0.6 or under non-mechanical ventilation (NMV) are not eligible for the study.
5. Female subject of no childbearing potential i.e. non-fertile, pre-menarche, permanently sterile (i.e. underwent hysterectomy, bilateral salpingectomy or bilateral ovariectomy) or post-menopausal (history of no menses for at least 12 months without an alternative medical cause) or

   Woman of childbearing potential* with a negative serum or urine pregnancy test (sensitive to 25 IU human chorionic gonadotropin [hCG]) and agree to use an adequate method of contraception for three months after the last dose of the IMP according to her preferred and usual life style. Adequate methods of female contraception for this study are: sexual abstinence (refraining from heterosexual intercourse), hormonal contraception (both progesterone-only or combined oestrogen and progesterone; both with inhibition of ovulation or where inhibition of ovulation is not the primary mechanism of action) intra-uterine device, bilateral tubal occlusion, condom use by male sexual partner(s) or medically-assessed successfully vasectomised male sexual partner(s).

   **A woman of childbearing potential is a woman between menarche and post-menopause (history of no menses for at least 12 months without an alternative medical cause) unless she has undergone hysterectomy, bilateral salpingectomy or bilateral ovariectomy*

   Male subject agreeing to use one of the following methods of birth control according to his preferred and usual life style for three months after the last dose of the investigational medicinal

product: sexual abstinence (refraining from heterosexual intercourse), use of condoms or medically-assessed successful vasectomy, or having a female sexual partner(s) who is using an adequate method of contraception as described above.

6. Signed informed consent provided by the subject, the relatives or the designated legal representative according to local guidelines.

Exclusion criteria

A patient will not be included in the study if he/she meets ANY of the following criteria:

1. Subjects with Hospital acquired (HAP)-, Health Care Associated (HCAP)- or Ventilator associated-pneumonia (VAP).
2. Subjects with pneumonia exclusively of viral or fungal origin*. Subjects with bacterial pneumonia co-infected with viruses and/or other microorganisms may be entered into the study.
   **Due to the short time window (up to 18 hours) between fulfilment of severity criteria (i.e. initiation of invasive mechanical ventilation or vasopressors, whichever comes first) and the start of the first dose of study treatment, patients with a pneumonia of suspected bacterial origin by any established standard diagnostic method routinely applied at the study site (e.g. urinary antigen test, rt-PCR) can be entered into the study (confirmation of bacterial origin must be obtained afterwards)*
3. Subjects with known or suspected *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia.
4. Subjects with an aspiration pneumonia.
5. Subjects with known active tuberculosis.
6. Subjects with a history of post-obstructive pneumonia.
7. Subjects with cystic fibrosis.
8. Subjects with any chronic lung disease requiring oxygen therapy at home.
9. Presence of infection in another organ location caused by same pathogen (e.g. pneumococcal meningitis in the context of pneumococcal pneumonia).
10. Subjects expected to have rapidly fatal disease within 72 hours after randomisation.
11. Inability to maintain a mean arterial pressure ≥50 mmHg prior to screening despite the presence of vasopressors and intravenous fluids.
12. Subjects not expected to survive for 3 months due to other pre-existing medical conditions such as end-stage dementia or other diseases.
13. Subjects with a history of malignancy in the 5 years prior to screening, except for successfully surgically treated non-melanoma skin malignancies.
14. Subjects with known primary immunodeficiency disorder or with HIV infection and acquired immune deficiency syndrome (AIDS) with CD4 count <200 cells/mm^3 or not receiving highly active antiretroviral therapy (HAART) for HIV.
15. Subjects receiving immunosuppressant therapy (including chronic treatment with any anti-tumour necrosis factor alpha (TNFα) or on chronic high doses of steroids (single administration of ≥2 mg/kg body weight for ≥2 weeks or 20 mg/day of prednisone or equivalent for ≥2 weeks).
16. Chronic granulocytopenia, not thought to be due to sepsis, as evidenced by an absolute neutrophil count <500 per µL >21 days prior to onset of pneumonia symptoms.
17. Subjects who received stem cell therapy, or allogenic transplantation (organ or bone marrow transplant) within the past 6 months.
18. Subjects receiving treatment with a biological agent (e.g. antibodies, cells), immunotherapy or plasma exchange treatment within the last 8 weeks.
19. Subjects currently receiving, or having received another investigational medication within 90 days prior to start of the study (or 5 half-lives of the investigational compound, whichever is longer).
20. CCI [redacted]

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21. Subjects with a known liver function impairment associated with liver cirrhosis (Child Pugh C) or known oesophageal varices.
22. Subjects hospitalised within the previous 15 days.
23. Conditions resulting in a New York Heart Association or Canadian Cardiovascular Society Class IV functional status.
24. End-stage neuromuscular disorders (e.g. motor neuron diseases, myasthenia gravis, etc.) or cerebral disorders that impair weaning.
25. Patients with quadriplegia (traumatic or otherwise).

ENDPOINTS:

Primary Safety Endpoints by Day 90

Safety measured throughout the study by the incidence of treatment emergent adverse events (TEAEs) judged related or not to study treatment, focussing on any adverse event of special interests (AESIs). Safety analyses will be performed based on the Safety Population.

An independent Data Monitoring Committee (DMC) will review safety data on a regular basis and ad hoc if needed. This DMC will be composed of a Chairman, expert in stem cells and former Chair of the Safety Committee of the completed CELLULA phase I trial, at least two Intensivists and an Independent Statistician. Membership, roles, responsibilities and operating procedures for the DMC will be specified in a separate independent DMC charter.

Subjects will be continuously monitored during and after treatment for:

- Frequency, duration, severity, seriousness, relatedness to study treatment, actions taken and outcome of adverse events (AEs), from time of signature of informed consent until Visit 11 (Day 90) or study discontinuation. AEs will start being recorded after signing the informed consent. AEs occurring from the beginning of the administration of study medication and until Visit 11 (Day 90) or study discontinuation will be analysed as TEAEs.
- Adverse events of special interest (see Sections 5.10 and 11.1.6 and also refer to the Investigators' Brochure (1)).
- Signs for hypersensitivity reactions such as anaphylaxis (changes in systolic and diastolic blood pressure, core temperature [tympanic, rectal or bladder], respiratory rate [non-ventilated patients], heart rate), at Days 1 and 3 (at Pre-dose and at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post each IMP infusion. Episodes of skin reactions and respiratory distress requiring therapeutic intervention and their description during the first 24 hours after the infusion of IMP.
- Changes in vital signs (daily: systolic and diastolic blood pressure, heart rate, core temperature [tympanic, rectal or bladder], respiratory rate [in non-ventilated patients]) as follows: Screening, Day 1 (at Pre-dose, and at 0.5h [±5 min], 1h [±10 min], 2h [±10 min], 4h [±20 min], 12h [±30 min] and 24h [±1 h] post each IMP infusion), Day 2 (at least 4 times), Day 3 (at Pre-dose, and at 0.5h [±5 min], 1h [±10 min], 2h [±10 min], 4h [±20 min], 12h [±30 min] and 24h [±1 h] post each IMP infusion), then at least 4 times daily while in the ICU or, if discharged from ICU at least once on Days 4, 5, 6, 7, 8-10, 14, 29, 90 or study discontinuation.
- Changes in 12-lead electrocardiogram (ECG) from Screening, Days 1 and 3 both 5 hours ± 1h post-study treatment administration.
- Changes in haematology and coagulation, clinical chemistry (at least including renal, liver, cholesterol and triglycerides profiles), and urine analysis at Screening, Day 1 Pre-dose, and then at least on Days 2, 3 (only haematology and coagulation), 4, 7, 14, 29, and 90 or study discontinuation.
- Anti-human leukocyte antigen complex (HLA)/donor antibodies (Abs) on Day 1 Pre-dose, Day 14 and Day 90 or study discontinuation.

Exploratory Safety Endpoints by Months 6 (Day 180), 12 (Day 365), 18 (Day 545) and 24 (Day 730) (phone calls)

- Relatedness to study treatment, actions taken and outcome of spontaneous SAEs will be

captured after Day 90.

Secondary Efficacy Clinical Endpoints

Efficacy analyses will be performed based on the Modified Intention-to-treat (mITT), Intention-to-treat (ITT), Clinically Evaluable (CE), Microbiological ITT (micro-ITT) and Microbiologically Evaluable (ME) populations.

Efficacy endpoints

1. Mechanical ventilator and vasopressor treatment-free days (number of days that a patient is alive and free from mechanical ventilation and vasopressors) over 28 days.
2. Percentage of patients alive and free of mechanical ventilation and free of vasopressors at Day 29.
3. Percentage of patients alive and free of mechanical ventilation at Day 29.
4. Ventilator free days (VFD) over 28 days. VFD are defined as one point for each day during the measurement period that subjects are both alive and free of mechanical ventilation (e.g., a patient who is extubated on Day 2 of the study and remains alive and free of the ventilator for the remainder of the 28-day study period would receive a VFD score of 26, whereas the patient who is ventilated until death on Day 2 would receive a score of zero).
5. Percentage of patients alive and free of vasopressors at Day 29.
6. Vasopressor treatment-free days over 28 days defined as one point for each day during the measurement period that subjects are both alive and free of vasopressors.
7. Time to end of invasive mechanical ventilation.
8. Time to end of invasive and/or non-invasive mechanical ventilation.
9. Time to end of vasopressors treatment.

sCABP Clinical Response

- CCI
- Clinical response visits at Day 8-10 and Day 29 or early discontinuation.
- Time to sCABP clinical cure.
- Duration of antibiotic treatment.
- Rate of pneumonia recurrence/reinfection after clinical cure. Pneumonia recurrence is defined as a new acute clinical episode of pneumonia, after clinical cure of the episode that qualified the patient for the study, based on the presence of two relevant signs (fever, tachypnoea, leukocytosis, or hypoxemia) and radiographic findings of new pulmonary infiltrate/s or clinically significant worsening of previous ones. If a bacterial pathogen isolated in the recurrent episode is phenotypically different from the one isolated in the previous episode this will be considered as reinfection.

- Time to recurrence/reinfection of pneumonia after clinical cure at sCABP clinical response assessments.

Survival

- 28-day all-cause mortality.
- 28-day sCABP-associated mortality.
- Survival at Days 7, 14, 29, and 90 visits.
- Time to death.

Other efficacy endpoints

- Time to discharge from ICU.
- Time to discharge from hospital.
- Length of stay (LOS) in ICU and hospital after randomisation.
- Number of ICU-free days over 28 days.
- Changes in Sepsis-related Organ Failure Assessment (SOFA) score daily during stay at ICU.
- Changes on chest X-ray (CXR) assessed at Screening, and then as medically required with at least one CXR per sCABP clinical response assessment until clinical cure from Days 1 to 29 and for pneumonia recurrence/reinfection assessment.
- Evolution of partial pressure of oxygen /fraction inspire oxygen (PaO_2/FiO_2) daily until Day 7.
- Need of mechanical ventilation or need of non-invasive ventilation 12 hours after the second IMP infusion.
- Use of rescue antibiotics i.e. addition or change of antibiotic treatments due to the occurrence of antibiotic resistance posterior to microbiology results at baseline or insufficient efficacy during the course of the study.

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[redacted]

STATISTICAL METHODS:

In general, data will be summarised by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, median and maximum value. Categorical data will be presented as counts and percentages. Individual patient data will be listed.

Safety analyses

All safety analyses will be only descriptive.

Adverse events (AEs) will be collected throughout the study duration. All AEs (recorded after the signature of the informed consent) and TEAEs (those recorded from the beginning of study medication administration) will be tabulated. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of an AE/TEAE for each unique System Organ Class (SOC) and Preferred Term (PT) will be tabulated. TEAEs will also be tabulated by severity and by the relationship to study medication in treatment groups as assessed by the Investigator. The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a SAE for each unique SOC and PT will be tabulated. SAEs will also be tabulated by severity and by relationship to study medication in treatment groups as assessed by the Investigator. The number and percentage of subjects (in each treatment group) prematurely discontinuing study treatment due to a TEAE will be tabulated by SOC and PT. Safety laboratory data will be presented by absolute and changes from baseline values by visit. Shift tables for each assessed laboratory parameter will be presented to summarise the change from Low, Normal, High values at baseline to 'on treatment' visit (Day 2) and post-treatment visits (Days 4, 7, 14, 29 and 90). The number and percentage of subjects with laboratory, vital signs, ECG, or physical examination abnormalities at baseline, subsequent visits, or ET from the study will be tabulated by treatment group. The results of all laboratory test results, physical examination findings, ECGs, and vital signs will be presented in data listings. All abnormalities will be assessed for being clinically significant or not as per investigator.

Efficacy analyses

Efficacy and biomarker analyses will be descriptive summaries in the safety population at the scheduled visits.

The change from baseline in SOFA scores and all other secondary efficacy and biological variables will be summarised using descriptive statistics.

All data, including derived values that are computed for use in summaries or analyses, will be listed.

Baseline values will be defined as the last value obtained prior to first dosing and the value used in the baseline summary will also be used as the baseline value for purposes of computing change from baseline.

Data might be treated or transformed, as appropriate (e.g. log- transformed or ranked). Details of any transformed data will be specified on the Statistical Analysis Plan (SAP).

Summary tables will indicate the number of patients with complete data for each measurement, event, or outcome. In general, no imputation of missing data will be made, and any exception on efficacy data would be detailed on the SAP.

The following subgroup analyses will be performed but not limited to: severity score, bacterial load, initial adequate or inadequate antibiotic treatment, concomitant treatment, sCABP clinical response (cure or non-response i.e. failure) or indeterminate, antimicrobial resistance profile, previous vaccination, and presence or not of bacteraemia. A thorough review will be performed when data for the primary endpoint are available and before database lock and unblinding, by a blinded Adjudication Committee (AC) of experts to assess subject evaluability and agree on sCABP clinical response assessment and patient assignment process e.g. validation based on the dose, the bacterial susceptibility profile to administered antibiotics and duration of antibiotics, molecular identification data, etc. Membership, roles and responsibilities and operating procedures for the AC as well as the subject evaluability criteria to be followed will be specified in a separate AC charter.

Data set to be analysed

The following analysis set will be defined:

- Safety: Includes all randomised patients who have received at least one dose of the study treatment irrespective of randomisation. The safety population will be the primary population for all the safety and efficacy analyses.

ANTICIPATED STUDY PERIOD:

October 2015: Ethics Committee (EC) / Health Authorities Cx611-0204 submission
December 2015: First Approval EC/Health Authorities
January 2017: First Patient In
December 2019: Last Patient In
March 2020: Last Patient Out (3 months follow-up)
June 2020: Database Lock Day 90 (3 months follow-up)
September 2020: Clinical Study Report Day 90 (3 months follow-up)
December 2021: Last Patient Out (2 years follow-up)
October 2022: Clinical Study Report Addendum (2 years follow-up)

Table 1. Schedule of Study Assessments

VISITS	**Screening**	**Visit 1 (V1)**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Early Termination (ET)**	**Safety[12] phone calls**			
Study days (allowed deviation days in brackets)		**Day 1 (D1)**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8-D10**	**D14 (±2)**	**D29 (±2)**	**D90 (±4)**		**D180 (±30)**	**D365 (±30)**	**D545 (±30)**	**D730 (±30)**
Informed consent	X																
Inclusion and exclusion criteria	X*	X*															
Medical history	X																
Physical examination	X	X*	X	X*	X	X	X	X	X	X	X	X	X				
Vital signs[1]	X	X[1]	X	X[1]	X	X	X	X	X	X	X	X	X				
Urine and Serum pregnancy tests	X[6]																
$Pa0_2/Fi0_2$	X	X*	X	X*	X	X	X	X					X***				
CURB-65	X																
APACHE II	X	X*															
SOFA score[2]	X	X*			X			X		X	X		X***				
ECG	X	X**		X**													
Chest X-ray	X	As per investigator's decision, at least 1 chest X-ray per sCABP clinical response assessment until clinical cure and for pneumonia recurrence/reinfections assessment															
Randomisation	X																
Study Treatment administration		X[7]		X													
Signs of hypersensitivity reactions		X[8]		X[8]													
sCABP clinical response assessments									X	X	X		X***				

VISITS	Screening	Visit 1 (V1)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Early Termination (ET)	Safety[12] phone calls			
Study days (allowed deviation days in brackets)		**Day 1 (D1)**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8-D10**	**D14 (±2)**	**D29 (±2)**	**D90 (±4)**		**D180 (±30)**	**D365 (±30)**	**D545 (±30)**	**D730 (±30)**
Pneumonia recurrence / reinfection										X	X	X	X				
Pathogen identification and susceptibility testing	X[9]	As per investigator's decision from D1 to D29[9]. Pathogen identification and susceptibility testing will be collected from follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well.											X***				
Pneumococcal urine antigen	X																
Haematological & Coagulation / Biochemical tests / Urinalysis	X	X*	X	X* (only haematol. & coag.)	X			X		X	X	X	X				
Proximal Lower Limb Compression Ultrasonography.						X[11]	X[11]										
CCI [redacted]																	
CCI [redacted]																	
CCI [redacted]																	
Adverse events	←----------throughout the study (starting from the signature of the informed consent)----------→												X	Only SAEs			
Prior/Concomitant treatments****	X	←----------throughout the study----------→											X				

* Pre-study treatment administration ** 5 hours ± 1h post-study treatment administration *** If applicable **** Fluids excluded

[+] CCI [redacted] [++] Only anti-HLA/Donor Abs [+++] If ET is after V11 (Day 90) only anti-HLA/Donor Abs [+++ +] Only if ET is before V9 (Day 14)

1. Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder), respiratory rate (in non-ventilated patients) will be measured as follows: Screening, Day 1 (at Pre-dose, and at 0.5h [±5 min], 1h [±10 min], 2h [±10 min], 4h [±20 min], 12h [±30 min] and 24h [±1 h] post IMP dose), Day 2 (at least 4 times i.e. every 6h±1h), Day 3 (at Pre-dose, and at 0.5h [±5 min], 1h [±10 min], 2h [±10 min], 4h [±20 min], 12h [±30 min] and 24h [±1 h] post IMP dose), Days 4, 5, 6, 7, 8-10, 14, 29, 90 or study discontinuation. If in the ICU at least 4 times daily i.e. every 6h±1h, if discharged

from ICU at least once. When more than one measurement is available for screening, Day 2 and Day 4 onwards only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.

2. Full SOFA: Cardio-vascular, Respiration, Coagulation, Liver, CNS and Renal.
3. CCI
4. CCI
5. CCI
6. A rapid diagnosis using urine pregnancy test may be performed for inclusion, awaiting the serum pregnancy test for confirmation.
7. Start of first infusion of IMP must be within the first 18h of patients fulfilling at least one of the two major criteria of severity for CABP (i.e. initiation of ventilation support or vasopressors, whichever comes first).
8. Signs of hypersensitivity reactions or anaphylaxis: vital signs (systolic and diastolic blood pressure, heart rate, core temperature and respiratory rate in non-ventilated patients) will be assessed at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) after the start of the infusion, in addition the patient will be monitored for skin reactions and episodes of respiratory distress requiring therapeutic intervention during the first 24 hours after the infusion.
9. Pathogen identification and susceptibility testing: During Screening (if possible within a timeframe that allows to keep the 18 hour window between fulfilment of the severity criteria for the pneumonia and start of treatment with Cx611) and as medically required afterwards (at least one further pulmonary sample). For the confirmation of the causative pathogen of the bacterial pneumonia, pulmonary, pleural, blood and urine samples will be collected and analysed by any established standard diagnostic method routinely applied at the study site including classical microbiology and/or any other methods (please refer to Section 7.2.2.1). Pathogen identification and susceptibility testing will be collected from follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well. Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence.
10. At 8-12 hours post-administration.
11. Can be performed on Day 5 or Day 6.
12. Long-term safety follow-up: four follow-up phone calls will be made to the patient, at Months 6 (Day 180), 12 (Day 365), 18 (Day 545) and 24 (Day 730), by the investigational staff to investigate any spontaneous report on his/her health status. Up to three phone call attempts will be done and if not successful, a contact will be established with the patient's GP. The investigator will report any SAE and will liaise with the patient's GP for obtaining further documentation on the investigation of the SAE.

Abs=antibodies, APACHE=Acute Physiology and Chronic Health Evaluation, CABP=Community-acquired bacterial pneumonia, CNS=central nervous system, coag=coagulation, CRF=case report form, CCI CURB-65=Confusion, elevated blood urea nitrogen level, respiratory rate, and blood pressure plus age ≥65 years score, D=Day, eASCs=Adipose-derived Stem Cells, ECG=Electrocardiogram, CCI, ET= Early Termination, FiO_2=Fraction of inspired Oxygen, GP=general practitioner, haematol=haematology, CCI h= hour, ICU=Intensive care unit, CCI, IMP=investigational medicinal product, Min= minute; CCI PaO_2=Partial pressure of Oxygen, CCI CCI sCABP=severe community-acquired bacterial pneumonia, SAE=serious adverse event, SOFA=Sequential Organ Failure Assessment, CCI CCI, V=Visit

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1 List of Abbreviations

Abs	Antibodies
AC	Adjudication committee
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
APACHE	Acute Physiology and Chronic Health Evaluation
APTT	Activated partial thromboplastin time
ATIMP	Advanced therapy investigational medicinal product
BAL	Broncho Alveolar Lavage
BL	Baseline
CA	Competent authority
CABP	Community-acquired bacterial pneumonia
CAP	Community-acquired pneumonia
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CCI	[redacted]
CTA	Clinical Trials Authorisation
CURB	Confusion, elevated blood urea nitrogen level, respiratory rate, and blood pressure (score)
CURB-65	Confusion, elevated blood urea nitrogen level, respiratory rate, and blood pressure plus age ≥65 years score
CXR	Chest X-ray
DMC	Data Monitoring Committee
DMSO	Dimethyl sulfoxide
eASCs	Expanded Adipose-derived Stem Cells
EC	European commission
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EEA	European Economic Area
EOS	End Of Study
ETA	Endotracheal Aspiration
EU	European Union
FiO_2	Fraction of inspired Oxygen
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HAART	Highly active antiretroviral therapy
HAP	Hospital acquired pneumonia
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen complex
ICH	International Conference on Harmonization
ICU	Intensive care unit
IEC	Independent ethics committee
IFN	Interferon
IL	Interleukin
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
IRT	Interactive Response Technology
IV	Intravenous

kg	Kilogram
LOS	Length of stay
LPS	Lipopolysaccharide
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MIP-2	Macrophage inflammatory protein-2
CCI	[redacted]
CCI	[redacted]
PaO_2	Partial pressure of Oxygen
PBMC	Peripheral blood mononuclear cells
PNA FISH	Peptide nucleic acid fluorescent in situ hybridization
PSB	Protected specimen brush
PT	Preferred term; prothrombin time
RANTES	Regulated on activation normal T cell expressed and secreted
RBC	Red blood cell count
REB	Regional Ethics Board
RNA	Ribonucleic acid
rt-PCR	Real-time polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical analysis systems
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse reaction
sCABP	Severe community-acquired bacterial pneumonia
SD	Standard deviation
CCI	[redacted]
SoC	Standard of Care
SOC	System organ class
SOFA	Sequential Organ Failure Assessment
SOM	Study Operations Manual
SOP	Standard operating procedure
TEAE	Treatment – emergent adverse events
CCI	[redacted]
TLR	Toll-like receptor
TNF	Tumour necrosis factor
CCI	[redacted]
VAP	Ventilator associated-pneumonia
VFD	Ventilator free days
WBC	White blood cell count

3.2 Definition of Terms

Competent Authority	A government body or government appointed body that has legal authority to approve or disapprove clinical studies

4 STUDY ADMINISTRATIVE STRUCTURE

COORDINATING INVESTIGATORS

OVERALL STUDY COORDINATOR

Name: PPD
Address:

Phone:
Fax:
E-mail:

CLINICAL PROJECT COORDINATORS

Name: PPD
Address:

Phone:
Fax:
E-mail:

Name:
Address:

Phone:
Fax:
E-mail:

Name:
Address:
Phone:
Fax:
E-mail:

COORDINATOR HOST BIOMARKERS

Name: PPD
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Name: PPD
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Phone :
E-mail:

MEDICAL MONITOR

Name: PPD
Address:
Phone:
Fax:

DRUG SAFETY OFFICER

Name: PPD
Address:
Phone:
E-mail:

CONTRACT RESEARCH ORGANISATION (CRO)

Name: PPD
Address:
Phone:
Fax:

5 INTRODUCTION

5.1 Background: Severe Community-acquired Bacterial Pneumonia

Community-acquired pneumonia (CAP) is the most common cause of death associated with infectious disease and the sixth most common cause of death in the United States (2,3). When CAP is caused by bacterial pathogens, it is named a community-acquired bacterial pneumonia (CABP). It has been defined by the Infectious Diseases Society of America as an acute infection of the pulmonary parenchyma that is associated with at least some symptoms of acute infection (i.e., chest pain, cough, sputum production, difficulty of breathing, chills, rigors, and fever), accompanied by the presence of a new infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia, in a patient not hospitalised or residing in a long-term– care facility for ≥14 days before onset of symptoms (4).

Around one third of cases with severe CABP (sCABP) are caused by *Streptococcus pneumoniae*. Other common pathogens are *Haemophilus influenzae*, *Staphylococcus aureus* and *Moraxella catarrhalis*. Atypical cases are caused by *Mycoplasma pneumoniae*, *Chlamydophila pneumonia* and *Legionella* species (5). In about one third of subjects, the organism remains unidentified (6).

CABP represents a public health problem of substantial magnitude, with an overall annual incidence ranging 1.6-10.6/1,000 adult population in Europe (7). This incidence increases with age, from 18.2 cases per 1,000 patient-years in patients aged 60 to 69 years up to 52.3 cases per 1,000 patient-years in those older than 85 years (8). The number of cases requiring hospitalisation is around 267 per 100,000 people (9). More than fifty percent of hospitalised patients with CABP develop severe sepsis during the course of the disease (10), and around 10% are admitted to the intensive care unit (ICU) (2). The incidence of sCAP has increased in the last decade by 128%, from 12.8 admissions per ICU in 1996 to 29.2 admissions in 2004, compared to a 24% rise in total ICU admissions (11).

A CABP leading to organ dysfunction (severe sepsis) is considered severe (sCABP). Patients with sCABP suffer either a respiratory failure that requires invasive mechanical ventilation and/or a severe hypotension that requires vasopressors. Approximately fifty percent of patients that initiate mechanical ventilation require vasopressors later on, and fifty percent of patients requiring vasopressors are intubated afterwards (12). The presence of at least three of other minor criteria (respiratory rate >30 breaths/min; arterial oxygen pressure/fraction of

inspired oxygen (PaO2/FiO2) ratio <250; multilobar infiltrates; confusion; blood urea nitrogen level >20 mg/dL; leukopenia; thrombocytopenia; hypothermia; or hypotension requiring aggressive fluid resuscitation) may also suggest a severe CABP (4). To aid in deciding whether a given patient can be treated as an outpatient or should be admitted to the hospital, severity scores (such as the Pneumonia Severity Index [PSI]; the confusion, elevated blood urea nitrogen level, respiratory rate, and blood pressure [CURB] score; and the CURB plus age ≥65 years [CURB 65] score) have been described; these scores stratify patients with CABP into mortality risk groups (4,13).

Despite effective antibiotic therapy, the mortality rate remains unacceptably high. Outpatients' CABP has a mortality rate of <5% (14). However, when hospitalisation is required, the mortality of CABP reaches 12% and increases to 22% if the patient is admitted to the ICU (14). In patients requiring mechanical ventilation, mortality may be as high as 25%, and increases up to 50% in patients also requiring vasopressor support (15,16). Among elderly (≥65 years) ICU patients with sCAP requiring mechanical ventilation, the mortality rate reaches 55% (17).

Irrespective of severity of initial presentation, the development of sepsis-related complications (delayed septic shock, adult respiratory distress syndrome [ARDS], and extrapulmonary organ dysfunction) during ICU stay is associated with a significantly higher ICU mortality: 57–100% (18). sCABP in patients admitted to the ICU has shown little improvement during the last 20 years, with an all-cause 28-day mortality rate up to 43% in subjects with a baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥25 (19). Septic shock is associated with the highest mortality, approaching 50% (20). Despite advances in antibiotic treatment and ICU care, these high rates demonstrate the need for additional interventions, even in patients who receive adequate antimicrobial therapy (4,21).

Severe sepsis is a life-threatening syndrome characterised by an infection-induced organ dysfunction and/or hypoperfusion abnormalities, caused by a dysregulated host response (22). Sepsis occurs when the response of the immune system to fight the infection triggers a systemic inflammation that damages multiple organ systems, causing them to fail. Inflammatory molecules, such as tissue factor (TF) (23), are pathologically expressed and released into the bloodstream, with consequent activation of coagulation and inflammatory processes. Septic shock is diagnosed when hypotension persists despite adequate fluid resuscitation or when perfusion abnormalities occur, which may lead to death. Although

severe sepsis may be associated to all types of infections (genitourinary, abdominal, skin and soft tissue, device-related, central nervous system or endocarditis), CABP is the most common source of infection (around 40% of cases) (24), and it is associated with the highest mortality (31-40%) (25). Several studies have shown increased pulmonary and circulating inflammatory cytokine levels in patients with sCABP (26,27). Among patients admitted to the ICU, higher circulating inflammatory cytokine levels correlated with the presence of bilateral pneumonia, bacteraemia, need for mechanical ventilation, and higher APACHE II and multiple organ dysfunction syndrome (MODS) scores (26,27). Taken as a whole, the findings of these studies indicate that degree and duration of the systemic inflammation have a strong effect on final outcome in patients with sCABP. In other words, in sCABP, deaths are not due to failure to eradicate the microorganism causing pneumonia, but are closely related to inadequate host response. Excessive cytokine response in patients with sCAP has been linked in many studies with deleterious effects and poor prognosis (18,28).

5.2 Current Treatment of sCABP and Sepsis

According to current guidelines, all patients with sCABP and severe sepsis or septic shock require close monitoring and must be admitted to the ICU (4,22). Drug therapy is complex, and includes broad-spectrum antibiotics, corticosteroids, inotropic agents, and vasopressors, as well as oxygen and volume resuscitation with large amounts of intravenous fluids. The antimicrobial therapy must start in the first hour and, after 6 hours, the patient must be re-evaluated (4). A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone is the most common antibiotic combination in ICU patients (4). If a combined pneumococcal and *Pseudomonas* infection is suspected, an antipseudomonal b-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin, levofloxacin, an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone are recommended. For community-acquired methicillin-resistant *Staphylococcus aureus* infection, vancomycin or linezolid are usually added (4). The treatment lasts for a minimum of 5 days, or until the patient is afebrile for 48-72 hours and does not have more than one CABP-associated sign of clinical instability (4).

The treatment of severe sepsis and septic shock has been recently reviewed (22). Overall, it is based on the following recommendations (summarised):

1. Initial resuscitation: goals during the first 6 hours of resuscitation:

a) Central venous pressure 8–12 mm Hg

b) Mean arterial pressure (MAP) ≥65 mm Hg

c) Urine output ≥0.5 mL/kg/hr

d) In patients with elevated lactate levels (≥4 mmol/L) targeting resuscitation to normalise lactate.

2. Diagnosis

a) Cultures as clinically appropriate before antimicrobial therapy

b) Imaging studies to confirm a potential source of infection

3. Antimicrobial Therapy

a) Administration of effective intravenous antimicrobials within the first hour of septic shock and severe sepsis

b) Empiric anti-infective therapy active against likely pathogens

c) Antimicrobial regimen reassessed daily for potential de-escalation

d) Use of biomarkers to assist in the discontinuation of empiric antibiotics

e) Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult-to-treat, multi drug resistant bacterial pathogens

Despite all these interventions, patients with sCABP and sepsis have a low survival rate, reflecting the limited effectiveness of current therapy (20). There is an unmet medical need, but the number of new drugs currently in development is small.

5.3 Cell Therapies Based on Adult Stem Cells

Stem cells are unspecialised cells capable of dividing and regenerating for long periods of time (29). Due to their unique properties, they are being investigated for treating many diseases. Until the discovery of adult stem cells, research was limited due to ethical concerns over the use of embryonic stem cells. Adult stem cells are found in various parts of the body, such as the brain, bone marrow, blood, skin, heart and adipose tissue, but not all of them can be easily cultured *in vitro* (30).

Adult mesenchymal stem cells (MSCs) are a stem cell population that can be isolated, expanded in culture, and characterised *in vitro* and *in vivo,* according to the criteria of the

International Society for Cellular Therapy (29). In the recent years, adult MSCs have emerged as potent therapeutic tools based not only on their differentiation potential, but also on their capacity to modulate immune responses and their low immunogenicity. Compared with other cell types, MSCs have lower levels of Major Histocompatibility Complex (MHC) Class I antigens, and do not express MHC Class II or co-stimulatory molecules (CD40, CD80 or CD86) (29). Short persistence of allogeneic MSCs *in vivo* and little rejection by T cells allow their potential use as allogeneic treatment (31–34). They also express high levels of protectors of complement-associated lysis (CD55 and CD59), and show strong indoleamine 2,3-dioxygenase (IDO) induction. This enzyme is one of the key regulators of tryptophan catabolism and may inhibit activated T cells proliferation and cause halted growth of microorganisms. *In vitro*, MSCs may differentiate into mesenchymal-type cells (trilineage differentiation into adipocytes, osteoblasts, and chondrocytes) (35). MSCs are negative for CD45, CD34, CD14, or CD11b, CD79a, or CD19 and HLA-DR, and positive for a variety of other markers, including CD73, CD90, and CD105 (29).

5.4 Advantages and Potential Risks of Expanded Adipose-derived Stem Cells (eASCs)

MSCs have been isolated from multiple tissues of mesodermal origin, such as bone marrow, adipose tissue, umbilical cord or placenta (30). Expanded adipose-derived stem cells (eASCs) can be obtained in a technically simple way from human lipoaspirates containing subdermal adipose tissue, and constitute an easily accessible and exceptionally abundant source of stem cells (36). Progenitor cells represent 2% of the total cells of the Stromal Vascular Fraction (SVF) of the fat tissue, whereas the equivalent cell type on bone marrow only represents 0.002% of total cells.

Although their immunosuppressive properties are the same as those described for bone marrow-derived MSCs, their ribonucleic acid (RNA) and protein expression profiles are different (37). eASCs lack the expression of ligands for natural killer (NK) activation receptors. The eASCs display a lower susceptibility to NK cell-mediated lysis when compared with bone marrow-MSCs (38). Thus, eASCs may remain in the tissue long enough to balance the immune response before being cleared (38).

The potential benefit and relative lack of acute safety issues of MSCs administration has been suggested by a growing number of non-clinical and uncontrolled clinical studies in a large number of pathologies (39). Potential risks associated with the administration of eASCs may include ectopic tissue or tumour formation, unwanted local or systemic immune response and

transmission of adventitious agents (40,41). Moreover, the intravenous (IV) infusion of such cells may result in events of thromboembolism (40,42–44). These risks may be considered as adverse events of special interest (AESI) by investigators (please refer to the Investigators' brochure (1)).

5.5 Mechanism of Action of eASCs: Immunomodulatory properties

Data from *in vitro* and animal studies suggest that the possible mechanisms of action of eASCs are multiple. They have immunomodulatory properties, with both local and systemic effects. At short term, they modulate the inflammation status, shifting from Th1 to Th2 immune response. At long term, they may restore homeostasis through generation of immune cells with regulatory phenotype like regulatory T cells (Treg), regulatory B cells and M2 macrophages (45–47).

In *in vitro* studies, eASCs inhibited peripheral blood mononuclear cells (PBMCs), and more concretely CD4 + and CD8 + T cell proliferation in a dose dependent manner (ratio 1:25-1:200), both by cell contact-dependent mechanisms (48) and by releasing soluble factors (49), which was accompanied by a reduction of proinflammatory cytokines. Among the soluble factors, the following molecules have been described: hepatocyte growth factor (HGF), prostanglandin-E2 (PGE2), transforming growth factor (TGF)-β1, IDO, nitric oxide (NO), interleukin(IL)-10, hemeoxygenase-1 (HO-1) and HLA-G5 (45). Many of these factors are released into small membranous vesicles called exosomes. *In vitro* studies demonstrated that exosomes from eASCs display similar immunosuppressive effects than eASCs, inhibiting the differentiation and activation of T cells (50).

An antiproliferative effect was observed on activated PBMCs and in an allogeneic way (i.e. it does not need human leukocyte antigen complex [HLA] matching) (51,52). The generation of Tregs has been also observed *in vitro* (53–55), although it is unknown if they are created *de novo* or expanded from pre-existing Tregs (56). eASC activity *in vivo* can be modulated through toll-like receptors (TLRs) signalling (57). These receptors have been linked to rejection and inflammatory diseases (e.g. Crohn's disease, rheumatoid arthritis or sepsis), because they may recognise pathogen components or self-antigens similar to pathogen-derived components or tissue danger signals produced upon injury. However, activation of eASCs by TLR ligands *in vitro* has not been reported to interfere with their low immunogenicity. eASCs also promoted B-cell migration through the secretion of chemotactic factors (38).

Due to all these properties, eASCs are being investigated for the treatment of human autoimmune, acute and chronic inflammatory pathologies and healing disorders. In a study in patients with Crohn´s disease, they have already demonstrated efficacy in the repair and regeneration of damaged tissue (58). In the local treatment of inflammatory diseases with tissue damage and/or wounds, the eASCs establish an environment that accelerates healing (59). In the systemic treatment of diseases with an acute inflammatory component (patients with acute myocardial infarction), the eASCs migrate to the inflammatory environment and suppress inflammation, avoiding tissue damage (60).

eASCs can be administered locally (Cx601, cell suspension, being investigated for the treatment of complex perianal fistulas in Crohn's disease patients), intravenously (Cx611, in development for early rheumatoid arthritis and severe sepsis) or by intra-lymphatic administration (Cx621, candidate for the treatment of autoimmune diseases) (1).

5.6 Safety of Cx611

TiGenix has conducted a full spectrum of studies of eASCs in 6 animal models, 3 indications and 5 routes of administration (1). With the IV formulation Cx611, the results from the pharmacokinetics and biodistribution studies demonstrated very limited migration and reduced persistence (61). Toxicology single and repeat dose studies with the IV route found no toxicological findings, except from some cases of pulmonary embolism in rat studies. Tumorigenicity (*in vitro* and *in vivo*) studies comprised cytogenetic analyses, growth kinetics and senescence studies, telomerase activity studies, c-myc expression studies and anchorage independent growth. None of them showed any sign of tumorigenicity (1).

The key safety findings from the preclinical studies are the following:

- Distribution studies in animal models indicate that Cx611 administered intravenously accumulate mainly in the lung and can be detected to a lesser extent in some other tissues: heart, liver, kidney, jejunum, ileum, colon and cecum. The persistence of the cells was limited as cells were detected at Days 2 and 14 after injection but not at later time points;
- Cx611 administered intraperitoneally in mice with colitis accumulated preferentially in the inflamed areas of colon and secondary lymphoid organs (mesenteric lymph nodes and spleen), indicating that eASCs have a potential to migrate to the site of inflammation;

- Tumorigenicity and transformation:
  - Karyotype: No aberration could be detected in any clinical sample.
  - C-myc expression, telomerase activity and test of soft agar: No concerns arose from those tests.
  - Tumour formation: *In vivo* tumorigenicity studies clearly demonstrate the lack of any tumour formation.
  - Senescence: The growth of all eASCs used in the preclinical program was monitored and doubling populations were established, showing a linear growth. Doubling populations upper limit has been established within the routine manufacturing process in order to avoid any potential senescence phase of the cells.
- Differentiation: eASCs do not differentiate spontaneously into a certain lineage. Differentiation processes require inductive signals and permissive environment. The *in vitro* differentiation assays have demonstrated that differentiation is highly reduced with expansion.

TiGenix studies demonstrate the lack of tumours and opportunistic infections. This fact is demonstrating on one side that eASCs are not tumorigenic and well tolerated and on another side that the potential over suppression of eASCs which might subsequently lead to spontaneous tumours or opportunistic infections is not occurring. Therefore there is no concern on potential tumorigenicity from allogeneic eASCs. This is in agreement with recent review on the risks of mesenchymal stromal cell therapy in which it is stated that tumorigenesis is likely to be an extremely uncommon event (62).

With regard to the IV administration route, when a very high number of eASCs were administered in animals by IV route, manually or by a high infusion rate, respiratory problems immediately after eASCs infusion were observed, likely due to eASC aggregation and bolus formation in the lungs. These adverse events observed in small animals have not been reported in the phase Ib/IIa clinical trial in rheumatoid arthritis (Cx611-0101, EudraCT Number: 2010-021602-37) when up to 4 million cells/kg were administered at an infusion rate of 4 mL/min (62), nor in the phase I trial in healthy volunteers injected with lipopolysaccharide, whose results are presented below (see Section 5.8) (1). However, in

order to control this potential risk associated to the IV administration route, the respiratory function will be controlled during and shortly after the IV administration of Cx611.

5.7 Efficacy of Cx611 in Animal Sepsis Models

Current treatments inadequately address the complex immune-modulatory pathways that intervene in the pathogenesis of sepsis secondary to sCABP. Cx611 is an intravenously-administered product of allogeneic eASCs in development for early rheumatoid arthritis and severe sepsis. Cx611 offers a novel mechanism of action that is potentially able to address the underlying immune dysregulation through multiple pathways. It has demonstrated its efficacy in several studies with mainly two animal models of sepsis (endotoxemia caused by lipopolysaccharide (LPS) administration and caecal ligation followed by puncture) by significantly reducing mortality through a combination of reduced inflammation, production of anti-microbial effectors, and increased phagocytosis (45).

In a mouse model of sepsis, Cx611 infusion to septic animals decreased the levels of inflammatory mediators (TNF-α), IL 6, IL1b, IL12, interferon gamma (IFN-γ), regulated on activation normal T cell expressed and secreted (RANTES) and macrophage inflammatory protein-2 (MIP-2)) and increased IL-10 in the major affected organs, and diminished the inflammatory infiltration into the peritoneal cavity, lung, liver and intestine, and showed anti-microbial effects reducing bacterial burden in major affected organs (63). In another pre-clinical study in mice, treatment with eASCs (1×10^6 cells/animal) decreased the mortality to 40% within 26 h, compared to the 100% in the untreated septic group, decreased inflammatory cytokines, increased IL-10 and inhibited splenocytes apoptosis (64). In an endotoxemic rat model, treatment with eASCs decreased the level of inflammatory cytokines in the lung and serum, reduced inflammatory changes in the lung, prevented apoptosis in the kidney and improved multi-organ injury (65). In a pneumonia mouse model, treatment with MSCs showed reduced bacterial counts as a consequence of the release of the anti-microbial peptide LL-37 by the cells (66).

5.8 Phase I Results With Cx611 in Healthy Volunteers

The results from a Phase I, single centre, and placebo controlled clinical trial to investigate safety, tolerability and to assess the effect of Cx611 on the human response to lipopolysaccharide in healthy male volunteers are presented below (1).

This trial, codenamed CELLULA, was designed to confirm the safety and demonstrate the anti-inflammatory effect of Cx611 on the sepsis-like clinical symptoms and immunological response elicited by an IV administration in healthy volunteers of a bacterial endotoxin (lipopolysaccharide), a potent pro-inflammatory constituent of the outer membrane of Gram-negative bacteria, which elicits an inflammatory response inducing sepsis-like clinical symptoms. The trial was a placebo controlled, parallel group study (3 doses of Cx611: 250,000 cells/kg, 1 and 4 million cells/kg, and placebo groups) in 32 healthy male volunteers. Primary endpoints were vital signs and symptoms, laboratory measurements and functional assays of innate immunity (1).

No serious adverse events (SAEs) or respiratory problems were reported (1). Few adverse events (AEs) were observed in 5 subjects, resolved on the same day, all with mild intensity and not related to the study medication, except from one episode of itching throat and legs, self-resolving and not due to angioedema or allergy. It was considered of a moderate severity and probably related to eASCs effect (1).

The analysis of vital signs and symptoms revealed a lack of effect of eASCs infusion compared to placebo, except for an enhanced febrile response with the highest tested dose of 4 million cells/kg. The laboratory measurements and functional assays of innate immunity analysed on the blood samples of the subjects at different time points up to 24 hours after LPS injection revealed, in addition to the expected and transient activations of cytokines, endothelial cells and neutrophils, and coagulation and fibrinolysis factors in all groups, some significant differences between eASCs and placebo groups, mainly caused by the highest tested dose of 4 million cells/kg. Indeed the cytokine analysis showed that the 4 million cells/kg dose was associated with an enhanced response (higher levels compared to placebo within the first hours after LPS administration) of the pro-inflammatory interleukins IL-6, IL-8 and the anti-inflammatory IL-10 and tumour growth factor β (TGF-β). Although none of the administered doses had a significant effect on the release of the pro-inflammatory cytokines TNF-α, IL-1β and IL-12p40 compared to placebo, a trend towards lower levels of IL-12p40 was observed in the 4 million cells/kg dose group. Some procoagulant effects (higher levels of D-dimer and thrombin-antithrombin complexes [TATc]) and an attenuated release of tissue-type plasminogen activator (tPA) were also observed in this group compared to placebo, as well as an enhanced nucleosome release (1).

The eASCs infusion did not influence the neutrophil activation (elastase, MPO, LL-37), nor the endothelial cell activation (E-selectin, ICAM-1, VCAM-1), nor the reduced responsiveness of blood leukocytes upon stimulation with bacterial agonists and T cell stimulation induced after IV LPS injection (1).

In conclusion, although some effects on cytokine release and coagulation factors were observed with the highest tested dose, the Phase I study could not demonstrate a significant effect of eASCs infusion in many of the evaluated variables. One possible explanation is that the LPS model may not be suitable for evaluating the efficacy of eASCs, because the brief effect of a low dose of LPS on the immune system may be insufficient to detect the activity of Cx611 (67). Another hypothesis that could explain these results is that the anti-inflammatory effect of Cx611 requires preactivation of immune cells by an infectious agent (like in sepsis) (67). The phase Ib/IIa study in patients with sCABP will allow understanding the mechanism of action of eASCs in this inflammatory underlying disease. Although there was no safety concern in this phase I study in 32 healthy volunteers, an independent Data Monitoring Committee (DMC) will closely and regularly monitor the safety along the study. The DMC members' responsibilities, the timing and purpose of DMC meetings, the Early Safety/Trial Integrity Reviews of DMC meetings will be described in a DMC charter, signed by all DMC members.

5.9 Rationale

A program of non-clinical pharmacology, biodistribution and safety studies has been conducted with Cx611. Preclinical data from the investigational medicinal product dossier (IMPD) indicate that allogeneic eASCs show anti-inflammatory and immunomodulatory effects *in vitro* and *in vivo*, providing therapeutic benefit when administered in experimental models of acute inflammatory diseases such as sepsis. These anti-inflammatory and immunomodulatory capacities rely on the expression of IDO (indoleamine 2, 3-dioxygenase) and the generation of immune cells with regulatory role such as Tregs or regulatory macrophages. In addition, eASCs have anti-microbial effects as they release peptides with antimicrobial properties (LL-37) and increase the phagocytic capacity of monocytes, macrophages and neutrophils (45). eASCs can sense inflammation and therefore can migrate to the site of inflammation and also to lymphoid organs.

Toxicology and biodistribution studies using different routes of administration demonstrated a limited distribution and viability of human Cx611 in immunodeficient animals with no

indication of extensive migration of Cx611 after IV administration. Moreover, no toxicity or specific adverse effects upon administration were found, including ectopic growth tissue, neoplasia, tumour development (no tumour development was found in mice tested subcutaneously with a dose of 10 million cells/mouse) or appearance of opportunistic infections. No tumorigenic behaviour after long term *ex vivo* culture of eASCs has been found. In addition, a decreased differentiation capacity of the cells with extended expansion of eASCs has been observed.

From an allogeneic point of view, TiGenix research indicates that allogeneic Cx611 do not trigger immune response by the host immune system by using PBMCs from healthy donors cultured several times *in vitro* with autologous or allogeneic eASCs. Studies performed in intravenously treated patients with rheumatoid arthritis indicated that three administrations generated allo-antibodies in 16.9% of the patient population. In comparison, the IV administration of allogeneic eASCs could be similar as a blood transfusion in terms of generation of allo-antibodies that might reject the product in a further administration.

Therefore, our preclinical understanding of the allogeneic eASCs shows that these cells are well tolerated and have therapeutic capacities (in experimental models and in samples from patients) which make them an excellent source of cells for cell therapy. Based on the clinical experience up to now, there are no known specific adverse events that can be attributed to the use of allogeneic eASCs.

Based on this, the potential indication developed by TiGenix for allogeneic eASCs administered intravenously is severe sepsis.

In summary, available preclinical and clinical results on cellular therapy with Cx611 have shown that the overall benefit-risk balance is acceptable, and suggest that it may be well tolerated treatment for sCABP associated with severe sepsis. The limited possible risks associated with the administration of Cx611 may include tumour formation, unwanted local or systemic immune response and transmission of adventitious agents. There is also a potential risk associated with the mode of administration of cells clustering as demonstrated in small animals, possibly leading to embolisms after IV administration. Although all ICU patients present with coagulation disorders due to various factors, this risk will be considered as an AESI (please refer to the Investigators' Brochure (1)).

The current phase Ib/IIa study is proposed to assess the safety of two 80 mL allogeneic Cx611 central line infusions (from a single, healthy donor) on Days 1 and 3 at a dose of 160 million cells per infusion (320 million cells total), in an add-on therapy design compared to a placebo control group, for the treatment of sCABP and sepsis. As a secondary objective, the study will explore the efficacy of Cx611 for treating sCABP. An immunological monitoring will be also done to further understand the absence of relevant alloreactivity in these patients and how the allogeneic treatment is affecting the patient. The immunological follow up will include: the pattern of pro- and anti- inflammatory cytokines before and after treatment in serum, to demonstrate immunological signals of efficacy; the measurement of anti-donor specific antibodies, to ensure that the treatment is safe and does not induce a significant antibody response; the profile of circulating cells, to address the patient inflammatory status; the response of PBMCs in response to stimulation and the control of the changes on the T cell proliferation caused by the Cx611 treatment, to understand the mode-of-action of Cx611.

The completion of this study will contribute to the basic knowledge on stem cells and their mode-of-action, and has a large translational character. The study results will be critical for the design of further confirmatory clinical trials in terms of definition of endpoints, key biomarkers and sample size determination.

5.10 Risk Assessment

The preclinical (pharmacology, pharmacokinetic and toxicology) profile of Cx611 supports its development as a potential treatment for sCABP. The current study is being conducted to investigate safety and tolerability and to explore the efficacy of Cx611 co-administered with standard of care (SoC) in patients with sCABP, as outlined in the rationale for the study (Section 5.9). The preclinical and clinical safety findings are summarised as part of the background information (Sections 5.5-5.8) and are described in detail in the Investigators Brochure (1).

Important potential risks of allogeneic stem cell administration might include tumour formation, unwanted local and systemic immune response, transmission of adventitious agents and, when administered intravenously, thromboembolism (40,42–44) and local pulmonary inflammation from immunologic origin (reported in a literature report after IV injection of stem cells in dogs (68)). Also, sustained engraftment of eASCs with an ability to differentiate into various cell types could potentially lead to ectopic tissue formation in the

recipient, although analysis of tissues following mesenchymal stromal cell therapy in humans indicated limited long-term engraftment and no ectopic tissue formation (69).

During the clinical trial programs of Cx611, Cx601 or Cx621, no important risks have been identified so far. No dose-dependent safety concern or toxicity could be identified, no ectopic tumour formation, nor hypersensitivity reaction, and no thromboembolic event to the lungs were reported. In clinical study Cx611-0101 doses up to 4 million eASC cells per kg body weight were injected intravenously on 3 consecutive occasions with a 1-week interval without any report of pulmonary embolism (1). The production of allogeneic antibodies in some patients has not been reported to be associated to any adverse events so far (1).

This was observed in the phase I study of Cx611 in healthy human volunteers. In this study no clinically relevant electrocardiogram (ECG) findings or corresponding AEs were reported, where 32 subjects were exposed to single doses of Cx611 up to 4 million eASC cells per kg body weight.

The potential safety concerns were carefully assessed for their relevance to application of the medication in clinical settings. A 240 mL/h infusion rate has been established to prevent any risk of thromboembolism, and lung function will be continuously monitored during and after the infusion.

In spite of the above, the low number of subjects treated so far does not permit any conclusion of safety. Investigators should especially be alerted to the potential risks described above and any sign or symptom that could be suspicious for such an event should be carefully assessed.

The Sponsor will immediately notify the Investigators and responsible Ethics Committees if any additional safety or toxicology information becomes available during the study after review by the DMC.

6 STUDY OBJECTIVES

The purpose of this randomised, multicentre, double blind, placebo controlled, phase Ib/IIa study is to assess the safety, tolerability and efficacy of eASCs (Cx611) administered intravenously as adjunctive therapy, therefore in addition to SoC therapy, to patients with sCABP.

The key objectives of this study are to:

6.1 Primary Objective

- Investigate the safety profile of two allogeneic Cx611 80 mL infusions administered through a central line within 3 days (on Days 1 and 3) at a dose of 160 million cells each (320 million cells total). To monitor any adverse event and potential immunological host responses against the administered cells during 90 days of follow-up after the first infusion.

6.2 Secondary Objective

- Explore the clinical efficacy of Cx611 in terms of a reduction of the duration of mechanical ventilation and/or need for vasopressors and/or improved survival, and/or clinical cure of the sCABP, and other efficacy-related endpoints (see section 10.1.3)

6.3 Exploratory Objectives

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7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This will be a Phase Ib/IIa, randomised, double blind, parallel groups, placebo controlled and multicentre trial to assess the safety and efficacy of a new therapy with eASCs (Cx611) for the treatment of sCABP.

The study will permit concomitant SoC treatment of the sCABP (including antibiotic and standard therapy in the ICU) and Cx611, in an add-on design. Subjects will receive SoC therapy according to local guidelines plus two 80 mL central line infusions at 240 mL/h (on Days 1 and 3) of IV allogeneic treatment administration of Cx611, at a fixed dose of 160 million cells per infusion, or placebo.

This study will enrol approximately 85 adult male and female subjects with sCABP, who will be randomised to receive Cx611 or placebo in a 1:1 design. It is expected to have equal distribution between the Cx611 and placebo treatments due to the 1:1 randomization design. Each subject will receive two 20-30 minute central line infusions (active or placebo) according to a pre-defined randomisation list.

In order to balance mechanical ventilation and vasopressors requirement between groups, a stratified allocation will be considered based on CABP severity criteria at inclusion:

- Shock requiring vasopressors, or
- Respiratory failure requiring invasive mechanical ventilation, or
- Both.

In each stratum, patients will be randomised 1:1 to Cx611 or placebo.

The Screening duration will be around 18 hours, treatment duration will be three days and the total study duration per subject will be two years.

There will be a total of 12 visits per subject: Screening visit and on Days 1, 2, 3, 4, 5, 6, 7, 8-10, 14, 29 and 90. For all visits scheduled after hospital discharge, costs of travel to hospital (such as taxi) will be reimbursed by the Sponsor.

The double blind design will be maintained until the primary safety and secondary efficacy endpoints have been assessed (i.e. at Day 90). The study participants (Sponsor, investigators and site team members) will be unblinded after all Day 90 data have been collected.

Long-term follow-up: Study site personnel will give four follow-up phone calls to the patient, at Months 6 (Day 180 ±30 days), 12 (Day 365 ±30 days), 18 (Day 545 ±30 days) and 24 (Day 730 ±30 days), to assess any spontaneous report of a health event from him/her. Up

to three phone call attempts will be done and if not successful, a contact will be established with the patient's General Practitioner (GP) or family doctor. The investigator will report any SAE and will liaise with the patient's GP or family doctor for obtaining further documentation to appropriately assess the SAE.

An approximate 18-hour Screening period is scheduled to determine a patient's eligibility for inclusion in the study. Subjects may be screened at the emergency department, but will be treated and receive the study medication (Cx611 or placebo) in the ICU.

The start of the first infusion of Cx611 or placebo will occur as early as possible in ICU within the first 18 hours of patients fulfilling at least one of the two major criteria of severity for CAP (i.e. from the initiation of invasive ventilation support or vasopressors, whichever comes first), after patient's eligibility is confirmed. The day of administration of the first dose will be considered the Day 1 of the study and study days are considered as calendar days, not as 24-hour days.

If the patient is unable to comprehend the scope of the trial prior to enrolment due to altered mental status associated with the underlying pneumonia or any other disease: written informed consent to participate in the study must be obtained from the patient's legally acceptable representative, as required by national laws, respective regulations and Institutional Review Boards/Independent Ethics Committees/Regional Ethics Boards (IRB/IEC/REB). Written informed consent should be sought from the patient as soon as he/she becomes capable of comprehending the scope of the trial.

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administration. Safety and efficacy assessments will also be performed at different time points during the study period.

The study consists of the following periods:

- **Screening visit (around 18 hours)** starts, when not exempted according to local legislation, with signature of informed consent. Screening procedures will be performed so that first infusion of Cx611/placebo can be started **as early as possible** within the first 18 hours of patients fulfilling at least one of the two major criteria of severity for CAP (i.e. from the initiation of mechanical ventilation support or vasopressors, whichever comes first), after patient's eligibility is confirmed.
- **Baseline** (BL) **(Day 1)** data is the last assessment prior to initiation of study treatment.

- **Treatment period (Days 1 and 3)** starts with the administration of first dose (Day 1) and ends with the second dose administration of Cx611/placebo (Day 3).
- **Clinical Response visit (Day 14 ± 2)** is the time of the assessment of the clinical response at 14 ± 2 days after the first dose of Cx611/placebo. Clinical response will be also assessed at visits on Days 8-10 and 29 ± 2.
- **Primary Safety Endpoint visit (Day 90 ± 4)** is performed at 90 ± 4 days after the first dose of Cx611/placebo.
- **Premature discontinuation** can occur if the patient withdraws from the study before Day 90, and leads to ET visit.
- **Long-term safety follow-up: phone calls** are performed at **Month 6 ±30 days, Month 12 ±30 days, Month 18 ± 30 days** and **Month 24 ± 30 days** after the first dose of Cx611/placebo.

7.2 Study Procedures

7.2.1 Schedule of Study Assessments

The study assessments described in the sections below are presented in detail in Section 10 (safety, efficacy and immunological assessments and demographic data and baseline characteristics). Recording and reporting of AEs is described in detail in Section 11.

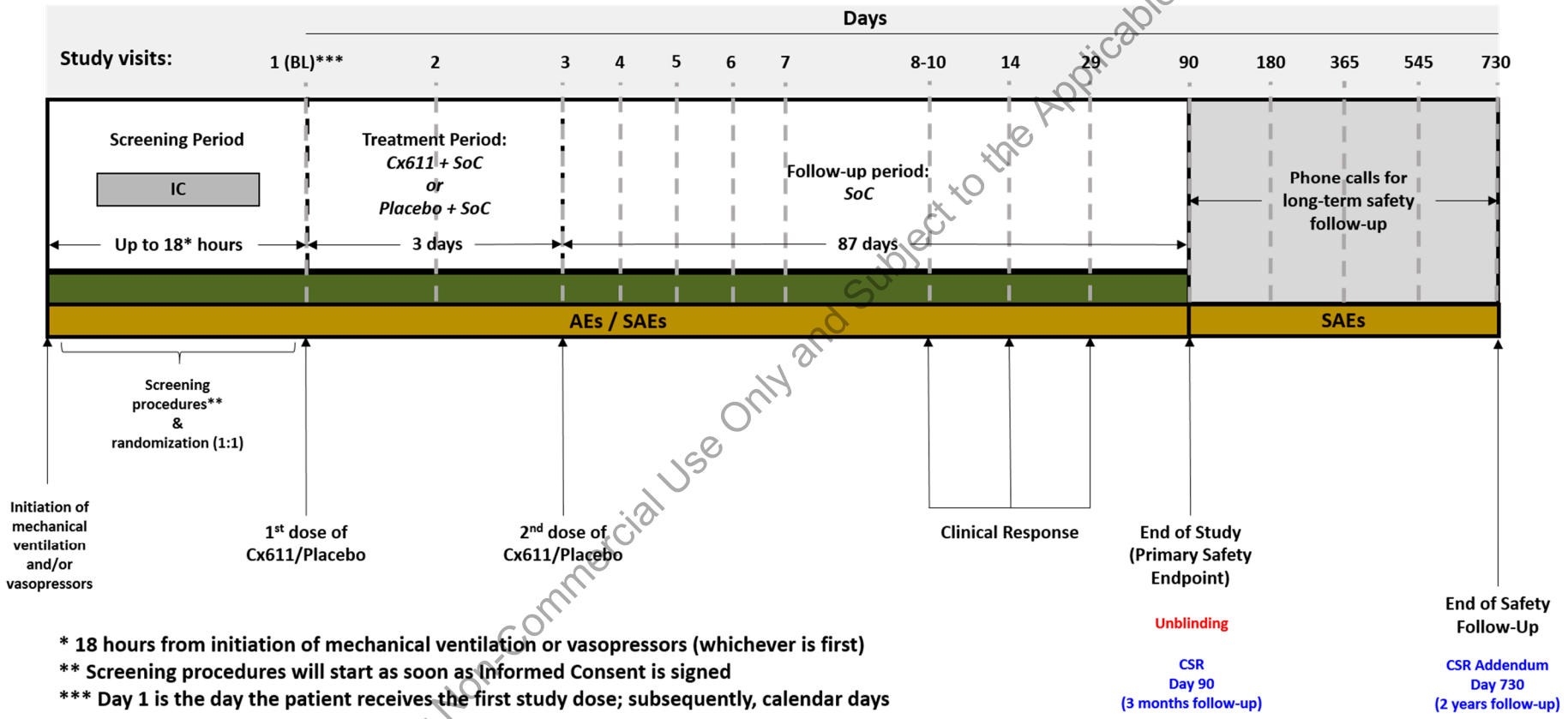
The timing of all study assessments is shown in Table 1 in Section 1.

7.2.2 Study Flow Chart

Table 1 in Section 1 shows a schematic representation of the assessments during the study. The overall study design is depicted in Figure 1 below.

Apart from the Screening visit, there will be 11 scheduled visits plus four phone calls at Month 6 ± 30 days, Month 12 ± 30 days, Month 18 ± 30 days and Month 24 ± 30 days for long-term safety follow-up. If there is a premature discontinuation for any reason before Day 90, the patient will undergo an ET Visit.

Figure 1. Study Design



* 18 hours from initiation of mechanical ventilation or vasopressors (whichever is first)
** Screening procedures will start as soon as Informed Consent is signed
*** Day 1 is the day the patient receives the first study dose; subsequently, calendar days

7.2.2.1 Screening Period

Screening visit will take place promptly once the patient presents clinical evidence that one of the two major criteria of severity for CABP are being met (i.e. need for mechanical ventilation or vasopressors, whichever comes first) and after informed consent is obtained, unless exempted by applicable local legislation.

Before any study procedure, **as soon as sCABP is clinically diagnosed and indication for initiating mechanical ventilation and/or treatment with vasopressors is met**, written informed consent to participate in the study must be obtained from the patient's legally acceptable representative, as required by local laws and guidelines (written informed consent should be sought from the patient as soon as he/she becomes capable of comprehending the scope of the trial).

Screening period will last around 18 hours. Throughout this period, the patient's eligibility for study entry will be assessed based on the inclusion and exclusion criteria (Section 8).

Note: The start of the first administration of the Cx611/placebo will occur within 18 hours of patient fulfilling at least one of the two major criteria of severity for CABP (i.e. from the initiation of invasive mechanical ventilation support or vasopressors, whichever comes first). Screening and randomisation procedures should be built into the patient recruitment process to allow for this to happen.

The following procedures will be performed and recorded and/or data collected from the patient´s clinical records during the Screening period:

- Informed consent.
- Assessment of inclusion/exclusion criteria.
- Demographic data and complete medical history including previous and current diseases and allergies, immunological status (i.e. previous pregnancies and/or transplants and/or blood transfusions), previous anti-pneumococcal vaccination and risk factors for pulmonary embolism as applicable by inclusion and exclusion criteria (history of previous deep venous thrombosis or pulmonary embolism; history of chronic congestive heart failure; hormone replacement therapy or oral contraceptive therapy; antiphospholipid antibody syndrome; hereditary thrombotic risk [antithrombin deficiency, protein C and protein S deficiencies, activated protein C resistance; factor II –prothrombin- G20210A

mutation, hyperhomocysteinemia], thrombophilia; fracture of pelvis, hip or long bones; lower limb orthopaedic surgery; malignancy; major general surgery).

- Prior antibiotic and non-antibiotic treatments for CABP and treatments for other diseases (within the last 2 weeks); concomitant treatments for sCABP and other diseases (concomitant medication page will be completed, including all medication taken by the patient at the time of the visit).
- Physical examination including weight and height.
- Assessment of clinical signs and symptoms of pneumonia.
- Vital signs measurement (systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and, in non-ventilated patients, respiratory rate). If more than one measurement is available during screening period, only the highest and lowest values measured for each vital sign will be recorded in the case report form (CRF).
- Serum pregnancy test in women of childbearing age (a rapid diagnosis using urine pregnancy test may be performed for inclusion, awaiting the serum pregnancy test for confirmation).
- PaO_2/FiO_2 (if more than one reading is available during the screening period then the lowest value will be recorded). A conversion table (SO_2 % to PaO_2 mmHg and O_2 l/min to FiO_2 % is provided in Appendix E).
- CURB-65 (Confusion, Urea >7 mmol/L, respiratory rate ≥30 breaths/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure), age ≥65 years) score when severity criteria are met and before mechanical ventilation is applied (see Appendix B).
- APACHE II score assessment at admission to ICU.
- Sequential Organ Failure Assessment (SOFA) score at admission to ICU.
- 12-lead ECG.
- Chest X-ray (CXR).
- Pathogen identification and susceptibility testing: For the confirmation of the causative pathogen of the bacterial pneumonia, pulmonary, pleural, blood and urine samples will be collected and analysed by any established standard diagnostic method routinely applied at the study site including classical microbiology and/or any other methods. Pulmonary

samples can be obtained by bronchoalveolar lavage (BAL) and/or mini-BAL/protected specimen brush (PSB) and/or by endotracheal aspiration (ETA) for intubated patients, and sputum production for non-ventilated patients. Samples will be rapidly processed for Gram stain and culture and/or other established standard rapid diagnostic system, e.g. peptide nucleic acid fluorescent in situ hybridization (PNA FISH) or Cepheid GeneXpert for *S. aureus*, urinary antigen test for *S. pneumoniae* or *Legionella*, or real-time polymerase chain reaction (rt-PCR). Should a bacterial pathogen grow in culture, susceptibility testing against the standard local antibiotic panel for the pathogen will be performed according to the site´s practice. Pathogen identification and susceptibility testing will be collected from follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well. Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence.

- Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements), CCI [redacted].
- Urine samples for urinalysis (according to local laboratory requirements) and pneumococcal urine antigen (according to local laboratory requirements).
- Assessment of eligibility criteria and approval call to CCI [redacted] See Section 8.2.
- Randomisation of the patient.
- AEs assessment and recording (from the time of signing the informed consent).

7.2.2.2 Visit 1: Study Day 1 (BL)

Day 1 is considered to be the calendar day in which first dose of study medication is administered.

1) If the first dose of study medication starts on the <u>same calendar day</u> of Screening, after having performed all the assessments of Screening period above (7.2.2.1) please proceed with the following:

- Pre-study product administration:
  - Blood samples for anti-HLA/donor antibodies (Abs) CCI [redacted]
  - Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients).
- Start IV administration of study product (Cx611 or placebo) **as early as possible and within the first 18 hours of patient fulfilling at least one of the two major criteria of severity for CABP (i.e. from the initiation of invasive mechanical ventilation support or vasopressors, whichever comes first**).
- During and post-study product administration:
  - Duration of infusion.
  - Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients) at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post investigational medicinal product (IMP) infusion.
  - Signs of hypersensitivity reactions or anaphylaxis (the patient will be monitored for skin reactions and episodes of respiratory distress requiring therapeutic intervention during the first 24 hours after the infusion of IMP).
- Post-study product administration (only):
  - 12 lead ECG. 5 hours ± 1h post IMP infusion
  - CCI [redacted]
- Pre, during and post-study medication administration: AEs/ treatment emergent adverse events (TEAEs) assessment and recording including any AESI.

2) If the first dose of study medication starts the calendar day after the Screening procedures, then the following assessments will be performed:

- Pre-study medication administration:
  - Review of inclusion/exclusion criteria.

- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients).
- PaO_2/FiO_2 (if more than one reading is available on the same day then the lowest value will be recorded).
- APACHE II score assessment.
- SOFA score assessment and recording.
- *If applicable (and as per investigator´s decision)*: CXR, pulmonary and blood samples for culture (results will be recorded in the CRF).
- Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements), anti-HLA/donor Abs CCI [redacted]
- Urine samples for urinalysis (according to local laboratory requirements).

- Start IV administration of study medication (Cx611 or placebo) **as early as possible and within the first 18 hours of patient fulfilling at least one of the two major criteria of severity for CABP (i.e. from the initiation of invasive mechanical ventilation support or vasopressors, whichever comes first**).
- During and post-study medication administration:
  - Duration of infusion.
  - Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients) at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post IMP.
  - Signs of hypersensitivity reactions or anaphylaxis (the patient will be monitored for skin reactions and episodes of respiratory distress requiring therapeutic intervention during the first 24 hours after the infusion of IMP).

- Post-study medication administration:
  - 12 lead ECG. 5 hours ± 1h post IMP infusion.
  - CCI [redacted]
- Pre, during and post-study medication administration: AEs/TEAEs assessment and recording including any AESI.

7.2.2.3 Visit 2: Study Day 2

- Concomitant treatments for sCABP and other diseases. Concomitant medication page will be updated.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs at least 4 times (i.e. every 6 hours±1h): systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). When more than one measurement is available for Day 2, only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that time point.
- PaO_2/FiO_2 (if more than one reading is available on the same day then the lowest value will be recorded).
- *If applicable (and as per investigator´s decision):* CXR, pulmonary and blood samples for culture (results will be recorded in the CRF).
- CCI [redacted]
- Urine samples for urinalysis (according to local laboratory requirements).
- TEAEs assessment and recording including any AESI.

7.2.2.4 Visit 3: Study Day 3

- Pre-study product administration:
  - Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.

- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). When more than one measurement is available for Day 3, only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- PaO_2/FiO_2 (if more than one reading is available on the same day then the lowest value will be recorded).
- Blood samples for haematological and coagulation tests (according to local laboratory requirements).
- *If applicable (and as per investigator's decision)*: CXR, pulmonary and blood samples for culture (results will be recorded in the CRF).

- IV administration of study product (Cx611 or placebo) (48 hours ± 2 hours after the start of infusion of the first IMP dose).
- Post-study product administration:
  - Duration of infusion.
  - Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients) at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post IMP infusion.
  - Signs of hypersensitivity reactions or anaphylaxis (the patient will be monitored for skin reactions and episodes of respiratory distress requiring therapeutic intervention during the first 24 hours after the infusion of IMP).
  - 12 lead ECG. 5h±1h post IMP infusion.
  - CCI [redacted]

- Pre, during and post-study product administration: TEAEs assessment and recording including any AESI.

7.2.2.5 Visits 4-7 (Study Days 4, 5, 6 and 7):

- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients,). On Days 4, 5, 6, 7 if patient is in the ICU at least 4 times daily (i.e. every 6h±1h), if discharged from ICU at least once. When more than one measurement is available for Days 4, 5, 6 or 7 only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- PaO_2/FiO_2 (if more than one reading is available on the same day then the lowest value will be recorded).
- *If applicable (and as per investigator´s decision):* CXR, pulmonary and blood samples for culture (results will be recorded in the CRF).
- **Only at Days 4 and 7:**
    - Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements).
    - SOFA score assessment and recording.
    - Urine samples for urinalysis (according to local laboratory requirements).
- **Only at Days 5 or 6:**
    - Proximal lower limb compression ultrasonography.
- **Only at Day 7:**

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- TEAEs assessment and recording including any AESI.

7.2.2.6 Visit 8: Study Days 8-10

- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). On Days 8-10 if patient is in the ICU at least 4 times daily (i.e. every 6h±1h), if discharged from ICU at least once. When more than one measurement is available only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- *If applicable (and as per investigator's decision):* pulmonary and blood samples for culture (results will be recorded in the CRF).
- CXR
- sCABP Clinical Response assessment.
- TEAEs assessment and recording, including any AESI.

7.2.2.7 Visit 9: Study Day 14 ± 2

- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). On Visit 9 if patient is in the ICU at least 4 times daily (i.e. every 6h±1h), if discharged from ICU at least once. When more than one measurement is available only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- SOFA score assessment and recording.
- *If applicable (and as per investigator's decision):* pulmonary and blood samples for culture (results will be recorded in the CRF).
- CXR.

- sCABP Clinical Response assessment and recording.
- Pneumonia recurrence / reinfection assessment and recording (see page 8 for definition). Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence. Pathogen identification and susceptibility testing data will also be collected from pneumonia recurrence follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well.
- Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements), anti-HLA/donor Abs & CCI [redacted]
- Urine samples for urinalysis (according to local laboratory requirements).
- TEAEs assessment and recording, including any AESI.

7.2.2.8 Visit 10: Study Day 29 ± 2

- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). On Visit 10 if patient is in the ICU at least 4 times daily (i.e. every 6h±1h), if discharged from ICU at least once. When more than one measurement is available, only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- SOFA score assessment and recording.
- *If applicable (and as per investigator´s decision):* pulmonary and blood samples for culture (results will be recorded in the CRF).
- CXR.
- sCABP Clinical Response assessment and recording.

- Pneumonia recurrence/reinfection assessment and recording (see page 8 for definition). Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence. Pathogen identification and susceptibility testing data will also be collected from pneumonia recurrence follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well.
- Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements CCI [redacted]
- Urine samples for urinalysis (according to local laboratory requirements).
- TEAEs assessment and recording, including any AESI.

7.2.2.9 Visit 11: Study Day 90 ± 4

- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). On visit 11 if patient is in the ICU at least 4 times daily (i.e. every 6h±1h), if discharged from ICU at least once. When more than one measurement is available only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- *If applicable and as per investigator´s decision (e.g. clinical suspicion of pneumonia recurrence):* CXR, pulmonary and blood samples for culture (results will be recorded in the CRF).
- Pneumonia recurrence / reinfection assessment and recording (see page 8 for definition). Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence. Pathogen identification and susceptibility testing data will also be collected from pneumonia recurrence follow-up pulmonary/blood/respiratory/pleural cultures performed as per investigator´s decision as well.

- Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements) and anti-HLA/donor Abs (4.5 mL EDTA).
- Urine samples for urinalysis (according to local laboratory requirements).
- TEAEs assessment and recording, including any AESI.

7.2.2.10 Long-term safety follow-up (phone calls at Month 6 [Day 180 ± 30 days], Month 12 [Day 365 ± 30 days], Month 18 [Day 545 ± 30 days] and Month 24 [Day 730 ± 30 days]

- Patients will be contacted via a phone contact and SAE data will be collected via the Safety Follow Up Form and reported in the SAE Report Form.

7.2.2.11 Early Termination

If the patient discontinues the study for any reason before Day 90, perform the following:

- ET date and reason.
- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Physical examination including assessment of clinical signs and symptoms of pneumonia.
- Vital signs: systolic and diastolic blood pressure, heart rate, core temperature (tympanic, rectal or bladder) and respiratory rate (in non-ventilated patients). When more than one measurement is available, only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.
- *If applicable (and as per investigator's decision):* PaO_2/FiO_2 and SOFA score assessment and recording, sCABP Clinical Response assessment and recording, pneumonia recurrence / reinfection assessment and recording, CXR, pulmonary and blood samples for culture (results will be recorded in the CRF.
- Blood samples for haematological, coagulation and biochemical tests (according to local laboratory requirements), anti-HLA/donor Abs CCI [redacted]
- CCI [redacted]

- Urine samples for urinalysis (according to local laboratory requirements).
- AEs/TEAEs assessment and recording, including any AESI.

7.2.2.12 Unscheduled Phone-call Follow-up (If Applicable)

Unscheduled phone-calls are proposed for safety follow-up in case the patient cannot attend to any visits (e.g. due to a bone fracture) or for any contact requested by the patient between scheduled visits. In these phone calls, perform the following:

- Unscheduled phone-call follow-up date and reason.
- AEs assessment and recording, including any AESI.
- Concomitant medication page will be updated with treatment for sCABP and other diseases as it applies.
- Remind the patient to visit the investigator at the next scheduled visit or for an end of study (EOS) visit as soon as possible (if applicable).

7.3 Discussion of Study Design, Including the Choice of Control Groups

This is a multicentre, randomised, double blind, parallel-group, placebo controlled, exploratory concept study. The selected dose of the experimental medication has been chosen on the basis of the safety results obtained in the Phase Ia/IIb in rheumatoid arthritis and Phase I in healthy male volunteers challenged with LPS, studies previously performed by TiGenix. The double blind design is needed to ensure unbiased data collection. The study will be unblinded (Sponsor, investigators and site team members) after the analyses at Day 90 of the primary safety and secondary efficacy variables for all subjects. The two-year follow-up will allow long-term safety data collection.

7.4 Study Period

Screening period will last around of 18 hours. Treatment period will be 3 days (administration on Days 1 and 3). During and after the treatment period, efficacy assessments will be performed at different time points until Day 90 ±4 after the first dose of study medication (Day 1); safety assessments will be performed at different timepoints until Day 90 ±4 after the first dose of study medication (Day 1).

Long-term safety follow-up will include four safety follow-up phone calls made to the patient at Day 180 ±30 days, Day 365 ±30 days, Day 545 ±30 days and Day 730 ±30 days.

7.5 End of Study

The EOS is defined as the date of the subject's last scheduled visit (Day 90 ±4 days) or early withdrawal from study prior to Day 90 ±4 days.

8 SELECTION OF STUDY POPULATION

8.1 Number of Subjects

The number of 180 patients in total (i.e. 90 patients per group) was deemed to be sufficient to fulfil the objectives of this exploratory study.

The study will be conducted in approximately 20 centres across Belgium, France, Lithuania, and Spain. Subject enrolment distribution across sites is expected to fluctuate throughout the duration of the study, but no single centre is expected to enrol >20% of the study subject total.

The specific inclusion and exclusion criteria for enrolling patients in this study are described below (Section 8.3, Inclusion Criteria and Section 8.4, Exclusion Criteria). All the inclusion and exclusion criteria should be fulfilled before including a patient into the study.

8.2 Screening Log

Each participating centre will keep a log of all screened patients with sCABP. The investigator is requested to record the reason(s) for not including patients who were screened but not enrolled.

Due to the short time window (up to 18 hours) between fulfilment of severity criteria (i.e. from the initiation of invasive mechanical ventilation support or vasopressors, whichever comes first) and start of administration of the first dose of study treatment, patients with a sCABP, either suspected and/or later confirmed its bacterial origin by any established standard diagnostic method routinely applied at the study site (e.g. urinary antigen test, rt-PCR), can be entered into the study.

After performing the screening visit and verifying inclusion (see Section 8.3) and exclusion (see Section 8.4) criteria and subject´s eligibility, the investigator will place a screening and approval call to the CCI physicians to be provided with a randomisation authorisation number. No patient will be randomised without this authorisation number. CCI personnel will also be available for consultation in case of screening doubts and for medical advice of subject´s management. The CCI will keep record of the conversations with investigators in a dedicated database and available for review by the sponsor on a monthly basis at least.

8.3 Inclusion Criteria

The reference population will consist of adult patients with a sCABP, admitted to the ICU. All of them must comply with the following inclusion criteria:

1. Adult subjects of either gender (aged ≥18 years and ≤80 years old).
2. Body weight between 50 kg and 100 kg.
3. Clinical diagnosis of acute (developed within ≤21 past days) community-acquired bacterial pneumonia based on the presence of two relevant signs (fever, tachypnoea, leukocytosis, or hypoxemia) and radiographic findings of new pulmonary infiltrate/s.
4. Subjects with pneumonia of sufficient severity requiring ICU management and with at least one of the two following major criteria of severity present for less than 18 hours:
    a. Requiring invasive mechanical ventilation for respiratory failure due to pneumonia, or
    b. Requiring treatment with vasopressors (i.e. dopamine >5 µg/kg/min or any dose of epinephrine, norepinephrine, phenylephrine or vasopressin) for at least 2 hours to maintain or attempt to maintain systolic blood pressure (SBP) >90 mm Hg (or MAP >70 mm Hg) after adequate fluid resuscitation (i.e. for shock).

    NOTE: Patients that are for 18 hours or more under high flow nasal cannula (HFNC) at ≥50 litres per minute and FiO2 ≥0.6 or under non-mechanical ventilation (NMV) are not eligible for the study.
5. Female subject of no childbearing potential i.e. non fertile, pre-menarche, permanently sterile (i.e. underwent hysterectomy, bilateral salpingectomy or bilateral ovariectomy) or post-menopausal (history of no menses for at least 12 months without an alternative medical cause)

    or

    Woman of childbearing potential* with a negative serum or urine pregnancy test (sensitive to 25 IU human chorionic gonadotropin [hCG]) and agree to use an adequate method of contraception for three months after the last dose of the IMP according to her preferred and usual life style. Adequate methods of female contraception for this study are: sexual abstinence (refraining from heterosexual

intercourse), hormonal contraception (both progesterone-only or combined oestrogen and progesterone; both with inhibition of ovulation or where inhibition of ovulation is not the primary mechanism of action), intra-uterine device, bilateral tubal occlusion, condom use by male sexual partner(s) or medically-assessed successfully vasectomised male sexual partner(s).

**A woman of childbearing potential is a woman between menarche and post-menopause (history of no menses for at least 12 months without an alternative medical cause) unless she has undergone hysterectomy, bilateral salpingectomy or bilateral ovariectomy*

Male subject agreeing to use one of the following methods of birth control according to his preferred and usual life style for three months after the last dose of the IMP: sexual abstinence (refraining from heterosexual intercourse), use of condoms or medically-assessed successful vasectomy, or having a female sexual partner(s) who is using an adequate method of contraception as described above.

6. Signed informed consent provided by the subject, the relatives or the designated legal representative according to local guidelines.

8.4 Exclusion Criteria

A patient will not be included in the study if he/she meets ANY of the following criteria:

1. Subjects with Hospital acquired (HAP)-, Health Care associated (HCAP)- or Ventilator associated-pneumonia (VAP).
2. Subjects with pneumonia exclusively of viral or fungal origin*. Subjects with bacterial pneumonia co-infected with viruses and/or other microorganisms may be entered into the study.

**Due to the short time window (up to 18 hours) between fulfilment of severity criteria (i.e. initiation of invasive mechanical ventilation or vasopressors, whichever comes first) and the start of the first dose of study treatment, patients with a pneumonia of suspected bacterial origin by any established standard diagnostic method routinely applied at the study site (e.g. urinary antigen test, rt-PCR) can be entered into the study (confirmation of bacterial origin must be obtained afterwards).*

3. Subjects with known or suspected *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia.
4. Subjects with an aspiration pneumonia.
5. Subjects with known active tuberculosis.
6. Subjects with a history of post-obstructive pneumonia.
7. Subjects with cystic fibrosis.
8. Subjects with any chronic lung disease requiring oxygen therapy at home.
9. Presence of infection in another organ location caused by same pathogen (e.g. pneumococcal meningitis in the context of pneumococcal pneumonia).
10. Subjects expected to have rapidly fatal disease within 72 hours after randomisation.
11. Inability to maintain a mean arterial pressure ≥50 mmHg prior to screening despite the presence of vasopressors and intravenous fluids.
12. Subjects not expected to survive for 3 months due to other pre-existing medical conditions such as end-stage dementia or other diseases.
13. Subjects with a history of malignancy in the 5 years prior to screening, except for successfully surgically treated non-melanoma skin malignancies.
14. Subjects with known primary immunodeficiency disorder or with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) with CD4 count <200 cells/mm^3 or not receiving highly active antiretroviral therapy (HAART) for HIV.
15. Subjects receiving immunosuppressant therapy (including chronic treatment with any anti-TNFα) or on chronic high doses of steroids (single administration of ≥2 mg/kg body weight for ≥2 weeks or 20 mg/day of prednisone or equivalent[1] for ≥2 weeks).
16. Chronic granulocytopenia, not thought to be due to sepsis, as evidenced by an absolute neutrophil count <500 per μL >21 days prior to onset of pneumonia symptoms.

[1] See appendix A for dose equivalence between different types of corticosteroids

17. Subjects who received stem cell therapy, or allogenic transplantation (organ or bone marrow transplant) within the past 6 months.
18. Subjects receiving treatment with a biological agent (e.g. antibodies, cells), immunotherapy or plasma exchange treatment within the last 8 weeks.
19. Subjects currently receiving, or having received another investigational medication within 90 days prior to start of the study (or 5 half-lives of the investigational compound, whichever is longer).
20. CCI [redacted]
21. Subjects with a known liver function impairment, associated with liver cirrhosis (Child Pugh C) or known oesophageal varices.
22. Subjects hospitalised within the previous 15 days.
23. Conditions resulting in a New York Heart Association or Canadian Cardiovascular Society Class IV functional status.
24. End-stage neuromuscular disorders (e.g. motor neuron diseases, myasthenia gravis, etc.) or cerebral disorders that impair weaning.
25. Patients with quadriplegia (traumatic or otherwise).

8.5 Removal of Patients From Therapy or Assessment

In accordance with the Declaration of Helsinki, patients, or upon their legally authorised representatives' decision, will be free to withdraw from the study at any time if they wish so, for any reason specified or unspecified. Withdrawal from the study will not affect or detriment the patient's further care or treatment.

In addition, patients may be withdrawn from study treatment and assessments at any time, if deemed necessary by the Investigator or the study sponsor.

Potential reasons for withdrawal of patients from this study are:

- Occurrence of adverse events that justify the withdrawal from the study.
- The decision of a subject to withdraw from the study.
- Major protocol deviations.

A patient may also discontinue the treatment and/or study assessment prematurely, before the 90 days of scheduled follow-up, for several reasons. Potential reasons for premature discontinuation of patients from therapy and/or study assessments are:

- Pregnancy: Pregnant subjects will be withdrawn from further study treatment but not from the study (all assessments will continue until EOS visit). In addition, the pregnant subject will be followed for safety reasons until the end of the pregnancy.
- Subject is lost to follow-up.

The reason and date the subject early terminates or is withdrawn from the study will be documented in the CRF (e.g. lost to follow-up, consent withdrawn, AEs, etc.). If a subject is withdrawn from further treatment with the study product, the Investigator will attempt to complete all study assessments. If a subject is withdrawn from further assessments, the Investigator will attempt to complete all ET procedures (see Section 7.2.2.10). All AEs occurring 30 days after the last IMP infusion will be recorded and should be followed up according to Section 11.2.

Patients have the right to withdraw their consent at any time; in that case all data collected until the time of withdrawal will be used in the analyses, unless it is otherwise required by the patient or local regulations.

8.6 Handling and Replacement of Withdrawals

Randomised subjects who withdraw their consent or are removed should undergo the ET visit. These data will be registered in the CRF in the ET section.
Subjects who receive any dose of study treatment and who subsequently withdraw, or are withdrawn, from the study, regardless of the reason, will not be replaced.

8.7 Premature Termination of the Study

The Investigator or TiGenix may terminate this study prematurely for any reasonable cause. The IECs and Competent Authority (ies) (CAs) should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or to potential study patients.

- A decision on the part of TiGenix to suspend or discontinue the development of the IMP.

- The inability to enroll participants in the study in a reasonable timeframe.

If the CA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA can suspend or prohibit the study. Before the CA reaches its decision it shall, except where there is an imminent risk, ask the Sponsor and/or the Investigator for their opinion, to be delivered within one week (Directive 2001/20/European Commission (EC), Article 12, Section 1).

If the study is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the study patients or their legally authorised representatives and should assure appropriate therapy and follow-up for the patients.

9 TREATMENT OF SUBJECTS

9.1 Investigational Products

9.1.1 Treatment Regimens

Cx611 is a suspension of human eASCs of allogeneic origin, containing CryoStor® CS10 (sterile buffered solution) as excipient, dispensed in disposable vials, with no microbial preservative agents. The cells will be given on Days 1 and 3 at a dose of 160 million cells (2 million cells / mL, total volume 80 mL) each day through a 20-30 minute (240 mL/hr) IV central line infusion after dilution with Ringer Lactate solution. Total dose 320 million cells.

Placebo (CryoStor® CS10 and Ringer Lactate) will be given also through a 20-30 minute (240 mL/hr) IV central line infusion at the same quantity (total volume of 80 mL) and following the same schedule than the active treatment.

To ensure the double blinding, the primary packaging of Cx611 and placebo will be identical and the administration of the medication will be masked. In addition, a specific blinding plan at each site will document all personnel involved in the trial and their responsibilities as per the assignment with regard to the blind (see section 9.4).

9.1.2 Identity of Investigational Product(s): Dosage Form, Dose and Administration Route

Investigational product (Advanced Therapy Investigational Medicinal Product [ATIMP])

Drug substance

Expanded human viable allogeneic mesenchymal adult stem cells extracted from adipose tissue (eASCs).

eASCs is presented as a frozen cell suspension of expanded human viable allogeneic mesenchymal adult stem cells, derived from adipose tissue of subdermal origin.

The subdermal adipose tissue is obtained from an allogeneic selected healthy donor through liposuction. Donation procurement and testing are carried out according to the applicable regulation, in particular *Directive 2004/23/EC* and therefore under the implementation of *Directives 2006/17/EC*, *2006/86/EC* and *Royal Decree 1301/2006.*

Excipients

CryoStor® CS10, animal-free and protein-free, defined cryopreservation medium containing 10% (v/v) dimethyl sulfoxide (DMSO) (70).

Physicochemical and biological properties

The IMP consists of an allogeneic stem cell suspension in sterile buffered solution containing CryoStor® CS10 as excipient. This excipient constitutes an optimised biopreservation media for cells and tissues to preserve cells in ultra-low temperature environments (-80ºC to -196ºC), which enables to maintain the characteristics of the drug substance, eASCs during the freezing, storage, and thawing process. CryoStor® CS10 contains 10% of DMSO in the formulation as cryopreservant.

At the time of administration, the frozen product is thawed by adding an isotonic solution, i.e. Ringer lactate, to obtain an individual cell suspension that, afterwards, can be injected in humans.

Frozen product appearance is a white homogeneous solid, which becomes a clear yellowish suspension when thawed. The product is supplied as a frozen cell suspension for infusion containing 16 million cells/mL in single-use vials. The vials are tightly closed with rubber stoppers and sealed with a cap.

The product had an initial re-test period of 18 months if stored at -140°C or below. This re-test period has been extended and updated expiry dates are reflected in the Interactive Response Technology (IRT).

For administration eASCs will be thawed and diluted in Ringer Lactate. The material contained in the vials will be transferred to infusion bags for further dilution prior to IV administration. Detailed instructions on preparation of the medication will be provided to sites.

It is recommended that the administration of the reconstituted product starts not later than 45 minutes once the product is removed from the cryopreservation chamber to ensure the administration is completed within 75 minutes.

Placebo

The study placebo will consist of vials containing CryoStor® CS10 that will have similar external appearance to that of the verum product and will be thawed, diluted and prepared for

IV administration with Ringer Lactate as described for the eASCs, following the same administration schema.

9.1.3 Packaging and Labelling

Packaging and labelling of the Cx611 will be performed by TiGenix according to Good Manufacturing Practice (GMP) principles and local regulation. Products' labelling will report the following information:

- Name and address and contact phone of the Sponsor.
- The reference of the trial: code.
- Pharmaceutical dosage form and administration route.
- The number and units of the dosage form, batch number and expiry date.
- The statement "clinical research sample".
- Storage conditions.
- The investigator's name and the site name.
- The statement "This medicine may contain cells of human origin".
- Use according to the instruction manual included.

Container

The product is supplied as a frozen cell suspension for infusion containing 16 million cells/mL in single-use vials. The vials are tightly closed with rubber stoppers and sealed with a cap.

The packaging material is made up by:

- Primary package: polyolefin plastic sterile vials with sterile rubber stopper and seal.
- Labels printed in black ink by thermal transfer printer.

Secondary packaging: cardboard box with external labelling, containing two vials duly labelled.

The diluent buffer (Ringer's lactate solution) is supplied in plastic bags (the same packaging from the manufacturer).

A stock of diluents together with the ancillary materials for the preparation and the administration of the IMP will be supplied duly labelled to the participating sites.

9.1.4 Storage and Disposition of Study Medication

Both Cx611 and placebo vials will be shipped under temperature controlled conditions, using appropriate transport for biological samples. Shipping material is also duly labelled and will contain the package content list.

The IMP must be stored at -140ºC or below (liquid nitrogen or cryogenic freezers).

Specific instructions will be provided within a separate Study Operations Manual (SOM).

9.1.5 Handling of Study Medication

Study medication will be shipped by specialised courier to the hospital pharmacy or designated site storage facility, according to local practice and/or regulations.

The Drug Administrator or Designee will maintain adequate records of the receipt and disposition of shipment to the site, temperature excursion as well as the corresponding accountability. All used and unused vials of Cx611 and placebo should be destroyed at site as per the local standards.

The administration must be performed by authorised personnel with appropriate protocol training.

The SOM that will be provided to the site will ensure an appropriate training.

9.2 Method of Assigning Patients to Treatment Groups

Treatments will be allocated following a pre-established randomisation list, which will take into account, in order to balance different factors between the study treatments, a stratified allocation using the following criteria:

- shock, or
- invasive mechanical ventilation, or
- both

In each stratum, patients will be randomised 1:1 to Cx611 or placebo.

During Screening, after confirmation of inclusion/exclusion criteria, all eligible patients will be randomised via IRT to one of the treatment arms. After performing the screening visit and verifying inclusion and exclusion criteria and subject´s eligibility, the investigator will place a screening and approval call to the CCI physicians to be provided with a randomisation authorisation number. No patient will be randomised without this authorisation number.

CCI personnel will also be available for consultation in case of screening doubts and for medical advice of subject´s management. The CCI will keep record of the conversations with investigators in a dedicated database and available for review on a monthly basis at least. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfils all the inclusion/exclusion criteria. The IRT will assign a randomisation number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the package of IMP to be dispensed to the patient at each administration date. The package of IMP will include 2 vials of Cx611 or placebo properly labelled.

Prior to assigning the randomisation number, the site will inform the IRT provider about the stratum of the patient. The randomisation numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomisation list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers, taking into account the stratum, to randomisation numbers. These randomisation numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of the IRT provider using a validated system that automates the random assignment of medication numbers to packs containing the IMP.

The randomisation scheme for patients will be reviewed and approved by clinical team or a member of the Biostatistics Quality Assurance Group.

9.3 Selection of Doses in the Study

Dose identification for the clinical trial in cell therapy does not follow the same models used for traditional drugs. The models used to determine the dose of a drug are based on the studies in Phase I, in which different aspects are assessed such as the metabolism up to the excretion of the product. A cell therapy medicinal product consists of cells and not of isolated molecules. Therefore, cell products are not subject to commonly defined laws in pharmacokinetics and pharmacodynamics of traditional products. An example is the absence of metabolism in hepatic cytochromes that obviously should not happen. For these reasons, the decision related to a dose administration in cell therapy, even though based on scientific data, does not follow traditional diagram.

The safety and feasibility of IV eASC administration has been demonstrated in earlier phase I studies: a phase Ia/IIb in rheumatoid arthritis (1) where repeat doses (3 administrations one week apart) of 1, 2 and 4 million cells /kg were tested in 46 patients, and a phase I study in healthy volunteers in a LPS challenge trial, where a single dose of 0.25, 1 and 4 million cells /kg were tested in 24 healthy volunteers.

The dose schedule in the present study consists of two IV administrations of 160 million cells two days apart (Days 1 and 3). This dose is equivalent to a dose of 2 million cells/kg in a subject of 80 kg. No safety concerns have been detected under any of the tested doses, nevertheless in the latest phase I LPS response study in healthy volunteers , the highest dose, showed some proinflammatory and procoagulant effect. Thus, the 2 million cells/kg was selected by a Clinical Advisory Board as thought to better fulfil the safety requirements.

9.4 Blinding

Treatments will be prepared (by unblinded personnel) for administration in a blinded location. The infusion can be started (bag and system connected to pump and to central catheter and pump started) by blinded or unblinded personnel, however follow-up of infusion and assessments pre-, during and post-infusion will be done by blinded personnel. Once reconstituted, the IMP will be masked to prevent any potential breach of the double blind design.

In addition, the double blind will be preserved by having unblinded and blinded team at the site. There will be a specific blinding plan at every site, which will document all personnel involved in the trial and their responsibilities as per the assignment with regard to the blind. This blinding plan will be agreed and signed by TiGenix and the corresponding site responsible(s), before any inclusion at that site.

In particular, the study nurse (or designated personnel) who will prepare the treatment for administration will remain unblinded but the investigator/s (or designated personnel) will administer the treatment, collect the AEs and evaluate the clinical outcomes of sCABP in a blinded fashion. The unblinded study nurse or unblinded designated personnel will NOT be allowed to participate in any efficacy or clinical assessment during the study.

The unblinded personnel are not allowed to share information about the treatment with any member of the blinded team.

If the investigator deems that unblinding is necessary for the appropriate clinical care of the participant, he or she will be able to perform an emergency unblinding at any time via the IRT used for patient randomization. In this case the investigator will promptly document and explain the unblinding to the sponsor.

9.5 Prior and Concomitant Therapy

All additional treatment(s) being taken by the patients on entry into the study (prior to study treatment) or any time during the study (concomitant treatment) must be documented on the appropriate pages of the CRF (trade name and/or generic name).

Subjects will also receive SoC therapy as per local guidelines, with IV and/or oral antibiotics or other drugs, either alone or in combination. Details for dose and frequency of administration of SoC therapy (as well as warnings, precautions, and contraindications) can be found in the referenced summaries of product characteristics for the specific drugs selected by the investigator as SoC therapy. Investigators will be instructed to select only country-approved therapies.

9.6 Prohibited Medications

The following medications and therapies will be prohibited during the study. In the event of a question, the CCI should be contacted.

- Chemotherapy for neoplasms or other diseases.
- Immunosuppressant therapy (including chronic treatment with any anti-TNFα) or chronic high doses of steroids (single administration of ≥2 mg/kg body weight or 20 mg/day of prednisone or equivalent for ≥2 weeks)*.

  **Concomitant steroids for septic shock are allowed; the doses recommended by current guidelines* (22) *(hydrocortisone 200–300 mg/day, for 7 days) do not exceed ≥2 mg/kg of equivalent prednisone units (see Appendix A for corticosteroid conversion table).*
- Stem cell, organ or bone marrow transplant.
- Treatment with biological agents (e.g. antibodies, cells) or with plasma exchange treatment.
- Other investigational medicinal products.

9.7 Treatment Adherence

Treatment adherence will be ensured because treatment will be injected by trained clinical staff at Visit 1 (Day 1) and Visit 3 (Day 3).

9.8 Drug Accountability

Drug accountability will be performed at the site by the unblinded personnel trained and designated for this task.

9.9 Treatment Compliance

Cx611 (eASCs) and placebo will be administered under the supervision of the study nurse, or delegated professional, thus ensuring treatment compliance for all patients.

10 STUDY ASSESSMENTS

10.1 Safety, Efficacy and Additional Endpoints

10.1.1 Primary Safety Endpoints by Day 90

Safety measured throughout the study by the incidence of TEAEs judged related or not to study treatment, focusing on any AESI. Safety analyses will be performed based on the Safety Population.

The independent DMC will review safety data on a regular basis and ad hoc if needed. This DMC will be composed by a Chairman, expert in stem cells and former Chair of the Safety Committee of the completed CELLULA phase I trial, at least two Intensivists and an Independent Statistician. Membership, roles, responsibilities and operating procedures for the DMC will be specified in a separate independent DMC charter.

Subjects will be continuously monitored during and after treatment for:

- Frequency, duration, severity, seriousness, relatedness to study treatment, actions taken and outcome of AEs, from time of signature of inform consent until Visit 11 (Day 90) or study discontinuation. AEs will start being recorded after signing the informed consent. AEs occurring from the beginning of the administration of study medication and until Visit 11 (Day 90) or study discontinuation will be analysed as TEAEs.
- AESI (see Sections 5.10 and 11.1.6 and also refer to the Investigators' Brochure (1)).
- Signs for hypersensitivity reactions such as anaphylaxis (changes in systolic and diastolic blood pressure, core temperature [tympanic, rectal or bladder], respiratory rate [non-ventilated patients], heart rate), at Days 1 and 3 (at Pre-dose and at 0.5h [±5 min], 1h [±10 min], 2h [±10 min], 4h [±20 min], 12h [±30 min] and 24h [±1 h] post each IMP infusion. Episodes of skin reactions and respiratory distress requiring therapeutic intervention and their description during the first 24 hours after the infusion of IMP.
- Changes in vital signs (daily: systolic and diastolic blood pressure, heart rate, core temperature [tympanic, rectal or bladder], respiratory rate [in non-ventilated patients]) as follows: Screening, Day 1 (at Pre-dose, and at 0.5h (±5 min), 1h (±10

min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post each IMP infusion), Day 2 (at least 4 times), Day 3 (at Pre-dose, and at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post each IMP infusion), then at least 4 times daily while in the ICU or, if discharged from ICU, then at least once on Days 4, 5, 6, 7, 8-10, 14, 29, 90 or study discontinuation.

- Changes in 12-lead ECG from Screening, Days 1 and 3 both 5 hours ± 1 hour post-study treatment administration.
- Changes in haematology and coagulation, clinical chemistry (at least including renal, liver, cholesterol and triglycerides profiles), and urine analysis at Screening, Day 1 Pre-dose, and then at least on Days 2, 3 (only haematology and coagulation), 4, 7, 14, 29, and 90 or study discontinuation.
- Anti-HLA/donor Abs on Day 1 Pre-dose, Days 14 and 90 or study discontinuation.

10.1.2 Exploratory Safety Endpoint by Months 6 (Day 180), 12 (Day 365), 18 (Day 545) and 24 (Day 730) (Phone Calls)

- Relatedness to study treatment, actions taken and outcome of spontaneous SAEs will be captured after Day 90.

10.1.3 Secondary Efficacy Clinical Endpoints

Efficacy analyses will be performed based on the safety population.

Efficacy endpoints

1. Mechanical ventilator and vasopressors treatment-free days (number of days that a patient is alive and free from mechanical ventilation and vasopressors) over 28 days.
2. Percentage of patients alive and free of mechanical ventilation and free of vasopressors at Day 29.
3. Percentage of patients alive and free of mechanical ventilation at Day 29.
4. Ventilator free days (VFD) over 28 days. VFD are defined as one point for each day during the measurement period that subjects are both alive and free of mechanical ventilation (e.g., a patient who is extubated on Day 2 of the study and remains alive and free of the ventilator for the remainder of the 28-day study period would receive a VFD score of 26, whereas the patient who is ventilated until death on Day 2 would receive a score of zero).

5. Percentage of patients alive and free of vasopressors at Day 29.
6. Vasopressor treatment-free days over 28 days defined as one point for each day during the measurement period that subjects are both alive and free of vasopressors.
7. Time to end of invasive mechanical ventilation.
8. Time to end of invasive and/or non-invasive mechanical ventilation.
9. Time to end of vasopressors treatment.

sCABP Clinical Response

- Clinical response visit at Day 14±2.
- Clinical response visits at Day 8-10 and Day 29 or early discontinuation.
- Time to sCABP clinical cure.
- Duration of antibiotic treatment.
- Rate of pneumonia recurrence/reinfection after clinical cure. Pneumonia recurrence is defined as a new acute clinical episode of pneumonia, after clinical cure of the episode that qualified the patient for the study, based on the presence of two relevant signs (fever, tachypnoea, leukocytosis, or hypoxemia) and radiographic findings of new pulmonary infiltrate/s or clinically significant worsening of previous ones. If a bacterial pathogen isolated in the recurrent episode is phenotypically different from the one isolated in the previous episode this will be considered as reinfection.
- Time to recurrence/reinfection of pneumonia after clinical cure at sCABP clinical response assessments.

Survival

- 28-day all-cause mortality.
- 28-day sCABP-associated mortality.
- Survival at Days 7, 14, 29, and 90 visits.
- Time to death.

Other efficacy endpoints

- Time to discharge from ICU.
- Time to discharge from hospital.
- Length of stay (LOS) in ICU and hospital after randomisation.

- Number of ICU-free days over 28 days.
- Changes in SOFA score daily during stay at ICU.
- Changes on CXR assessed at Screening, and then as medically required with at least one CXR per sCABP clinical response assessment until clinical cure from Day 1 to Day 29 and for pneumonia recurrence/reinfection assessment.
- Evolution of PaO_2/FiO_2 daily until Day 7.
- Need of mechanical ventilation or need of non-invasive ventilation 12 hours after the second IMP infusion.
- Use of rescue antibiotics, i.e. addition or change of antibiotic treatments due to the occurrence of antibiotic resistance posterior to microbiology results at baseline or insufficient efficacy during the course of the study.

10.1.4 Exploratory Biological Endpoints

CCI

10.2 Demographic and Other Baseline Characteristics

10.2.1 Demographic Characteristics

The following demographic will be collected at the Screening visit:

- Date of birth/age

- Gender
- Race (if applicable)

10.2.2 Other Baseline Data

The following baseline data will be collected at the Screening visit:

- CURB 65
- *Streptococcus pneumoniae* antigen in urine
- Pathogen identification and susceptibility testing. Pulmonary samples can be obtained by BAL and/or mini-BAL/PSB and/or by ETA for intubated patients, and by sputum production for non-ventilated patients. Samples will be rapidly processed for Gram stain and culture and/or other established standard rapid diagnostic system, e.g. PNA FISH or Cepheid GeneXpert for *S. aureus*, urinary antigen test for *S. pneumoniae* or *Legionella*, or rt-PCR. Should a bacterial pathogen grow in culture, susceptibility testing against the standard local antibiotic panel for the pathogen will be performed according to the site´s practice. Pathogen identification and susceptibility testing will also be performed in case of clinical suspicion of pneumonia recurrence.
- CXR will be assessed at Screening, and then as medically required with at least one CXR per sCABP clinical response assessment until clinical cure from Day 1 to 29 and for recurrence/reinfection assessment. Text from radiologist or ICU physician study CXRs reports will be printed signed and dated. CXRs images will be kept by the investigator in the patient´s clinical record and available for review by Adjudication Committee (AC) or DMC.

10.2.3 Medical History, Prior and Concomitant Medications and Procedures

Medical history will be recorded at the Screening visit including immunological status (i.e. previous pregnancies and/or transplants and/or blood transfusions). Prior medication taken within 2 weeks before the inclusion in the study will be recorded at the Screening visit. Concomitant medication and procedures (e.g. tracheostomy) will be recorded on the concomitant medication log/page of the CRF throughout the study.

The duration of each infusion of study medication will be recorded on the CRF.

10.3 Safety Assessments

10.3.1 Safety Variables

The following safety variables will be measured:

- All AEs (including TEAEs).
- Physical examination including signs and symptoms of pneumonia.
- Signs for hypersensitivity reactions or anaphylaxis.
- Vital Signs.
- 12-lead ECG
- Laboratory Safety Assessments.
- Anti-HLA/donor antibodies.

The timing of the assessments is described in Table 1, Section 1.

10.3.2 Adverse Events

AEs will be recorded from the time of signing the informed consent to Visit 11 (Day 90). AEs occurring from the beginning of the administration of study medication and until Visit 11 (Day 90) or study discontinuation will be analysed as TEAEs. From Day 90 and up to two years after Day 1, the investigator will report any SAE. For further information of definitions and reporting of AEs, SAEs, and AESIs see Section 11 below.

10.3.3 Physical Examination

All patients will undergo a complete physical examination at Screening, Day 1 (Pre-dose), Days 2, 3 (Pre-dose), Days 4, 5, 6, 7, 8-10, 14, 29, 90, or study discontinuation, including the following parameters:

- Height (only at Screening).
- Weight (only at Screening, Days 3, 14, 29, or study discontinuation).
- A systematic physical examination covering all body systems.
- A clinical assessment (presence of signs and symptoms) of AESI, i.e. thromboembolic events and hypersensitivity.

10.3.4 Assessment of Clinical Signs and Symptoms of Pneumonia

The following symptoms will be carefully checked during the physical examination:

- Difficulty breathing.
- Cough.

- Production of purulent sputum.
- Fever.
- Wheezing.
- Chest discomfort.
- Chest pain.
- Hypotension.
- Tachycardia.
- Tachypnoea.
- Hypoxemia.
- Clinical evidence of pulmonary consolidation (if CXR available).
- Elevated total white blood cell (WBC) count or leukopenia (if available).
- New infiltrates in a lobar or multilobar distribution (if CXR available).

10.3.5 Signs for Hypersensitivity Reactions or Anaphylaxis

In addition to the vital signs described in Section 10.3.6, all patients will be examined for signs and symptoms of skin reactions and respiratory distress requiring therapeutic intervention during the first 24 hours after the infusion, including the following parameters:

- Skin reactions such as rashes, hives, etc.
- Signs and symptoms of respiratory distress which require therapeutic intervention including drugs and/or changes in mechanical ventilation settings.

10.3.6 Vital Signs

The following vital signs will be assessed at Screening, Day 1 (at Pre-dose, and at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post each IMP infusion), Day 2 (at least 4 times i.e. every 6h ± 1h), Day 3 (at Pre-dose, and at 0.5h (±5 min), 1h (±10 min), 2h (±10 min), 4h (±20 min), 12h (±30 min) and 24h (±1 h) post each IMP infusion). At Days 4, 5, 6, 7, 8-10, 14, 29, 90, or study discontinuation: if in the ICU at least 4 times daily i.e. every 6h±1h, if discharged from ICU at least once:

- Systolic and diastolic blood pressures.
- Heart rate.
- Core temperature (tympanic, rectal or bladder).
- Respiratory rate (in non-ventilated patients).

When more than one measurement is available for screening, Day 2 and Day 4 onwards only the highest and the lowest value measured for each vital sign for that time period will be recorded in the CRF for that timepoint.

10.3.7 Electrocardiogram (ECG)

A 12-lead ECG used as part of the SoC in ICU will be performed during Screening and at Days 1 and 3 (Post-dose).

The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration, QT, QTc_B and QTc_F. Pathological changes in ECG tracing will be recorded as well.

All ECG tracings are to be printed, signed/dated and their assessment added to the patient's CRF. Print outs will be kept as source documentation and available for review by AC or DMC until the end of the study.

Additional ECGs may be performed in case of findings/need at investigators' discretion.

10.3.8 Laboratory Safety Assessments

Laboratory safety assessments will be performed locally, in each centre's laboratory. The tubes for blood and urine samples will be collected according to local laboratory requirements.

The samples for laboratory safety assessment will be taken at the following time points:

- During the Screening period.

- On Day 1 before the first infusion (as close as possible to the administration of the first dose; if first infusion is administered the same day of extraction of the Screening sample, there is no need to repeat the assessment).

- On study Days 2, 3 (only haematology and coagulation), 4, 7, 14 (±2), 29 (±2), 90 (±4) and at ET (if applicable).

The following laboratory safety parameters will be measured:

Haematology and Coagulation Parameters

Haematology and coagulation (tubes according to local laboratory requirements)	
WBC count	Monocytes absolute value and %
Red blood cell (RBC) count	Eosinophils absolute value and %
Haemoglobin (Hb)	Basophils absolute value and %
Haematocrit (HCT)	Platelets
Mean corpuscular volume (MCV)	Reticulocytes absolute value and %
Mean corpuscular haemoglobin (MCH)	D-dimer
Mean corpuscular haemoglobin concentration (MCHC)	Activated partial thromboplastin time (APTT). Partial Thromboplastin Time (PTT) only in case APTT is not performed locally.
Neutrophils absolute value and %	Prothrombin time (PT) and International Normalised Ratio (INR)
Lymphocytes absolute value and %	

Serum Biochemistry Parameters

Serum Biochemistry (tubes according to local laboratory requirements)	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Calcium	Aspartate aminotransferase (AST)
Urea	Creatine kinase (CK)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Lactate dehydrogenase (LDH)
Phosphate	Total Bilirubin
Glucose	Uric acid
Cholesterol	Chloride
Triglycerides	Conjugated bilirubin
Magnesium	Unconjugated bilirubin
Bicarbonate	Amylase
Total protein	

Urinalysis Parameters

Urinalysis (tubes according to local laboratory requirements)	
Leucocytes	RBCs
Protein	pH
Bilirubin	Nitrite
Urobilinogen	Specific gravity
Ketones	Glucose
Microscopy (as required upon anomalies in Urinalysis)	

Additional and repeat testing may be performed at the discretion of the Investigator.

10.3.9 Anti-HLA/donor Antibodies

For the analysis of anti-HLA donor-specific Abs, the tubes collected for evaluating CCI [redacted] will be used. On Day 90 (±4), where the T cell response sampling does not occur, the following tubes will be needed: 4.5 mL EDTA.

The assessment of anti-HLA/donor Abs will be performed at the following time points:

- On Day 1 before the first infusion.
- On study Days 14 (±2) and 90 (±4) and at ET visit (if applicable)

10.4 Efficacy Assessments

10.4.1 Ventilator-free Days

VFD over 28 days are defined as one point for each day during the measurement period that subjects are both alive and free of mechanical ventilation (71).

For example, a patient who is extubated on Day 2 of the study and remains alive and free of the ventilator for the remainder of the 28-day study period would receive a VFD score of 26, whereas the patient who is ventilated until death on Day 2 would receive a score of zero.

In patients with a tracheostomy, the last day of ventilator support will be considered the day of extubation.

The variables "Ventilator and vasopressors treatment-free days" and "vasopressors treatment-free days" will be calculated in a similar way (i.e. number of days that a patient is alive and both mechanical ventilation and vasopressors free days over 28 days; number

of days that a patient is alive and vasopressors free days over 28 days, respectively).

10.4.2 sCABP Clinical Response

Clinical Response will be assessed at Days 8-10, 14 (±2), 29 (±2) and at ET visit (if applicable) CCI

10.4.3 APACHE II and SOFA Scores

See appendices C and D.

10.5 Immunological Assessments

The analyses of the immunological parameters will be performed in the following central laboratories:

PPD

PPD

CCI

CCI

CCI

CCI [redacted]

10.6 Total Blood Volume

The total estimated volume of blood specifically collected for the study will be around 222.2 mL spread over 90 Days (4 mL x 1 = 4 for anti-donor antibodies; 40 mL x 4 = 160 mL for CCI [redacted] and 9.7 mL x 6 = 58.2 mL for CCI [redacted]).

For the calculation of this volume, routine determinations performed at local laboratories (blood culture at Screening, haematology, coagulation and blood chemistry at Screening and on Days 1, 2, 3 [only haematology and coagulation], 4, 7, 14, 29, 90 or study discontinuation) have not been taken into account.

10.7 Appropriateness of Measurements

Standardised methods for measurements of efficacy and safety will be used. The laboratory analyses of CCI [redacted], anti-HLA/donor Abs, CCI [redacted] will be performed by the respective central laboratories using validated assays.

11 ADVERSE EVENTS

The development of the IMP is under the "Detailed guidelines on good clinical practice specific to advanced therapy medicinal products" [Dec 2009 ENTR/F/2/SF/dn D (2009) 35810] and it implies that relationship to the procedure of administration of IMP (i.e. through intravenous central catheter) is also to be assessed for any adverse event reported among other obligations for specific reporting related to IMP administration and use.

All definitions listed below follow ICH E2A and apply for either IMP, its administration or procedure related to IMP administration.

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an (IMP, whether or not considered related to the IMP.

- Medical disorders, including concomitant diseases present at the time of signing the informed consent are only considered AEs if they worsen after this time. All baseline conditions should be recorded as part of Medical History.
- Changes in laboratory parameters (biochemistry, haematology, urinalysis), as well as abnormal results of other tests (worsening results), that are detected after the administration of study medication and that the investigator considers to be clinically relevant should be recorded as AEs or SAEs, provided that the definitions given in this section and in the 11.1.4 section ("Serious Adverse Event") are met, respectively. In contrast, clinically significant changes in laboratory parameters or other tests that are associated to the disease under study will not be rated as AEs or SAEs, unless the investigator judges them to be more serious than expected based on the patient condition.

For the purpose of this study, any clinical failure related to pneumonia or severe sepsis (persistence/progression of baseline signs/symptoms of pneumonia; or baseline radiographic abnormalities after at least 2 days of treatment; or development of new pulmonary/extra pulmonary clinical findings consistent with active infection, or development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy; or persistence/progression of baseline signs/symptoms of severe sepsis; or development of new signs/symptoms of severe sepsis) **will not be reported as an AEs as they will be captured as sCABP failures.**

11.1.2 Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means that a relationship between the IMP and the adverse event cannot be ruled out. In this study, AEs for which no investigator assessment is available (missing or unknown) are considered as adverse reactions.

11.1.3 Unexpected Adverse Reaction (uAR)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved IMP or the SmPC/ Product Information for a marketed drug).

Reports which add significant information on specificity or severity of a known, already documented Serious Adverse Reaction (SAR) constitute unexpected events. In the same way, when the outcome of the AR is not consistent with the applicable product information, this AR should be considered unexpected.

11.1.4 Serious Adverse Event (SAE)

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, or
- Results in persistent or significant disability/incapacity, or

- Is a congenital abnormality/birth defect, or
- Is a medically significant event or requires intervention to prevent at least one of the outcomes listed above, or
- Is a suspected transmission of an infectious agent

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situation, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. These events should also usually be considered serious. Examples of such adverse events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency (addiction) or drug abuse.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospital admission means that the patient has stayed at least 24 hours at the hospital or an emergency department for observation and/or treatment that could not have been made/administered at the physician's office or in an outpatient setting.

Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. Complications occurring during hospitalisation are AEs. If a complication extends a hospitalisation or meets any other seriousness criteria, the event will be considered a SAE.

The following reasons for hospitalisation or prolongation of hospitalisation are not considered AEs, and therefore not SAEs:

- Hospitalisation for administration of IMPs. Exception: Hospitalisation or prolonged hospitalisation for a complication of study treatment administration will be reported as a SAE.
- Hospitalisation to perform an elective treatment of a condition prior to subject entry into the study without worsening from its pre-existing condition.

- Hospitalisation for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, etc.) that are not related to an adverse event.
- Hospitalisation for standard monitoring of a pre-existing disease or medical condition that has not worsened (e.g. hospitalisation for coronary angiography in a patient with stable angina pectoris).
- Hospitalisation for ≤ 24 hours (attendance at the Emergencies).
- Other reasons may include: hospitalisations for elective cosmetic surgery, due to social reasons or due to convenience reasons.

11.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All Suspected Adverse Reactions which occur in the trial and that are both unexpected and serious.

11.1.6 Adverse Event of Special Interest (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g. DMC) might also be warranted (based on Council for International Organizations of Medical Sciences [CIOMS] VI).

The specific AEs considered as AESI for this study are:

1.-Thromboembolic events

2.- Hypersensitivity reactions such as anaphylaxis

The specific and systematic evaluation of these AESI by the investigator at study visits and time-points is documented in the physical examination section of the protocol (see section 10.3.3) and pre-infusion, during, and post-infusion of IMP (see section 10.3.5). Additional information will be required (as applicable).

11.2 Adverse Event Severity Assessment

Seriousness and Severity should not be confounded.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning (see Section 11.1.4). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Severity of the adverse events will be recorded at the time they occur and will be rated according to the following criteria:

- Mild (asymptomatic), an event easily tolerated by the patient, causing minimal discomfort that does not prevent the patient from fulfilling daily activities
- Moderate, symptomatic, but does not significantly interfere with function
- Severe, causes a significant interference with function

If severity of one event evolves over time only the worst severity category will be recorded.

Death itself is not an adverse event, but rather the outcome of a previously reported event, which should be described using medical terminology. Only in those cases where either no cause for death is known (e.g. sudden death, Death NOS) the event “death” should be reported.

The terms death/death of unknown cause and sudden death are clearly distinct and must not be used interchangeably.

11.3 Adverse Event Relatedness Assessment (Causality Assessment)

The investigator must establish, based on his clinical judgment and the information on IMP provided by the sponsor the causal relationship between the investigational product, its administration and the occurrence of the AE/SAE.

The expression: “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship. In this study, AEs that are considered

as related to IMP, including for which no investigator assessment is available (missing or unknown) are considered as adverse reactions. For AEs considered as not related to study treatment it is assumed that there is no reasonable causal relationship.

Detailed considerations to be taken into account on causality assessment include:

- associative connections (time or place: plausibility),
- pharmacological explanations,
- previous knowledge of the drug,
- presence of characteristic clinical or pathological phenomena,
- exclusion of other causes and/or absence of alternative explanations.

Other causes, such as: the natural history of other underlying diseases, including and namely the disease under study, concomitant treatments, other risk factors like surgical procedures, and time relationship of the event to the IMP need to be taken into account for the assessment.

Causal relationship to the IMP (Cx611 or Placebo) will be classified:

- RELATED NO: if the following circumstances apply,
  - Not related: if there is no reasonable temporal association between event or laboratory test abnormality onset and administration of the IMP or that can be reasonably explained by other factors, including underlying disease, complications, or concomitant medications. Clearly due to extraneous causes.
  - Unlikely: event or laboratory test abnormality, with a time to IMP administration that makes a relationship improbable (but not impossible). Diseases or other drugs provide plausible explanations.
- RELATED YES: if the following circumstances apply,
  - Possible: Event or laboratory tests abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal is lacking or unclear.
  - Probable: Event or lab tests abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Rechallenge not necessary.

- Definitive: Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (*an objective and specific medical disorder or a recognised pharmacological phenomenon*). Rechallenge (if necessary).

Causal relationship to the IMP administration process will be classified:

- RELATED NO: if the following circumstances apply,
  - Not related: if there is no reasonable temporal association between event and IMP administration process or that can be reasonably explained by other factors, including underlying disease, complications, or concomitant medications. Clearly due to extraneous causes.
  - Unlikely: event with a time to IMP administration process that makes a relationship improbable (but not impossible). Diseases or other drugs or administration processes provide plausible explanations.
- RELATED YES: if the following circumstances apply,
  - Possible: Event with reasonable time relationship to IMP administration process. Could also be explained by disease or other drugs or administration processes. Information on drug withdrawal (not re-administered) is lacking or unclear.
  - Probable: Event with reasonable time relationship to IMP administration process. Unlikely to be attributed to disease or other drugs or administration processes. Response to withdrawal (not re-administered) clinically reasonable.
  - Definitive: Event with plausible time relationship to IMP administration process. Cannot be explained by disease or other drugs or processes. Response to withdrawal plausible (not re-administration). Event definitive phenomenologically (an objective and specific medical disorder).

The relatedness of the event to the IMP administration process as well as the study drug will be assessed for all events (AEs and SAEs).

All unexpected SAEs related to the IMP will be considered for regulatory reporting purpose (SUSARs).

11.4 Adverse Event Collection Period

All AEs that occur from signature of the informed consent will be recorded, regardless of the intensity, seriousness or relationship to study drug, to visit 11 (Day 90) and in case of withdrawal up to 30 days after the last IMP administration. AEs occurring from the beginning of the administration of study medication and until EOS or study discontinuation will be analysed as TEAEs. After Day 90 or 30 days after last IMP administration for early discontinuation only SAEs will be reported by the investigator until Month 24 ± 30 days.

- Pre-existing conditions will be collected on the baseline "Medical History" electronic case report form (eCRF) module and will include, among others, active (symptomatic) diseases, diseases under treatment, chronic diseases and long term effects of past events present at the time of baseline assessment.
- Events that firstly occur within signature of the Informed Consent and administration of the study treatment [Non-Treatment Emergent Adverse Events (NTEAEs)] will be recorded. Any worsening of Medical History events along study treatment period will be subsequently recorded as AEs/SAEs as detailed in Section 11.1.1).
- Any AE that is ongoing at the last visit of the subject, either completed or withdrawn (as defined per protocol), should be followed up until the AE is resolved or stabilized or at least up to 30 days after the last protocol scheduled visit or last IMP dose administration (whatever is applicable).
- From Day 90 through Month 24, the follow-up incidental SAEs will be captured by phone contact with the patient and/or his/her GP (or family doctor) every 6 months.

All AEs elicited by the investigator during the defined AE collection period must be recorded in the eCRF as per detailed instructions in the corresponding section. When an AE meets the criteria of seriousness (SAE), it must also be recorded on the Immediately Reportable Event form and in the eCRF.

11.5 Adverse Event Reporting

11.5.1 Recording of Adverse Events

All adverse events occurring through Day 90 of the trial must be documented in the eCRF. This applies not only to those AEs supposedly related to the IMPs, but also to the

administration procedure or to any undesired experience, whether or not a causal relationship is suspected. SAEs captured by phone contact at Months 6 (Day 180), 12 (Day 365), 18 (Day 545), and 24 (Day 730) will be recorded in the SAE report form.

Whenever possible, attempts should be made by the Investigator to provide a specific "Diagnosis" or "Syndrome" in addition to a description of the reported signs and symptoms. AEs should be reported as separate individual events.

All AEs and Immediately Reportable Events (IREs) will be followed until they are resolved or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to a medical specialist. Follow-up can be wavered in specific cases after consultation with the Sponsor. This permission must be documented per case and retained in the Sponsor File.

Each follow up should be reported in a different Safety/IRE Report or Pregnancy Report Form as applicable. The final outcome of the IRE or pregnancy should be reported on a final Safety/IRE Report or Pregnancy Report Form.

All AEs must be reported regardless of whether or not they are considered related to IMP administration or administration procedure, with the exception of:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline "Medical History" eCRF module.
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents.
- Medical or surgical procedures (e.g. endoscopy, appendectomy); however, the condition leading to these procedures, rather than the procedure itself, should be considered as AE.
- The expected fluctuations of any disease(s) pre-existent, ongoing, or detected at study start (e.g. worsening of rheumatoid arthritis).

11.5.2 Immediately Reportable Events (IRE)

Events subject to immediate notification (within 24 hours), include but are not limited to:

- Serious Adverse Events (SAEs),
- Pregnancy of study subject (or female partner of a study subject),

- Medication errors, namely overdose, leading to a suspected adverse reaction,
- Accidental exposure,
- AE which leads to study drug discontinuation,
- AESI.

For these events the applicable Safety/IRE Report or Pregnancy Report Form will be used for reporting accordingly.

11.5.3 Immediately Reportable Event Reporting

All IREs will be reported by the investigator to the monitor responsible for the clinical trial and to Takeda PV Operations (i.e., CCI Such report will be made by e-mail (or fax) using the Safety/IRE Report or the Pregnancy Report Form as applicable.

The completed form should be made available to Takeda PV Operations (i.e., CCI) within 24 hours by sending it to the following e-mail address:

CCI

If electronic reporting of IREs is not possible, the form may be submitted via fax to:

CCI

Reporting of IREs by using the Safety/IRE Report Form does not exempt from the need to complete all information relating to such AEs in the specific CRF section.

Initial minimum information for reporting an adverse event should include the following:

- AE and onset date
- Patient identification, sex, and age (or date of birth)
- Information on IMP administration (dates of IMP infusions)
- Information on treatment for unexpected and reportable SUSAR (see below)
- Name and address of the reporting physician
- Causal relationship to the study treatment or IMP application process.

The complete Safety/IRE Report Form containing all information will be made available to the Sponsor (or designee) within the next 2 calendar days. If the SAE or IRE is still active at

the time of reporting or further information is obtained after initial communication, this information must be updated accordingly.

The Sponsor is the last responsible for appropriate qualification and reporting of safety information to the competent authorities, to the ECs/IRBs and to the investigators.

When a SAE is both unexpected and related to the IMPs (SUSAR) will require expedited reporting to the competent authorities and ECs:

- Fatal or life threatening SUSARs will be reported within 7 calendar days of the sponsor awareness of the event. Important additional information should be submitted within the following 8 calendar days. All follow-up information later received will be reported within 15 calendar days.
- All other SUSARs will be reported within 15 calendar days of the sponsor becoming aware of the event.

In order to comply with Good Clinical Practice (GCP) requirements, all information provided by and to the investigator will be kept in the Investigator File at the centre.

11.5.4 Pregnancy Reporting

Pregnancies of a female subject or the female partner of a male subject, occurring at least, while the subject is on protocol treatment or along the follow-up period, will be notified to the investigator and immediately communicated to the Sponsor (within 24 hours) using the Pregnancy Report Form and including the information in the eCRF.

In order to comply with this requirement, the completed form should be made available to the Sponsor (or designee) within 24 hours by sending it to the following e-mail address:

CCI

All pregnancies initiated during the patient´s participation in the trial (or up to 30 days after last IMP dose administration) which come to the knowledge of the investigator, after the closure of the clinical data base should be reported. A pregnancy as such is not an AE *per se* but it is important enough to be reported in 24 hours like SAEs/IREs to the Sponsor (or designee) to be recorded in the safety data base.

The pregnant subject or the subject´s consenting pregnant partner will be followed until the end of the pregnancy and the outcome of the pregnancy will be notified to the Sponsor (or designee) within 5 calendar days using a Pregnancy Report Form.

Any complication during the pregnancy, spontaneous or therapeutic abortion, stillbirth, neonatal death, birth defect/congenital anomaly, other serious infant condition must be reported and followed up as an SAE and reported using the Safety/IRE Report Form.

In the case of a live "normal" birth, the Sponsor (or designee) should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs, using the Safety/IRE Report Form.

In addition, any infant death after 30 days that the Investigator suspects to be related to the *in utero* exposure to the investigational medicinal product should also be reported.

Infants should be followed until 3 months after delivery to detect any complication or developmental impairment.

The Investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the Investigator and the female partner gives her permission.

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 Statistical and Analytical Plans

The statistical analysis will be performed by the Department of Biostatistics of CCI using SAS® Version 9.3 or later. A summary of the analysis to be detailed in the Statistical Analysis Plan (SAP) is presented here. A complete SAP will be written and finalized before data base closure.

12.1.1 Data Set to be Analysed

The following analysis set will be defined:

- **Safety**: Includes all randomised patients who have received at least one dose of the study treatment irrespective of randomisation. The safety population will be the primary population for all the safety and efficacy analyses.

12.1.2 Summary Statistics

In general, data will be summarised by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, median and maximum value. Categorical data will be presented as counts and percentages. Individual patient data will be listed.

12.1.3 Demographic and Other Baseline Characteristics

Patient disposition, demographic and other baseline data will be presented using summary statistics.

12.1.4 Safety Analysis

All safety analyses will be only descriptive.

Adverse events will be collected throughout the study duration. All AEs (recorded after the signature of the informed consent) and TEAEs (those recorded from the beginning of study medication administration) will be tabulated. Specific tables will be provided for AESI (thromboembolic events and hypersensitivity reactions).

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v15.0) and tabulated by system organ class (SOC) and by preferred term (PT).

The number and percentage of subjects in each treatment group reporting at least 1 occurrence of an AE/TEAE for each unique SOC and PT will be tabulated. TEAEs will also be tabulated by severity and by the relationship to study medication in treatment groups as assessed by the Investigator.

Subjects who experienced multiple adverse events within the same PT will be counted once for the summaries, using the worst severity.

The number and percentage of subjects in each treatment group reporting at least 1 occurrence of a SAE for each unique SOC and PT will be tabulated. SAEs will also be tabulated by severity and by the relationship to study medication in treatment groups as assessed by the Investigator. Listings of patients with SAEs, Deaths and AEs leading to discontinuation and individual narrative summaries for these cases will be provided.

The number and percentage of subjects (in each treatment group) prematurely discontinuing study treatment due to a TEAE will be tabulated by SOC and PT.

Safety laboratory data will be presented by absolute and change from baseline values by visit.

Shift tables for each assessed laboratory parameter will be presented to summarise the change from Low, Normal, High values at baseline to 'on treatment' visit (Day 2) and post-treatment visits (Days 4, 7, 14, 29 and 90).

The number and percentage of subjects with laboratory, vital sign, ECG, or physical examination abnormalities at baseline, subsequent visits, or ET from the study will be tabulated by treatment group. The results of all laboratory test results, physical examination findings, ECGs, and vital signs will be presented in data listings. All abnormalities will be assessed for being clinically significant or not as per investigator.

Physical Examination and signs of hypersensitivity reactions

Physical examination data and observed signs of hypersensitivity reactions will be summarised in tables.

Vital Signs, Electrocardiogram, haematology, coagulation, blood chemistry and urinalysis

All vital signs, haematology, coagulation, blood chemistry, urinalysis and ECG data will be listed by subject. All values outside the normal reference ranges will be flagged in this listing. In addition all subjects with clinically significant abnormal values will be flagged as well in

this listing and also summarised in separate listings. The number of subjects with at least one clinically significant abnormal value will be summarised. For ECG data, qualitative results will also be listed by time windows. The significant abnormal values will be pre-defined in the SAP before the database closure.

12.1.5 Efficacy and Biomarkers Analyses

The efficacy and biomarkers analyses will be descriptive summaries in the safety population at the scheduled visits.

The change from baseline in SOFA scores and all other secondary efficacy and biological variables will be summarised using descriptive statistics.

All data, including derived values that are computed for use in summaries or analyses, will be listed.

Baseline values will be defined as the last value obtained prior to first dosing and the value used in the baseline summary will also be used as the baseline value for purposes of computing change from baseline.

Data might be treated or transformed, as appropriate (e.g., log- transformed or ranked). Details of any transformed data will be specified on the SAP.

Summary tables will indicate the number of patients with complete data for each measurement, event, or outcome. In general, no imputation of missing data will be made, and any exception on efficacy data would be detailed on the SAP.

The following subgroup analyses will be performed but not limited to: severity score, bacterial load, initial adequate or inadequate antibiotic treatment, concomitant treatment, sCABP clinical response (cure or non response i.e. failure) or indeterminate, antimicrobial resistance profile, previous vaccination, and presence or not of bacteraemia. A thorough review will be performed by the AC when data for the primary endpoint are available to agree on patient assignment process e.g. validation based on the dose, the bacterial susceptibility profile to administered antibiotics and duration of antibiotics, molecular identification data, etc. Membership, roles and responsibilities and operating procedures for the AC as well as the subject evaluability criteria to be followed will be specified in a separate AC charter.

12.2 Determination of Sample Size

The results from this study are exploratory in nature, hence there is no hypothesis testing comparing outcomes between treatment arms.

Confidence intervals will be constructed to assess between-group differences in treatment effect. As little is known at present about the outcome measures used in the study for stem cells, this study will provide the initial dataset necessary for determining endpoints and making a preliminary estimate of effect size for the design of future efficacy-finding studies of Cx611 for the add-on therapy of severe community-acquired bacterial pneumonia in patients requiring mechanical ventilation and/or vasopressors administration.

The number of 180 patients in total (i.e. 90 patients per group) was deemed to be sufficient to fulfil the objectives of this exploratory study.

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% (conservative assumption).

For the main 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 SD equal to 10 for the variable number of ventilator-free.

12.3 Interim Analysis

An interim analysis of the primary endpoint is not planned for this study. The primary safety analysis at Day 90 will be performed as scheduled.

13 INVESTIGATOR/SPONSOR RESPONSIBILITIES

13.1 Ethics

13.1.1 Independent Ethics Committee (IEC)

This protocol and any amendments will be submitted to a properly constituted IEC, in accordance with the International Conference on Harmonization (ICH) guidelines, the applicable European Directives and local legal requirements, for approval of the study. Approval must be obtained in writing before the first patient can be recruited.

The Sponsor must receive the letter or certificate of approval from each IEC prior to delivery of ATIMP. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present in the IEC, it must be clear that none of these persons voted.

If there are any changes to the approved protocol (with the exception of emergency modifications required for the patient's safety), a protocol amendment will be issued by mutual agreement of the Co-ordinating Investigator and the Sponsor. The IECs must give their written approval of any substantial amendments likely to affect the safety of the patients or the conduct of the study. All other changes must be notified to them.

The Investigator will maintain records of all correspondence with the IEC.

13.1.2 Ethical Conduct of the Study

This investigation will only be performed after the appropriate regulatory authorities have issued a Clinical Trials Authorisation (CTA) for this study, which will be sought in parallel with the IEC approvals.

The appropriate regulatory authorities must give their written approval of any substantial amendments to the approved protocol or IMPD that are likely to affect the safety of the patients or the conduct of the study (with the exception of emergency modifications required for the patient's safety).

The body responsible for making the CTA submission will maintain records of all correspondence with the regulatory agencies.

The study will be conducted in compliance with the protocol, regulatory requirements, GCP, consolidated guidelines Committee for Proprietary Medicinal Products (CPMP)/ICH/135/95

(July 1996), adopted in the European Union (EU) by CPMP EU Commission Directive 2005/28/EC (GCP, April 2005) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

13.1.3 Patient Information and Consent

All patients or their legally authorised representatives will receive written and verbal information regarding the study at a prior interview. This information will emphasize that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason. All patients or legally authorised representatives will be given the opportunity to ask questions about the study and will be given ample time to decide whether to participate in the study.

Before any study-related procedures, the informed consent form will be signed and personally dated by the patient (or their legally authorised representative and/or relative and/or witness, as applicable) and by the person who conducted the informed consent discussion unless exempted under the conditions described in "Approval of inclusion by an independent physician in a case of emergency" below. A legally authorised representative and/or relative is required only if patient is unconscious or incapable to understand the nature of the study. A witness is required only if the participant is unable to write (such as blind or illiterate). If the consent has been given by the legally authorised representative or relative, the patient should be informed about their participation in the study and should have the opportunity to confirm or revoke their consent once they regain consciousness.

The consent includes information that data will be recorded, collected, processed and may be transferred to European Economic Area (EEA) or non-EEA countries in accordance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

The Informed Consent and Patient Information will be provided in the local language.

A copy of the patient information sheet including the signed consent form will be provided to the patient or their legally authorised representative and/or relative.

Approval of inclusion by an independent physician in a case of emergency

Many patients with sCABP cannot give their consent because they are not in the condition to understand or express an opinion and/or they are often unconscious or very confused. However, for the present study, only patients with sCABP may be included, because the study medication is targeted for this type of patients and may not work on patients that are just in the early stages of pneumonia or sepsis. Also, there is the need to do research within this area, since there are not many trials done in this type of patients.

The study cannot guarantee that the patient will benefit from his/her participation (because there is a placebo as comparator) but, based on the data from animal trials and on the data from prior safety trials in humans, the overall benefit-risk balance of Cx611 remains acceptable and low considering the high rate of death among these patients.

For all these reasons, if the informed consent cannot be obtained so that first dose of study medication cannot be started within 18 hours from the fulfilment of the severity criteria that suppose an immediate risk to the physical health of the patient (i.e. requirement of invasive mechanical ventilation and/or vasopressors treatment) because it is impossible to communicate with the patient and there is insufficient time to obtain informed consent from the patient's legal representative or relative, despite all reasonable efforts made by the investigator, the patient can participate in the study (if allowed by local regulations) when (i) the inclusion is approved, apart from the decision of the principal investigator, also by another independent physician and, where possible, (ii) a person linked to the patient by family or similar ties has been previously consulted. As soon as the patient recovers he/she should be informed about his/her participation in the study and should have the opportunity to sign the informed consent form for continued participation in the clinical trial.

In any case, no treatment will be given as part of the clinical trial if any of the people involved know that the patient or his legal representative is opposed to receiving the treatment.

The researcher will ensure that at the first opportunity, the patient or his/her legal representative is given detailed information about the treatment, as it would have been given to obtain informed consent, and signs the consent form for continuing participation in the clinical trial. The patient or his/her legal representative will be told that study participation can be stopped at any time, and this will not affect their rights or future treatment.

If a patient who is included in the study without signing the consent form (because they were

unconscious) dies before such signature and before their legal representative can be contacted, the researcher must try to locate the patient´s legal representative and give him/her information about the trial.

13.2 Patient Records and Source Data

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the patient is in a clinical study
- The identity of the study e.g. Study code
- Patient number
- That informed consent was obtained and the date and time
- Diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- Treatment with investigational product
- All prior, concomitant treatments and medications prescribed/administered (including dosage)
- All study-related procedures
- All information requested to be collected as specified in the protocol
- Date of study completion/termination

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRFs. Data reported in the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Signed sections of CRFs will be monitored and collected on a regular basis.

13.3 Access to Source Data and Documentation

The Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the IEC, if required. The Investigator will keep files of essential documents as defined by the ICH guidelines on GCP and local requirements. CCI will provide a suitable structure for the Investigator's site file, which the Investigator may update as and when necessary. The Investigator's site file must be available at monitoring visits and during an audit or inspection. The investigator site file should clearly record where the different source documents can be found.

13.4 Monitoring

The monitor will visit the study site on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements, CROs' procedures and any study specific documents such as CRF completion guidelines.

The monitor must be permitted to have access to all source documents needed to verify the entries on the CRF and other protocol-related documents, provided that patient confidentiality is maintained in accordance with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the CRFs.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained for all participants
- AEs have been reported as required
- Data are being accurately recorded in the CRFs
- IMP is being stored correctly, administered as per protocol and medication accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study
- The Investigator and the site are receiving sufficient information and support throughout the study.

Moreover, during monitoring visits the data recorded in the CRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the patient in the study i.e. source data verification.

The investigator must ensure that patient codification is maintained. On CRFs or other documents submitted to the Sponsor, patients must be identified only by number, and never by name. Documents identifying the patients (e.g., signed Informed Consent Forms) should not be sent to the Sponsor and CRO, and must be kept in strict confidence by the investigator.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the patient is hospitalised or dies in a hospital other than the study centre, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator must on request supply the sponsor/CRO with any required background data from the study documentation or clinical records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In the case of special problems and/or government queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

A close-out visit will be performed after study closure.

13.5 Sponsor's Obligations

The Sponsor must provide an Investigator's Brochure and, where appropriate, a IMPD, giving information about the chemistry, manufacture and controls, and the pharmacological and toxicological properties of the ATIMP and summarising any clinical experience of the compound. Additional information regarding the IMP should be provided to the Investigator when it becomes available. The Sponsor must also provide appropriate documentation on the clinical study supplies, including Certificates of Analyses and confirmation of GMP compliance in their manufacture.

A designated professional representative of the Sponsor will conduct visits at suitable intervals throughout the study. These visits will be for the purposes of verifying adherence to the protocol and the accurate and complete recording of data in the CRFs and medication inventory forms.

13.6 Investigator's Obligations

Prior to initiation of this study, the Investigator (or designee) at each study site will approve this protocol by signing the approval signature page. These signatures confirm that the study will be performed in compliance with the protocol. The Investigator (or designee) at each site must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated.

13.7 Data Management

Data management and handling will be conducted according to the study specific Data Management Plan in accordance with ICH guidelines and CCI standard operating procedures (SOPs), which will be prepared and approved before the end of the experimental phase of the study.

Data entry, validation, and data queries will be handled by the CCI Data Management Team. The data will be subjected to validation according to CCI SOPs in order to ensure accuracy in the collected CRF data.

Before database closure reconciliation will be performed between the SAEs entered in the safety database and the study database.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a study specific Data Management Report.

13.8 Quality Assurance and Audit

The sponsor has ethical, legal and scientific obligations to follow-up the trial progress in accordance with clinical research principles and regulations.

Audits or inspections, including source data verification, may be performed by representatives of CCI the Sponsor, a CA and/or an IEC. Therefore, direct access to source data and documentation will be provided for audit, for review by IEC and for any regulatory inspection.

The clinical protocol, clinical study report and the experimental phase may be audited to assure the integrity of the data and to comply with the Good Clinical Practice regulation.

The investigator is required to inform the sponsor immediately of an inspection requested by a regulatory authority. The sponsor will advise and help the investigator for an inspection.

13.9 Traceability of the Study Product

As the treatment of this study is qualified as an "ATIMP" (advanced therapy investigational medicinal product) it is subject to, among others, (i) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amended Directive 2001/83/EC and Regulation (EC) No 726/2004, and (ii) the 3 December 2009 EC GCP Guidelines.

TiGenix, the study site and the Investigator are each responsible for their respective duties and obligations in ensuring the traceability of the IMP in accordance with the EC GCP Guidelines and any other applicable legislation or regulation.

TiGenix shall ensure compliance with European and local legislation in relation to the donation and the donors of human cells (including consent, eligibility of donors, data protection and confidentiality, selection, evaluation and procurement) as laid down in Directive 2004/23/EC and its implementing Directives and local implementation.

TiGenix, as sponsor of the study and as manufacturer of the IMP, shall retain all donor related documentation of the starting material of the IMP, including all critical substances coming into contact with the cells or tissues it may contain, as well as all data relevant for the manufacturing of the IMP, and archive these until thirty (30) years after the expiry date of the resulting IMP.

To that effect, TiGenix shall set up a unique coding system whereby each IMP that is manufactured receives a unique code, based on the donor identification code, the master cell bank and the frozen medication product (the "Unique Code").

The study site shall establish and maintain a system of subject and product traceability that contains sufficient detail to allow linking of each Product delivered to the study site to the Study subject who received the Product and vice versa and the Unique Code, it being understood that the [study site] is not allowed to provide any personal data to any third party, including TiGenix, except as otherwise provided by law.

13.10 Record Retention

The sponsor and the Investigator/institution must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents are to be classified into two different categories: investigator's file, and patient clinical source documents.

The sponsor's and/or investigator's file will contain the protocol and all protocol amendments, a financial disclosure form, the CRFs and data clarification and query forms, IEC/Institutional Review Board (IRB) and Health Authority approval with correspondence, informed consent, medication records, staff curricula vitae and authorisation forms, and other appropriate documents/correspondence in accordance with ICH GCP and local regulations.

Patient clinical source documents include, but are not limited to, hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, X-ray, MRI, pathology and special assessment reports, consultant letters, etc.

Irrespectively of traceability obligations, these two categories of documents must be kept on file by the investigator for as long as is necessary to comply with applicable national and international regulations.

When source documents are required for the continued care of the patient, appropriate copies must be made for storing off site.

13.11 Protocol Deviations

Deviations to the study protocol will be documented in a Protocol Deviation Log and entered into the study-specific protocol violation database.

The classification of patients into protocol violators will be made during a meeting before database lock. The classification will be mutually agreed between the Sponsor and CCI before the database lock. Listings will indicate the allocation of patients by analysis set and the number of patients per analysis set will be recorded in the clinical study report.

13.12 Amendment of Protocol

Any change to a protocol must be considered to be an amendment if the documents have already been submitted to ECs/IRBs or Health Authorities. An amendment could therefore occur before or after the approval of these documents by ECs/IRBs or Health Authorities.

The amended protocol will be signed by the relevant personnel at TiGenix, CCI and the Investigator(s).

Depending on the contents of the amendment and local legal requirements, the amendment will be submitted to the relevant ECs and, where necessary, to the relevant competent authorities.

The Investigator should not implement any changes of the protocol, without agreement by TiGenix, CCI and prior review and documented approval/favourable opinion of the appropriate EC and, if legally required, competent authorities, except where necessary to eliminate an immediate hazard to the subjects, or when the change(s) involve only logistical or administrative aspects of the trial.

If an amendment substantially alters the trial design, increases the potential risk to the subjects or affects the treatment of the subject, then the information sheet must be revised and submitted to the relevant EC and, where necessary, to the relevant competent authorities, for review and approval. When a subject is currently undergoing trial procedures and is affected by the amendment, then the subject must be asked to consent again using the new information sheet. The new information sheet must be used to obtain consent from new subjects before enrolment.

Non-substantial amendment

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., CRO monitors), or minor changes in the packaging or labelling of study product. The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate ECs/IRBs and Health Authorities (subject to national regulations).

Substantial amendment

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of subjects, and changes to the objectives or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Subject Information and Informed Consent. Substantial amendments must be approved by the appropriate ECs/IRBs, and in some jurisdictions by the Health Authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities, and must be signed by the investigators.

13.13 Insurance

The Sponsor will provide insurance or indemnify (legal and financial coverage) the Investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence or non-compliance with the protocol.

The compensation of the patient in the event of study-related injuries will comply with applicable regulations.

13.14 Confidentiality

All study information provided by TiGenix in relation to this study and not previously published is considered confidential information. Such information comprises the clinical protocol, any workbooks if applicable, CRFs, assessment methods, sponsor technical methods, and basic scientific data. This confidential information will be the property of TiGenix, must not be disclosed to third parties without prior written consent from the sponsor, and must only be used for the study purposes.

Information collected during the conduct of this clinical study is also considered to be confidential. Such information can be disclosed to the extent considered necessary by TiGenix.

13.15 Report and Publication

In order to allow use of information derived from this study and to ensure compliance with the applicable regulations, the investigator is committed to provide TiGenix all examination results and all data collected in this study. Except as required by law, information obtained during the study can only be provided to physicians and regulatory authorities by TiGenix.

TiGenix undertakes publishing the study results and report them at scientific meetings. The list of authors of the publication will be defined based on the authorship criteria by the International Committee of Medical Journal Editors (ICMJE), involvement in trial design, oversight, number of evaluable patients enrolled, analysis and interpretation of data and preparation of manuscript. The study will only be published once it has been completed and the final analysis is completed.

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15 SIGNATURES

See separate protocol signature page.

16 CLINICAL STUDY PROTOCOL AGREEMENT FORM

I have read the clinical study protocol entitled: "**A phase Ib/IIa, randomised, double blind, parallel group, placebo controlled, multicentre study to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the intravenous treatment of adult patients with severe community-acquired bacterial pneumonia and admitted to the intensive care unit. SEPCELL study**" and verified that it contains all necessary information for conducting the study.

I hereby confirm that:

- I have carefully read and understood this clinical study protocol
- My staff and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations.

I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason, such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study I will immediately communicate such a decision to the Sponsor.

I agree not to publish any part of the results of the study carried out under this clinical study protocol without consulting the Sponsor.

Principal Investigator: _____

Date: _____

Signature: _____

17 APPENDICES

APPENDIX A Corticosteroid Conversion Table

Glucocorticoid	Approximate equivalent dose (mg)	Half-life (hr)
Short-Acting		
Cortisone	25	8-12
Hydrocortisone	20	8-12
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone	5	18-36
Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 – 0.75	36-54
Dexamethasone	0.75	36-54

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APPENDIX B CURB-65 Score (Confusion, Elevated Blood Urea Nitrogen Level, Respiratory Rate, and Blood Pressure Plus Age ≥65 Years)

"CURB-65" severity score is calculated and one point is given for each of the following features present (range 0–5 points):

	Clinical Factor	Points
C	Confusion	1
U	Blood urea nitrogen > 19 mg/dL or > 7 mmol/L	1
R	Respiratory rate ≥ 30 breaths/min	1
B	Systolic blood pressure < 90 mm Hg or Diastolic blood pressure ≤ 60 mm Hg	1
65	Age ≥ 65	1

Source: Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377-82.

APPENDIX C APACHE II (Acute Physiology And Chronic Health Evaluation) Score

Age	*POINTS*
under 45	0
45-54	2
55-64	3
65-74	5
over 74	6

History of severe organ insufficiency or immunocompromised	
Yes, and non-operative or emergency post-operative patient	5
Yes, and elective post-operative patient	2
No	0

Temperature °C	
over 40.9	4
39-40.9	3
38.5-38.9	1
36-38.4	0
34-35.9	1
32-33.9	2
30-31.9	3
below 30	4

Mean arterial pressure (mm Hg)	
over 159	4
130-159	3
110-129	2
70-109	0
50-69	2
below 50	4

Heart rate (ventricular response)	
over 179	4
140-179	3
110-139	2
70-109	0
55-69	2
40-54	3
below 40	4

Respiratory Rate (non-ventilated or ventilated	
over 49	4
35-49	3

25-34	1
12-24	0
10-11	1
6-9	2
below 6	4

Oxygenation (use A-a gradient if FiO2 ≥ 50%, use PaO2 if FiO2 <50%)	
A-a gradient over 499	4
A-a gradient 350-499	3
A-a gradient 200-349	2
A-a below 200	0
pO2 > 70	0
pO2 = 61-70	1
pO2 = 55-60	3
pO2 below 55	4

Arterial pH	
over 7.69	4
7.60-7.69	3
7.50-7.59	1
7.33-7.49	0
7.25-7.32	2
7.15-7.24	3
below 7.15	4

Serum sodium (mMol/L)	
over 179	4
160-179	3
155-159	2
150-154	1
130-149	0
120-129	2
111-119	3
below 111	4

Serum potassium (mMol/L)	
over 6.9	4
6-6.9	3
5.5-5.9	1
3.5-5.4	0
3-3.4	1
2.5-2.9	2
below 2.5	4

Serum creatinine (mg/ dL)	
over 3.4 and ACUTE renal failure	8
2.0-3.4 and ACUTE renal failure	6
over 3.4 and chronic renal failure	4
1.5-1.9 and ACUTE renal failure	4
2.0-3.4 and chronic renal failure	3
1.5-1.9	2
0.6-1.4	0
below 0.6	2

Hematocrit (%)	
over 59.9	4
50-59.9	2
46-49.9	1
30-45.9	0
20-29.9	2
below 20	4

White blood count (total/cubic mm in 1000's)	
over 39.9	4
20-39.9	2
15-19.9	1
3.0-14.9	0
1.0-2.9	2
below 1.0	4
Glasgow Coma scale	
Eyes open	
Spontaneous	4
To speech	3
To pain	2
Absent	1
Verbal	
Converses / Oriented	5
Converses / Disoriented	4
Inappropriate	3
Incomprehensible	2
Absent	1
Motor	
Obeys	6
Localises pain	5
Withdraws (flexion)	4
Decorticate (flexion) rigidity	3
Decerebrate (flexion) rigidity	2
Absent	1

Score relative to GCS: 15 – (minus) Actual GCS

Source: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.

APPENDIX D SOFA Score

Table 1. Sequential Organ Failure Assessment (SOFA) score (5)

	Score				
Variables	0	1	2	3	4
Respiration: PaO_2/FiO_2	>400	301-400	201-300	101-200†	≤100†
Coagulation: platelets, $10^3/\mu L$	>150	101-150	51-100	21-50	≤20
Liver: bilirubin, µmol/L	<20	20-32	33-101	102-204	>204
Cardiovascular: hypotension	no hypotension	MAP* <70 mm Hg	Dopamine ≤5, or dobutamine (any dose)‡	Dopamine >5, or epinephrine ≤0.1, or norepinephrine ≤0.1‡	Dopamine >15, or epinephrine >0.1, or norepinephrine >0.1‡
Central nervous system: Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal: creatinine, µmol/L	<110	110-170	171-299	300-440	<440

*MAP – mean arterial pressure.
†With respiratory support.
‡Adrenergic agents administered for at least 1 h (dosages are in µg/kg/min).

Source: Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicentre, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793-800.

APPENDIX E Conversion Table SO_2 (%) to PaO_2 (mmHg) and O_2 (l/min) to FiO_2 (%)

O_2 SATURATION AND FiO_2 SYSTEM CONVERSIONS

O2 Saturation Conversion Table Pulse oximetry O_2 saturation may be used for calculating PaO_2/FiO_2 ratio when ABG is not available	
SaO_2 (%)	Calculated PaO_2
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Conversion Table for FiO_2 When Measured on Mask or Nasal Cannula or Nasopharyngeal catheter	
Nassal cannula	
100% O_2 Flow Rate (L/min)	FIO_2 (%)
1	24
2	28
3	32
4	36
5	40
6	44
Nasopharyngeal catheter	
4	40
5	50
6	60
Air Ambiant	21
Oxygen mask	
100% O_2 Flow Rate (L/min)	FIO_2 (%)
5-6	40
6-7	50
7-8	60
9	90
10	99+
Mask with Reservoir Bag	
100% O_2 Flow Rate (L/min)	FIO_2 (%)
6	60
7	70
8	80
9	90
10	95

*AARC Clinical Practice Guideline, Ia Vitro pH and Blood Gas Analysis and Hemoximetry, Respiratory Care, 38:505 -510, 1993.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	19-Dec-2019 23:32 UTC
	Clinical Science Approval	20-Dec-2019 10:11 UTC

NOTE-TO-FILE

From:	PPD
Date:	04 May 2020
Sponsor:	TiGenix, S.A.U. *A Wholly Owned Subsidiary of Takeda Pharmaceutical Company Limited*
Protocol:	**Clinical Study Protocol Cx611-0204, Version 7, dated 19-Dec-2019. (SEPCELL)**
Subject:	Clarification regarding the recent protocol amendment - Clinical Study Protocol Cx611-0204, Version 7, dated 19-Dec-2019
CC:	eTMF/ Site folder

Dear Site Investigator/ Study Coordinator,

The purpose of this Note-to-File is to provide some clarification regarding the recent protocol amendment - Clinical Study Protocol Cx611-0204, Version 7, dated 19-Dec-2019.

Efficacy Analyses

As you are aware, the statistical analysis was revised during the protocol amendment. Accordingly, all safety and efficacy data will be summarized using descriptive statistics only, (described in Protocol Section 12.1.2), without any statistical inference or sensitivity analyses based on different patient populations. Due to the early closure of enrolment, the total number of enrolled subjects is likely to be too low to detect any safety and efficacy signals; therefore, traditional statistical analysis including 95% confidence intervals and p-values may be misleading, and any sensitivity analyses based on different patient populations will be unnecessary.

As such, the description of the Secondary Efficacy Clinical Endpoints in the *Synopsis*, (page 9), needs to be corrected. The language below in blue font strikethrough is no longer applicable; the language in blue font underlined is the correction. Protocol *Section 10.1.3* correctly describes the analyses.

> **"Secondary Efficacy Clinical Endpoints**
> ~~Efficacy analyses will be performed based on the Modified Intention-to-treat (mITT), Intention-to-treat (ITT), Clinically Evaluable (CE), Microbiological ITT (micro-ITT) and Microbiologically Evaluable (ME) populations.~~
> ***Efficacy analyses will be performed based on the safety population.***"

CCI **Anti-HLA Antibodies**

Additionally, the protocol was amended to remove clinic visits and the accompanying physical examinations and laboratory testing at the Day 180 (Visit 12) and Day 365 (Visit 13) time points. As part of this, there will no longer be any protocol requirement for collection of lab samples after the subject

has completed Day 90 (Visit 11) on the study. This also applies to CCI anti-HLA donor antibodies – these will only be collected up to Day 90. There was an oversight in making this update to the *Schedule of Assessments* (Table 1) during the amendment. To clarify, here is the required schedule for these samples:

	Visit 1 Day 1 (pre-dose)	Visit 7 Day 7	Visit 9 Day 14	Visit 10 Day 29	Visit 11 Day 90	Early Termination (only if prior to D90)
CCI	X	X	X	X		
Anti-HLA/ Donor Abs	X		X		X	X

An excerpt of the *Schedule of Assessments* table is shown below with corrected footnote instructions indicating lab sample collection for CCI and anti-HLA donor antibodies up to Day 90 only. The language in blue font strikethrough is no longer applicable; the language in blue font underlined is the correction:

Table 1. Schedule of Study Assessments [EXCERPT ONLY]

VISITS	Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Early Termination (ET)	Safety[12] phone calls			
Study days (allowed deviation days in brackets)		Day 1 (D1)	D2	D3	D4	D5	D6	D7	D8-D10	D14 (±2)	D29 (±2)	D90 (±4)		D180 (±30)	D365 (±30)	D545 (±30)	D730 (±30)
CCI																	

* Pre-study treatment administration ** 5 hours ± 1h post-study treatment administration *** If applicable **** Fluids excluded

+ CCI ++ Only anti-HLA/Donor Abs +++ If ET is ~~after~~ *before* V11 (Day 90) only anti-HLA/Donor Abs +++ + Only if ET is before V9 (Day 14)

If you have any questions about these clarifications, or any of the other study procedures, please do not hesitate to contact your CCI Clinical Research Associate and/or me.