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

SAP Approve Date: 04MAR2020

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STATISTICAL ANALYSIS PLAN

A phase Ib/IIa, randomized, 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.

Sponsor Study Code: Cx611-0204

CCI Project Code: TIG006

Sponsor	Tigenix S.A.U., *A Wholly Owned Subsidiary of Takeda Pharmaceuticals Limited*
Product/Compound	Cx611 (eASCs)
Phase of the study	Ib/IIa
Author	PPD
Company	CCI
Address	PPD
Telephone number	PPD
Version	Final 2.0 **Date** 04MAR2020

SIGNATURES

Sponsor Study code: Cx611-0204

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Name, academic level, title:
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TABLE OF CONTENT

ABBREVIATIONS

ABS	antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
APACHE	Acute Physiology And Chronic Health Evaluation
aPTT	activated Partial Thromboplastin Time
ASC	Adipose-derived Stem Cells
ATC	Anatomical Therapeutic Chemical (Classification System)
BAL	Broncoalveolar Lavage
BNP	B-type Natriuretic Peptide
CABP	Community-Acquired Bacterial Pneumonia
CAP	Community-Acquired Pneumonia
CE	Clinically Evaluable
CI	Confidence Interval
CRF	Case Report Form
CCI	[redacted]
CSP	Clinical Study Protocol
CURB-65	Confusion, elevated blood urea nitrogen level, respiratory rate, and blood pressure plus age ≥65 years score
CXR	Chest X-Ray
DBP	Diastolic Blood Pressure
eASC	expanded Cx611 allogeneic Adipose-derived Stem Cells
ECG	electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
ET	Early Termination
ETA	Endo Tracheal Aspiration
FiO_2	Fraction of Inspired Oxygen
GGT	Gamma Glutamyl Transpeptidase
HLA	Human Leukocyte Antigen complex
HR	Heart Rate
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INR	International Normalised Ratio
IRE	Immediately Reportable Event
ITT	Intention-To-Treat
IV	intravenous
LDH	Lactate Dehydrogenase
LOS	length Of Stay
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
ME	Microbiological Evaluable

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intention-To-Treat
MSC	Mesenchymal Cells
OS	Overall Survival
CCI	[redacted]
PaO_2	Partial pressure of Oxygen
CCI	[redacted]
CCI	[redacted]
PSB	Protected Specimen Brush
PT	Preferred Term; Prothrombin Time
CCI	[redacted]
Q1, Q3	1st Quartile, 3rd Quartile
RBC	Red Blood cell Count
CCI	[redacted]
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCABP	Severe Community-Acquired Bacterial Pneumonia
SD	Standard Deviation
SoC	Standard of Care
SOC	System Organ Class
SOFA	Sepsis-related Organ Failure Assessment
CCI	[redacted]
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
CCI	[redacted]
CCI	[redacted]
VaFD	Vasopressor Free Days
VeFD	Ventilator Free Days
WBC	White Blood cell Count
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol (CSP) Final, version 6, dated September, 4th, 2019, and Final version 7, dated December, 19th, 2019.

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 [1,2]. When CAP is caused by bacterial pathogens, it is named a community-acquired bacterial pneumonia (CABP). 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 [3]. This incidence increases with age [4].

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 [5].

According to current guidelines, all patients with sCABP and severe sepsis or septic shock require close monitoring and must be admitted to the intensive care unit (ICU) [6,7]. Drug therapy is complex, and may include broad-spectrum antibiotics, corticosteroids, inotropics, and vasopressors, as well as oxygen supplementation and volume resuscitation with large amounts of intravenous fluids [6].

Stem cells are unspecialized cells capable of dividing and regenerating for long periods of time [8]. Adult mesenchymal cells (MSCs) are a stem cell population that can be isolated, expanded in culture, and characterized *in vitro* and *in vivo*, according to the criteria of the International Society for Cellular Therapy [8].

MSCs have been isolated from multiple tissues of mesodermal origin [9], Adipose-derived stem cells (ASCs) 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 [10].

Cx611 is an intravenously-administered product of allogeneic eASCs in development for 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 by significantly reducing mortality through a combination of reduced inflammation, production of anti-microbial effectors, and increased phagocytosis [11].

The results from a Phase I, single center, 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 shows no serious adverse events (SAEs) or respiratory problems, and few mild intensity adverse events (AEs), resolved on the same day [12].

An extensive program of non-clinical pharmacology, biodistribution and safety studies has been conducted with Cx611 (Investigational medicinal product dossier (IMPD) v.12 of 31Jul2017). Preclinical data from the 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. Moreover, no toxicity or specific adverse effects upon administration were found, including ectopic growth tissue, neoplasias, tumor or appearance of opportunistic infections. No tumorigenic behavior after long

term *ex vivo* culture of eASCs has been found. In addition, a decreased differentiation capacity of the cells with extended expansion of ASCs has been observed.

Therefore, our preclinical understanding of the allogeneic eASCs demonstrates that these cells are safe and have therapeutic capacities which make them an excellent source of cells for cell therapy. Based on the clinical experience up to now, there are no known specific safety issues that can be attributed to the use of allogeneic eASCs.

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 a safe treatment for sCABP associated with severe sepsis. The limited possible risks associated with the administration of Cx611 may include tumor 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 may be considered as an adverse event of specific interest by investigators [12].

The current Phase Ib/IIa study is proposed to confirm the safety of 2 allogeneic Cx611 central line infusions (from a single, healthy donor) on Days 1 and 3 at a dose of 160 million cells, in an add-on therapy design compared to a placebo-control group, for the treatment of sCABP and sepsis. As secondary objective, the study will explore the efficacy of Cx611 for treating sCABP. 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 preclinical (pharmacology, pharmacokinetics 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.

2 STUDY OBJECTIVES

2.1 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.

2.2 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.

2.3 Exploratory Objectives

- Safety data collection: SAEs collection via phone calls at Months 6 (Day 180), 12 (Day 365), 18 (Day 545) and 24 (Day 730),

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3 EFFICACY AND SAFETY ENDPOINTS

3.1 Primary Safety Endpoints by Day 90

- Frequency, duration, severity, seriousness, relatedness to study treatment, actions taken and outcome of adverse events (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 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 treatment emergent AEs (TEAEs).
- Adverse events of special interest (AESI).
- Signs of 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 24 h (±1 h) after the start of 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 24 h (±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 24 h (±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, Day 1 and Day 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.

3.2 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.

3.3 Secondary Efficacy Clinical Endpoints

Efficacy endpoints

- Mechanical ventilator and vasopressor treatment-free days
- Percentage of patients alive and free of mechanical ventilation and free of vasopressors at Day 29
- Percentage of patients alive and free of mechanical ventilation at Day 29
- Ventilator Free Days (VeFD) over 28 days (see definition in section 6.3.1)
- Percentage of patients alive and free of vasopressors at Day 29
- Vasopressor treatment-Free Days (VaFD) over 28 days (see definition in section 6.3.1)
- Time to end of invasive mechanical ventilation
- Time to end of invasive and/or non-invasive mechanical ventilation
- 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 clinical sCABP cure
- Duration of antibiotic treatment
- Rate of pneumonia recurrence/reinfection after clinical cure
- 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 Day 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 randomization
- Number of ICU-free days over 28 days
- Changes in Sepsis-related Organ Failure Assessment (SOFA) scores 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 Day 1 to Day 29 and for pneumonia recurrence/reinfection assessment
- Evolution of PaO_2/FiO_2 daily until Day 7
- Need for mechanical ventilation or need for 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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4 OVERALL STUDY DESIGN

4.1 Overview of Study Design

This is a Phase Ib/IIa, randomized, double-blind, parallel group, placebo-controlled, and multicenter study. It will be conducted in at least 20 centers across Europe.

Patients will receive SoC therapy according to local guidelines plus two 80 mL (240 mL/hr) intravenous (IV) central line infusions (on Day 1 and on Day 3) of Cx611 at a fixed dose of 160 million cells, or placebo.

The calendar day of administration of the first dose of Cx611 will be considered the Day 1 of the study. From Day 1 on study days will be considered as calendar days.

Screening period will be a maximum of 18 hours. There will be a total of 12 visits (Screening Visit + 11 scheduled visits) + 4 phone calls for long-term safety follow-up per patient, at the following time points:

Screening Visit	Day 0	Randomization
Visit 1 (Baseline)	Day 1	Treatment administration: 1st dose
Visit 2	Day 2	
Visit 3	Day 3	Treatment administration: 2nd dose
Visit 4	Day 4	
Visit 5	Day 5	
Visit 6	Day 6	
Visit 7	Day 7	
Visit 8	Day 8 – Day 10	
Visit 9	Day 14 (±2)	Clinical Response visit
Visit 10	Day 29 (±2)	
Visit 11	Day 90 (±4)	Primary Safety Endpoint visit
Phone call	Day 180 (±30)	Long-term safety follow-up at Month 6
Phone call	Day 365 (±30)	Long-term safety follow-up at Month 12
Phone call	Day 545 (±30)	Long-term safety follow-up at Month 18
Phone call	Day 730 (±30)	Long-term safety follow-up at Month 24

Note: premature discontinuation can occur if the patient withdraws from the study before Day 90, and leads to an Early Termination Visit.

More details are available in the CSR concerning the examinations, tests, etc. that will be performed during each visit.

4.2 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 study was initially planned to enrol approximately 180 adult male and female patients with sCABP, randomized to receive Cx611 or placebo in a 1:1 design.

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 standard deviation (SD) equal to 10 for the variable number of ventilator-free days.

Due to enrolment issues, the number of patients finally included in the study has been reduced to 92.

5 DATA SETS TO BE ANALYZED

All the patients must comply with the inclusion and exclusion criteria detailed in the CSP. The following analysis set will be used for the statistical analysis and presentation of data:

- **The safety population** will consist of all randomized patients who have received at least one dose of the study treatment irrespective of randomization. The safety population will be the population for all the safety and efficacy analyses.

6 STATISTICAL AND ANALYTICAL PLANS

The planned tables and listings are presented in Appendix 1.

6.1 Changes in the Planned Analyses

Unlike it is specified in the protocol, no subgroup analysis will be performed in this study.

Any changes in the statistical analyses once the SAP has been finalized and after locking the database should be documented and justified in a file note and the clinical study report.

6.2 Blind Review

Before database lock, and once the Data Management process has finished, a Blind Data Review Meeting will be performed before breaking the randomization code. In this meeting, important violations of eligibility criteria and other deviations from the protocol will be assessed in cooperation with Tigenix. Changes in the planned analysis decided in connection to the blind review will be included in Pre-Analysis Review Form, signed before code breaking.

6.3 Hypotheses and Statistical Methods

6.3.1 Global definitions

Baseline and Change from Baseline

Generally, a baseline measurement refers to the last non-missing assessment made before the first administration of investigational medicinal product (IMP) (e.g. screening and baseline visits). For example, this would apply to vital signs and laboratory data, where a difference from baseline is derived.

Change from baseline values will be reported as the difference between: value at the visit minus baseline value.

Relative Day

The relative day of an event is derived as follows:

For events on or after date of first administration of IMP:

Relative day = (Start date of the event) - (Date of first administration of IMP) +1.

For events occurring before the first administration of IMP:

Relative day = (Start date of the event) - (Date of first administration of IMP).

In this way, there will be no Day 0. So, Day 1 is the same day as the day of first administration of IMP, and Day -1 is the day before.

End of Study

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

Antibiotic medication for sCABP

These are the following medications, after coding, from both bacteriological data and concomitant medication data statements: Cefotaxime, Cetriaxone, etc. The list of antibiotic treatment for sCABP will be agreed with Takeda once we know all the drugs.

Non-antibiotic medication for sCABP

These are the following medication, after coding, from the following two statements: concomitant medication data and vasopressor therapy. The list of non-antibiotic treatment for sCABP will be agreed with Takeda once we know all the drugs.

Medication for other diseases

These are the medications, after coding, from both bacteriological data and concomitant medication data statements, that are not listed in the two previous definitions, i.e. antibiotic treatment for sCABP and non-antibiotic treatment for sCABP.

Ventilator Free Days (VeFD)

VeFD over 28 days are defined as one point for each day during the measurement period that patients are both alive and free of invasive mechanical ventilation, i.e.

VeFD = Number of days the patient is alive and free of invasive mechanical ventilation

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 VeFD 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.

Note1: 48-hour rule.

- If there is a gap between 2 ventilation periods, and this gap is less than 48 hours, then the patient will be considered as being ventilated during this period of time. For instance, if a patient is under ventilation for 2 days, then non-ventilated for 47 hours, and then ventilated for another 3 days, before being free of ventilation up to day 28, this patient provides 28-(2 days+47 hours+3 days) = 21 days free of mechanical ventilation.
- In contrast, if the gap between the 2 ventilation periods is ≥48 hours, it will not be considered as a ventilation period. For example, a patient under ventilation for 2 days, then non-ventilated for 48 hours, and then ventilated for another 3 days, before being free of ventilation up to day 28, provides 28-(2 days+3 days) = 23 days free of mechanical ventilation.

Note2: Patients discontinuing before Day 28.

- In case a patient withdraws before Day 28, VeFD will be considered only at the days before the day of discontinuation. For instance, if a patient had mechanical ventilation on Day 1, extubed on Day 5, and then stopped the study at Day 8, this patient contributes only with 2 days to the VeFD (Day 6 and Day 7 are the 2 only entire days free of mechanical ventilation). If a patient discontinued at Day 8, and did not have any mechanical ventilation at all during these 8 days, VeFD will be 7.

Note3: Patients who died before Day 28

- Patients who died before Day 28 will provide VeFD=0 in all the cases.

Vasopressor treatment-Free Days (VaFD)

VaFD over 28 days are defined as one point for each day during the measurement period that patients are both alive and free of vasopressors, i.e.

VaFD = Number of days the patient is alive and free of vasopressors

The same rules will be applied as for VeFD.

Ventilator and Vasopressors Free Days (VeVaFD)

Ventilator and vasopressors free days over 28 days are defined as one point for each day during the measurement period that patients are alive and free of invasive mechanical ventilation and free of vasopressors, i.e.

VeVaFD = Number of days the patient is alive and free of invasive mechanical ventilation and free of vasopressors

The same rules will be applied as for VeFD and VaFD.

Time to end of invasive mechanical ventilation

This is the time, in days, from the start date of invasive mechanical ventilation to the first stop date of invasive mechanical ventilation (i.e. first time the patient ends mechanical ventilation), or death:

(End date of invasive mechanical ventilation – Start date of invasive mechanical ventilation +1)*

* *Or date of death*

If one of the dates is missing, the time to end of invasive mechanical ventilation will be missing. If a date is incomplete, it will be estimated (cf. section 6.6, part 3).

Note: 48h rules is applied too (see above).

Time to end of invasive and/or non-invasive mechanical ventilation

This is the time, in days, from the start date of invasive or non-invasive mechanical ventilation to the first stop date of invasive or non-invasive mechanical ventilation (i.e. first time the patient ends mechanical ventilation), or death:

(End date of invasive mechanical ventilation – Start date of invasive mechanical ventilation +1)*

* *Or date of death*

If one of the dates is missing, the time to end of invasive mechanical ventilation will be missing. If a date is incomplete, it will be estimated (cf. section 6.6, part 3).

Note: 48h rules is applied too (see above).

Time to end of vasopressors treatment

This is the time, in days, from the start date of vasopressors treatment to the first stop date of vasopressors treatment (i.e. first time the patient ends vasopressors treatment), or death:

(End date of vasopressors treatment – Start date of vasopressors treatment +1)*

* *Or date of death*

If one of the dates is missing, the time to end of vasopressors treatment will be missing. If a date is incomplete, it will be estimated (cf. section 6.6, part 3).

Note: 48h rules is applied too (see above).

Duration of non-invasive mechanical ventilation

This is the cumulative time, in days, of all the periods of non-mechanical ventilation of a patient during follow-up.

In the case a patient started non-invasive mechanical ventilation and no stop date is available, the date of discharge from the hospital will be used as the end of non-invasive mechanical ventilation period.

Note: 48h rules is applied too (see above).

sCABP Clinical response

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[redacted]

Time to clinical cure

This will be defined as the time, in days, from the calendar day of administration of the first dose of Cx611, to the date at which the patient is clinically cured, i.e. sCABP clinical response is filled as "*Success*" in the CRF.

Time to clinical cure = Date of cure – Date of first administration of Cx611 +1

Duration of antibiotic treatment

It will be defined in days, as:

Stop date of antibiotic treatment – Start date of antibiotic treatment +1

Rate of pneumonia recurrence/reinfection after clinical cure and time to recurrence/reinfection of pneumonia after clinical cure at sCABP clinical response assessment

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, tachypnea, leukocytosis, or hypoxemia) and radiographic findings of new

pulmonary inflitrate/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.

For the patients reaching clinical cure, the time to recurrence/reinfection of pneumonia will be defined as the number of days, from clinical cure to the pneumonia recurrence or reinfection (the first one that occurred):

Earlier date of recurrence or reinfection – Date of cure +1

Time to death or Overall Survival (OS)

This will be calculated in days, from the calendar day of administration of the first dose of Cx611:

OS = Date of death – Date of first administration of Cx611 +1

Time to discharge from ICU/hospital

Since all patients are supposed to be hospitalized at the time of the Screening visit, the periods of hospitalizations before screening consent date, will not be considered.
Time to discharge from ICU/hospital will be defined, in days, as the time between informed consent date and the date of discharge from the ICU/hospital.
Note: the first hospitalization will be considered. A same hospitalization may be registered in various records, due to a change of service between ICU/general ward, or other reason; in this case the records will be considered as being the same hospitalization if the difference between the end date/time of the first record and the start date/time of the next one is ≤1 minute.

Time to discharge from ICU = Date of discharge from ICU – Date of informed consent signed

Time to discharge from hospital = Date of discharge from hospitalization (ICU or general ward) – Date of informed consent signed

Time to discharge is computed in days, but considering the time period (in hours) as fractions of days, i.e. a difference of 30 hours between informed consent and discharge from hospital would result to a time to discharge = 1,25 days.

If no time is available, only days will be computed, adding one day (+1) in the formula, i.e. if the date of discharge is the same day as informed consent, time to discharge = 1 day.

Length of stay (LOS) in ICU and hospital after randomization

This will be computed as the sum of all the ICU/hospitalization (resulting from pneumonia) days for a given patient, considering the period from the screening consent date (days of hospitalization pre-screening are not summed in the calculation of LOS), i.e. if a patient had only one hospitalization day during the follow-up, and this hospitalization was not in ICU, LOS will have the same value as the time to discharge from hospital.

$$\text{LOS} = \sum_{i=1}^{n} Date\ of\ discharge\ (i) - Date\ of\ admission\ (i)$$

Where, n is the total number of hospitalization (ICU or general ward) for a same patient.

Note: for the first hospitalization, date of informed consent is used rather than date of admission. For LOS, same rules are applied as for time to discharge for the difference between dates and times.

ICU-free days over 28 days

ICU-free days over 28 days will be defined as the number of days during which the patient was not in ICU, starting from the randomization date, to Day 29, or day of discontinuation, taking into account the entire day (24 hours) free of ICU stay. Note: ICU-free days will consider all the reasons of hospitalization.

Range of values for ICU-free days is 0-28, e.g.,

- A patient admitted to ICU before randomization or the day of randomization without discharging any day before Day 29, or discharging at any day and re-admitted to ICU the same day or the day after, will have a value of 0 day,
- A patient admitted at Day 1, and discharged the same day will have a value of 28 days,
- A patient admitted at Day 1, and discharged on Day 2, will have a value of 27 days,
- A patient admitted at Day 1, and discharged on Day 28, will have a value of 1 day,
- Etc.

Mortality due to index pneumonia

The cause of mortality due to index pneumonia, will be identified in the following assessments:
- Reason of death,
- Adverse events for which outcome is fatal.

6.3.2 Summary Statistics

Data will be presented using summary statistics, by treatment (placebo vs. Cx611) and overall.

Categorical data will be presented as counts and percentages.

Continuous data will be presented with sample statistics: n (number of observations), number of missing data, mean value and 95% confidence interval, standard deviation (SD), minimum value, first quartile (Q1), median, third quartile (Q3), and maximum value.

The number of digits behind the decimal point will be 1 in tables with percentages.

The summary statistics minimum and maximum will be presented to the same number of decimal places as that used to collect the data, while mean, median, Q1 and Q3 will be presented to one more decimal places, and standard deviation will be presented to two more decimal places. Arithmetic means and standard deviation are used for all variables but PaO_2/FiO_2 ratio. For PaO_2/FiO_2 ratio, the geometric mean and coefficient of variation will be used.

All the analysis will be performed using SAS® Version 9.3 or later.

In the survival analyses, in case an event did not occur for a patient at the end of the period, this patient will be censored at his/her last available date, i.e. discontinuation date, or last visit date available in the study if the discontinuation date is missing or unknown.

6.3.3 Patient Data Listings

Data collected in the CRF will be listed in Appendix 16.2. CRF check questions (e.g. laboratory samples taken [Yes/No]) and reminders will not be listed.

If not specified in the title of the listing, listings will be sorted by treatment arm, study center, patient number and visit.

In CRF modules where a date is recorded, the date and the relative day may be printed in the corresponding listing. In modules where both a start date and a stop date are recorded, a duration may also be included in the listing.

6.3.4 Demographic and Other Baseline Characteristics

The following demographic and baseline data will be described at baseline:

- Disposition of patients: inclusion and exclusion criteria at Screening and Visit 1, number of patients by visit, patient populations, reason for withdrawal
- Demographics: age (numerical and by group: <65, 65-<85, 85 or more), gender, race
- Medical history
- Prior (*) antibiotic and non-antibiotic treatments for sCABP (see definition above, 6.3.1)
- Prior (within the last 2 weeks *) treatments for other diseases (see definition above, 6.3.1)
- Serum pregnancy test (for women in childbearing age): results (positive, negative) for serum and urine tests
- CURB-65 score [13]: presence of the following 5 clinical factors (see table below) and total punctuation (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 mmHg or Diastolic blood pressure ≤60 mmHg	1
65	Age ≥ 65 years	1

- Streptococcus pneumoniae urine antigen (evaluation done or not, overall assessment: positive, negative)

- Chest X-ray (CXR): CXR performed or not at Screening (if no, reasons why not performed), overall assessment (normal, abnormal – clinically significant or not)
- Randomization data: stratified allocation criteria, treatment group.

(*) Prior medications are defined as any medication ended prior or at the date of first dose of IMP (Day 1).

6.3.5 Efficacy Analysis

All the analyses will be presented by treatment group (placebo vs. Cx611) and overall.

Ventilator Free Days (VeFD)

VeFD over 28 days will be described as well as the percentage of patients alive and free of invasive mechanical ventilation at Day 29.

Note: the percentage of patients alive and free of invasive mechanical ventilation at Day 29 will be done, based on the number of patients who have died before Day 29, or are still in the study at Day 29.

The following variables will be defined, calculated, and analyzed, in a similar way:

- Ventilator and vasopressors treatment free days: number of days that a patient is alive and both invasive mechanical ventilation and vasopressors free days over 28 days, and percentage of patients alive and free of invasive mechanical ventilation and free of vasopressors at Day 29.
- Vasopressor treatment-Free Days (VaFD): number of days that a patient is alive and vasopressors free days over 28 days, and percentage of patients alive and free of vasopressors at Day 29.

Time to end of invasive mechanical ventilation

This variable will be analyzed using Kaplan-Meier estimation (censoring the patients without any event at Day 29).

The following variables will be defined, calculated, and analyzed, in a similar way:

- Time to end of invasive and/or non-invasive mechanical ventilation (difference in days between start and end dates),
- Time to end of vasopressors treatment (difference in days between start and end dates).

Need of mechanical ventilation or need of non-invasive ventilation 12 hours after the second IMP infusion

The n (%) of patients with any invasive and/or non-invasive mechanical ventilation in the 12 hours after the second IMP infusion will be described.

sCABP Clinical response

It will be presented descriptively at Day 8-10, at Day 14 ±2, and at Day 29 or early discontinuation.

Time to clinical cure

Time to clinical cure will be analyzed by Kaplan-Meier estimation. The patients who are not cured at Day 90 will be censored at the date of last available clinical response assessment before Day 90.

Duration of antibiotic treatment

It will be analyzed using descriptive statistics in a table. For the listings, the duration will be added to the listings of concomitant medications.

Rate of pneumonia recurrence/reinfection after clinical cure and time to recurrence/reinfection of pneumonia after clinical cure at clinical response assessment

For patients who reach a clinical cure, the rates of pneumonia recurrence, and pneumonia reinfection will be analyzed globally, until Day 90, and the rate of recurrence/reinfection of pneumonia (defined as: any recurrence or reinfection at any time before Day 90) will be presented.

This will be analyzed by Kaplan-Meier estimation. The patients who don't have any recurrence or reinfection at Day 90 will be censored at the date of last available pneumonia recurrence/reinfection assessment before Day 90.

Time to death or Overall Survival (OS)

This will be analyzed by Kaplan-Meier estimation. The patients still alive at V11 (Day 90) will be censored at their last date available (V11 study date or early discontinuation date if before V11). Comparison of the distribution between treatments will be done using Log-rank test.

H_0: OS is the same between the two groups of treatment

H_1: OS is higher in one of the treatment group.

OS will be analyzed according to three criteria:

- Time to death: overall survival as described above; survival times at Days 7, 14, 29, and 90 will be presented.
- 28-day all-cause mortality: overall survival, but censoring all the data at Day 28, i.e. if a patient died after Day 28 but still alive at Day 28, he will be censored at Day 28, without considering the event (death) as having occurred,
- Mortality due to index pneumonia: death will be considered as an event, only if the cause of death is related to "*index pneumonia*" (see definition in section 6.3.1). If not, the patients will be censored at their date of death (for other reason), or last available date (V11 study date or early discontinuation date if before V11).

Time to discharge from ICU/hospital

Time to discharge from ICU/hospital will be analyzed by Kaplan-Meier estimation. The patients who remain in ICU/hospital at Day 90 will be censored at the date of their last available visit (V11 study date or early discontinuation date if before V11).

Length of stay (LOS) in ICU and hospital after randomization

This will be analyzed desriptively and by Kaplan-Meier estimation.

In the Kaplan-Meier estimations, the patients who are still at the hospital at the end of the study will be censored at the date of their last available visit (V11 study date or early discontinuation date if before V11).

ICU-free days over 28 days

This will be summarized with descriptive statistics.

Sepsis-related Organ Failure Assessment (SOFA) score

SOFA score is a mortality prediction score that is based on the degree of dysfunction of 6 organ systems (respiration, coagulation, hepatic, cardiovascular, neurological, renal; see below for details). Each item is scored from 0 to 4, 0 being the better level, and 4 the worst. Total score is hence ranged from 0 to 24, 24 being a state with a higher risk of mortality.

It is believed to provide a better stratification of the mortality risk in ICU patients given that the data used to calculate the score is not restricted to admission values. The SOFA score can be used to determine the level of organ dysfunction and the mortality risk in ICU patients) [14].

Details of SOFA score:

- Respiration: PaO_2/FiO_2 (mmHg)

0	1	2	3	4
>400	301-400	201-300	101-200 *	≤100 *

* with respiratory support

- Coagulation: platelets ($10^3/\mu L$)

0	1	2	3	4
>150	101-150	51-100	21-50	≤20

- Liver: bilirubin (µmol/L)

0	1	2	3	4
<20	20-32	33-101	102-204	>204

- Cardiovascular: hypotension

0	1	2	3	4

No	MAP<70 mmHg	dop≤5 or dob (any dose)	dop>5 or epi≤0.1 or nor≤0.1	Dop>15 or epi>0.1 or nor>0.1

MAP: mean arterial pressure, dop: dopamine, dob: dobutamine, epi: epinephrine, nor: norepinephrine

- Central Nervous System: Glasgow Coma Score

0	1	2	3	4
15	13-14	10-12	6-9	<6

- Renal: creatinine (µmol/L)

0	1	2	3	4
<110	110-170	171-299	300-440	<440

Only the results occurring during hospitalization at ICU will be considered in this analysis. The change from baseline in SOFA scores occuring during hospitalization at ICU (overall and by organ system) and all other secondary efficacy and biological variables will be summarized using descriptive statistics. 95% confidence intervals and exploratory p-values will be used to explore differences between treatment groups.

Differences between treatment groups will be analyzed using either the Student's t-test, or the Mann & Whitney U test, depending on the normality of the distributions.

Use of rescue antibiotics

Rescue antibiotics taken during the study will be described (n, %): any 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.

PaO_2/FiO_2 until Day 7

PaO_2 (mmHg) and FiO_2 (%) will be described over time, separately: evaluation performed or not (if no, reasons why not performed), and result.

6.3.6 Biological Analyses

Anti-HLA/Donor antibodies (ABS) CCI [redacted]

A descriptive table will be presented for the results of the following:

- Anti-HLA Donor-specific antibodies: preexisting antibodies, *de novo* generation as consequence of ASCs administration

CCI [redacted]

CCI [redacted]

CCI

[redacted]

6.3.7 Exposure to Treatment

The number of patients dosed at Day 1, Day 3 and both days, and the total dose administrated (in million cells/mL), and total volume administrated (in mL) will be presented by summary statistics.

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

6.3.8 Prior and Concomitant Medication

These are the following medication, after coding, from the following three statements: bacteriological data, concomitant medication data, and vasopressor therapy.

Concomitant medication will be separated in two groups: concomitant medication for sCABP, and concomitant medication for other diseases, according to the same definition used for the prior medication:

- Concomitant medication for sCABP. The list will be agreed with Takeda once we know all the drugs.
- Concomitant medication for other diseases: all other medications that are not for sCABP.

A concomitant medication will be defined as any medication started on or after Day 1 or any medication taken prior to Day 1 and continued after Day 1 during the study.
Prior and Concomitant medication will be summarized separately, as number of patients being treated with each type of medication/therapy classified according to Anatomical Therapeutic Chemical (ATC) level 3 group text, and World Health Organization (WHO) Drug Dictionary, Version 17.1 preferred name.

Prior medications are defined as any medication ended prior to or at the date of first dose of IMP (Day 1). Concomitant medications are defined as any medication started on or after Day 1 or any medication taken prior to Day 1 and continued after Day 1 during the study.

If the end date of a medication is missing, the start date will be considered: if the start date of the medication is before Day 1 or is missing, then the following rule will be applied: if the medication shows as ongoing in correspondant CRF, it is a concomitant medication. The rest of the cases will be evaluated and classified by the data quality review team.

Once the medications are categorized into prior or concomitant according to their dates, they will be summarized. Medications are registered as many times as they are administered to a

subject, and in the case the same subject has taken the same medication for more than one treatment interval within the same period (i.e., prior/concomitant), this subject is only counted once in this period and for this drug, on a preferred name level.

6.3.9 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1 or later (to be specified in the output) and tabulated by System Organ Class (SOC) and Preferred Term (PT).

In the tables, only treatment-emergent AEs (TEAEs) that appears within 90 days after first dose of IMP will be considered, i.e. AEs starting at/after the first administration of study medication, and in a range of 90 days after this first administration. AEs starting after 90 days will only be listed.

The reason for the above is that the study is cut at 90 days for newly enrolled patients in amendment #5, so the same rule should be applied the same rule for all the patients enrolled earlier or later.

Note: See section 6.6 to see how to manage partial/missing date of AEs.

A summary table will be presented with the following:

- Number of TEAEs
- Number of patients with any TEAE
- Number of patients with any Immediately Reportable Events (IRE),
- Number of serious TEAEs (TESAEs)
- Number of patients with any TESAE
- Number of TEAEs related to IMP
- Number of TEAEs related to study drug administration process
- Number of patients with any TEAE related to IMP
- Number of TEAEs of Special Interest (AESIs)
- Number of patients with any AESI, and
- Number of patients with any TEAE leading to study drug discontinuation

The same summary table will be repeated for TESAEs, AESIs, TEAEs excluding TESAEs, and TEAEs with a frequency >5%.

The following tables will be summarized by SOC and PT, within each treatment group:

- Number and percentage of patients reporting at least one occurrence of TEAE
- Number and percentage of patients reporting at least one occurrence of TESAE
- Number and percentage of patients prematurely discontinuing study treatment due to a TEAE
- Number and percentage of patients with at least one AESI.

The following TEAEs will also be tabulated by severity and relationship to study drug:

- TESAEs by treatment group.

General rules for tables and listings.

In all the tables, a certain AE is only counted once within each patient on a preferred term level.

If a patient has more than one event classified with the same preferred term, the the worst case will be used (worst severity, related to study drug).

In the listings, all AEs will be reported, meaning non-treatment emergent as well as TEAEs.

Listings of patients with SAEs, deaths, AEs leading to discontinuation and AESIs will be reported.

In listings of AEs the relative day counted from first administration of IMP (Day 1) will be presented. When an AE occurs at the same day that IMP is given, the time relative to time of dosing will be presented, if available. In the case that a given event is reported with changes in severity , only the worst grade will be presented and data related to the event will include dates of initiation (first day occurred) and stop (date of finalization/outcome), if available.

Severity (or intensity) of AE:

AEs are classified according to their severity gradation as Mild, Moderate, and Severe.

Relationship to study drug (causality) of AE:

AEs are classified as related (possible, probable or definitive) or not related (not related, unlikely) to study drug, unknown, or not applicable.

Adverse events of special interest:

- Thromboembolic events
- Hypersensitivity reactions such as anaphylaxis.

6.3.10 Other Safety Assessments

Vital Signs

Absolute values and changes from baseline will be described at each assessment visit. The following parameters will be assessed: systolic blood pressure (SBP, in mmHg), diastolic blood pressure (DBP, in mmHg), heart rate (HR, in beats per minute), core temperature (tympanic, rectal or bladder, in ºC) and in non-ventilated patients, respiratory rate (in breaths per minute).

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.

Vital signs were performed at several timepoints:

- At screening visit, only lowest and highest values were recorded, and both will be presented in the table, listing and figures.

- At Day 1 and Day 3, vitals signs were recorded at the following timepoints: pre-treatment, post-treatment (not all the patients), 0.5h, 1h, 2h, 4h, 12h, and 24h. All these timepoints will be presented in the table, listing and figures.
- At other days (Day 2, and after Day 3), vital signs should have been recorded at 4 timepoints: 0-<6 hours, 6-<12 hours, 12-<18 hours, 18-<24 hours. If this is not the case (i.e. vital signs recorded at any time, with more than 4 measurements in a same day), the data should be grouped by programming according to these 4 periods of times. Note: the first timepoint is 0.5h as for Days 1-3, so if the measure was taken at 12:00, we consider it is 0.5h after start of the visit, and so on for the following timepoints.

In the table, the lowest and highest values for each of these periods will be presented. In the listing, all the values recorded will be presented. In the figures of individual values, the values will be presented by visit and timepoints (4 intervals defined above), and in case there are >1 measure in a same interval, the median value will be used. In the box-plot figures, the statistics will be made on all the values, and the data presented by visit and timepoints.

Observed individual and mean values will be displayed graphically over time.

Clinical Laboratory Measurements

Laboratory values will be presented as absolute values and changes from baseline, in their standard international unit. The following parameters will be asessed:

- Hematology and coagulation: WBC count (10^9/L), RBC count (10^{12}/L), hemoglobin (g/dL), haematocrit (%), MCV (fL), MCH (pg), MCHC (g/dL), neutrophils (10^9/L and %), lymphocytes (10^9/L and %), monocytes (10^9/L and %), eosinophils (10^9/L and %), basophils (10^9/L and %), platelets (10^9/L), reticulocytes (10^9/L and %), D-dimer ng/mL), aPTT (seconds and %), PTT (seconds), PT (seconds and %), INR (ratio).
- Biochemistry: sodium (mmol/L), potassium (mmol/L), calcium (mmol/L), urea (mmol/L), creatinine (mg/dL), albumin (g/L), phosphate (mmol/L), glucose (mg/dL), cholesterol (mg/dL), triglycerides (mg/dL), magnesium (mmol/L), bicarbonate (mmol/L), total protein (g/L), alkaline phosphatase (UI/L), alanine aminotransferase (UI/L), aspartate aminotransferase (UI/L), creatinine kinase (UI/L), GGT (UI/L), LDH (UI/L), total bilirubin (mg/dL), uric acid (mg/dL), chloride (mmol/L), conjugated bilirubin (µmol/L), unconjugated bilirubin (µmol/L), amylase UI/L).
- Urinalysis: specific gravity, pH, leucocytes, protein, bilirubin, urobilinogen, ketones, microscopy, red blood cells, nitrite, glucose.

Laboratory parameters by visit will also be presented categorically according to abnormalities and clinical significance (normal, out of range – clinically significant, or not). Abnormalities will be flagged in the listings with information if clinically significant or not.

Shift tables that show the number of subjects who changed from low, normal or high at baseline to low, normal or high at each post-baseline time of assessment will be presented.

In case laboratory values are below the limit of quantification, the value corresponding to the limit of quantification will be used when summarising data (e.g. if the result is <x.x then the value x.x will be used in the statistical analysis).

For discrete urinalysis parameters, the number of positive and clinically significant observations (according to the CRF) will be tabulated by visit.

Physical Examination

The following information will be described: height (only at screening), weight (at screening, Days 3, 14, 29 or study discontinuation), and physical examination at all visits (if normal, abnormal; clinically significant or not) covering all body systems: head, eye, ear, nose, throat, vascular system, respiratory, gastrointestinal, musculoskeletal, dermatological, nervous system, genitourinary system and others (to be specified).

Lower Limbs Compression Ultrasonography.

An ultrasonography report, including the presence or absence of deep venous thrombosis will be presented in the Listings on an individual patient basis.

Clinical signs and symptoms of pneumonia

Descriptive statistics of clinical signs and symptoms of pneumonia will be described over time: difficulty breathing, cough, production of purulent sputum, fever, wheezing, chest discomfort, chest pain, hypotension, tachycardia, tachypnea, hypoxemia, elevated total WBC count or leukopenia (if available), clinical evidence of pulmonary consolidation (only if chest X-ray is available), new infiltrates in a lobar or multilobar distribution (only if chest X-ray is available).

ECG

Absolute values and changes from baseline for 12-lead ECG will be described. The following parameters will be assessed: rhythm (beats per minute), ventricular rate (beats per minute), PR interval (msec), QRS duration (msec), QT duration (msec), QT_{CB} duration (msec), QT_{CF} duration (msec), and overall assessment (normal, abnormal – clinically significant or not).

A summary table will be provided with the number of patients with at least one significant abnormal value by visit.

Abnormalities will be flagged in the listings with information if clinically significant or not.

APACHE II score

APACHE-II score (all items and total scores) will be described at Screening visit and Baseline visit if available.

APACHE II is a severity-of-disease classification system (Knaus et al., 1985 [15]). It is applied within 24 hours of admission of patient to an ICU: an integer score from 0 to 71 is computed based on several measurements. Higher scores correspond to more severe disease and a higher risk of death.

Signs of hypersensitivity reactions

The following signs will be described at Day 1 and Day 3: anaphylaxis (changes in SBP, DBP and HR), skin reactions and respiratory distress requiring therapeutic intervention during the first 24 hours after the infusion.

Pathogen identification, rapid diagnostic and gram stain

Description of the samples with the method of collection:

- Blood: gram stain, culture,
- Pleural: gram stain, culture,
- Respiratory: bronchoalveolar lavage (BAL), mini-BAL, protected specimen brush (PSB), endotracheal aspiration (ETA), sputum,
- Other diagnostic method.

6.4 Level of Significance, Multiple Comparisons and Multiplicity

If applicable, all statistical tests will be 2-sided and will be performed using a 5% significance level.
No adjustment for multiple comparisons or corrections for multiplicity are planned.

6.5 Adjustment for Covariates

Not applicable.

6.6 Handling of Dropouts and Missing Data

No imputation algorithms will be adopted to replace missing values.

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

(1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date,…] indicates differently).

(2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

(3) In the event that any date is incomplete after Data Management processing and this date needs to be used for calculation (eg. time since primary diagnosis), the following will be assigned for the incomplete date:

- if no field is available: no imputation will be performed.
- if only the year is available: Day “01” and month of “July” will be imputed.
- if the month and year are available: Day “15” will be imputed.

6.7 Multicenter Studies

Not applicable.

6.8 Examination of Subgroups

No subgroup analysis will be performed.

6.9 Interim Analysis

No interim analysis is planned in this study.

6.10 Data monitoring

Not applicable.

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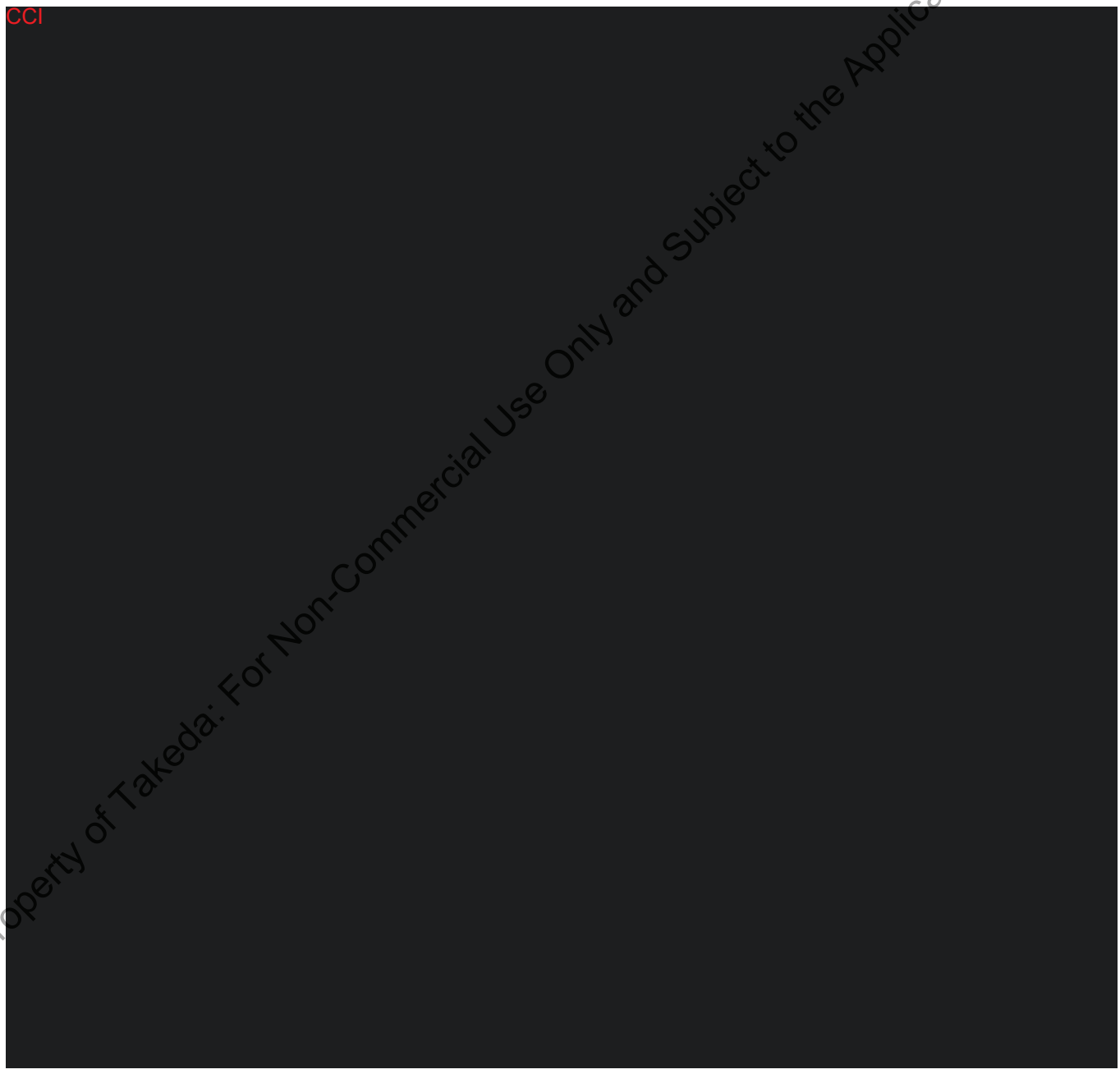
8 APPENDIX 1

CCI



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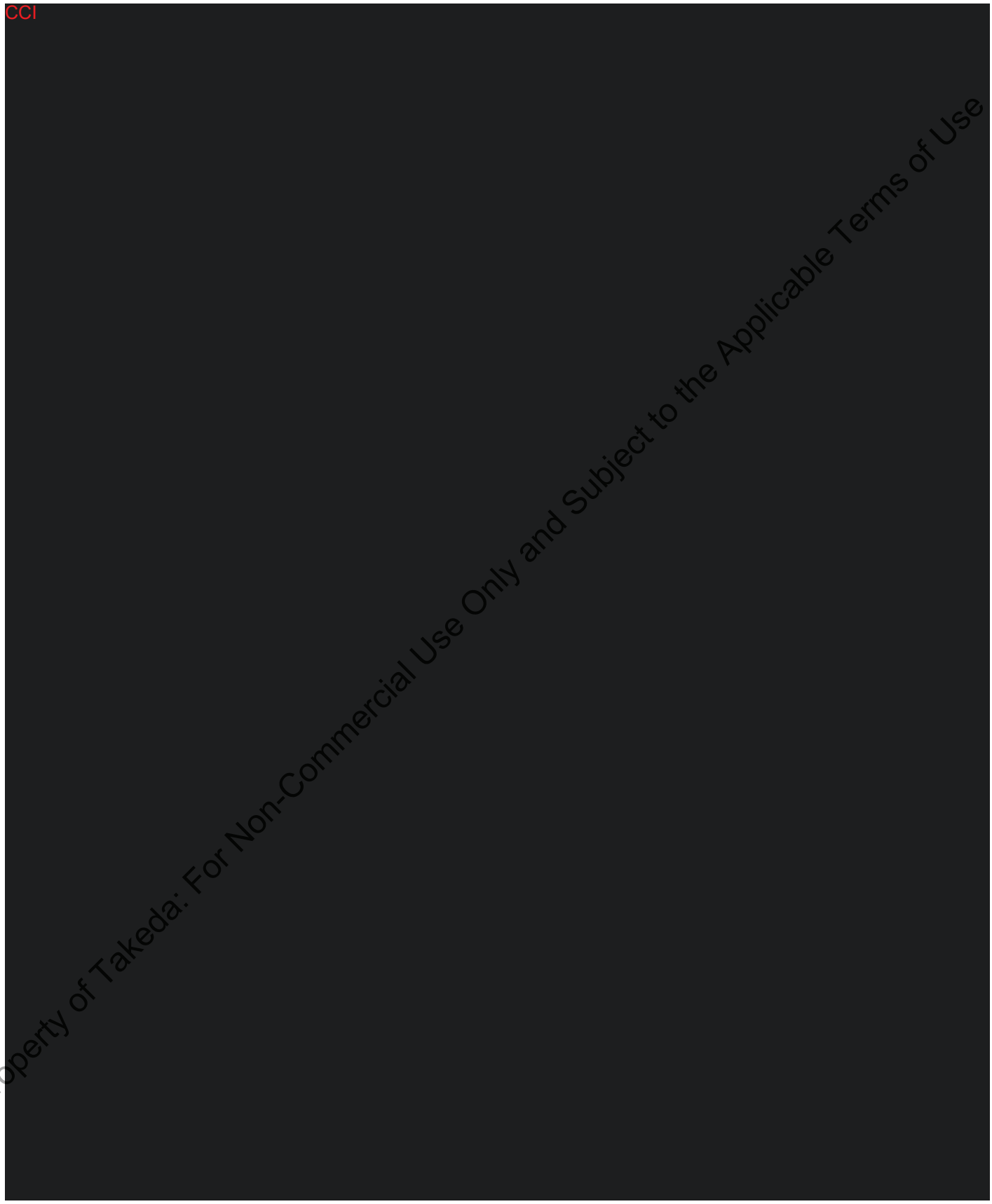

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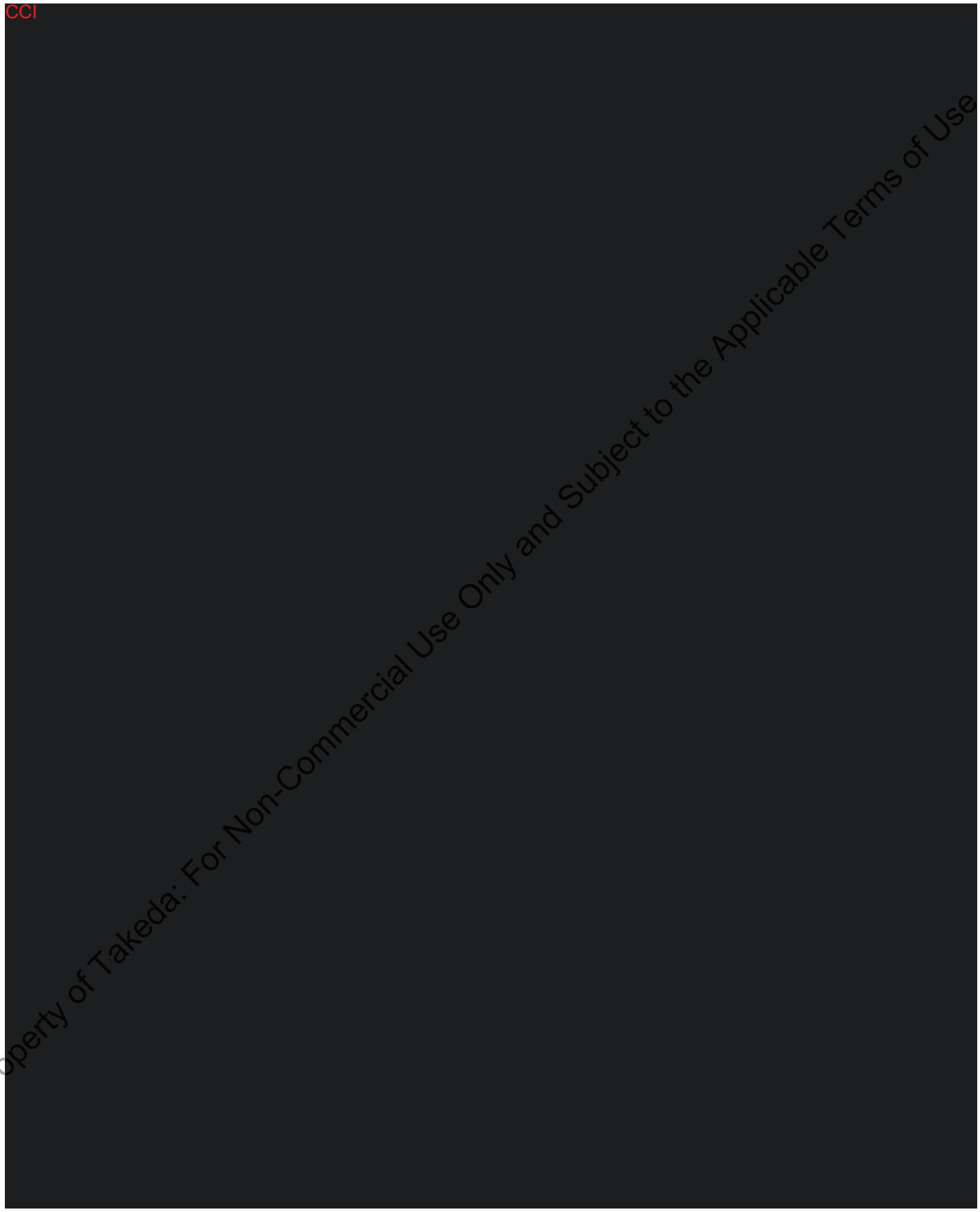

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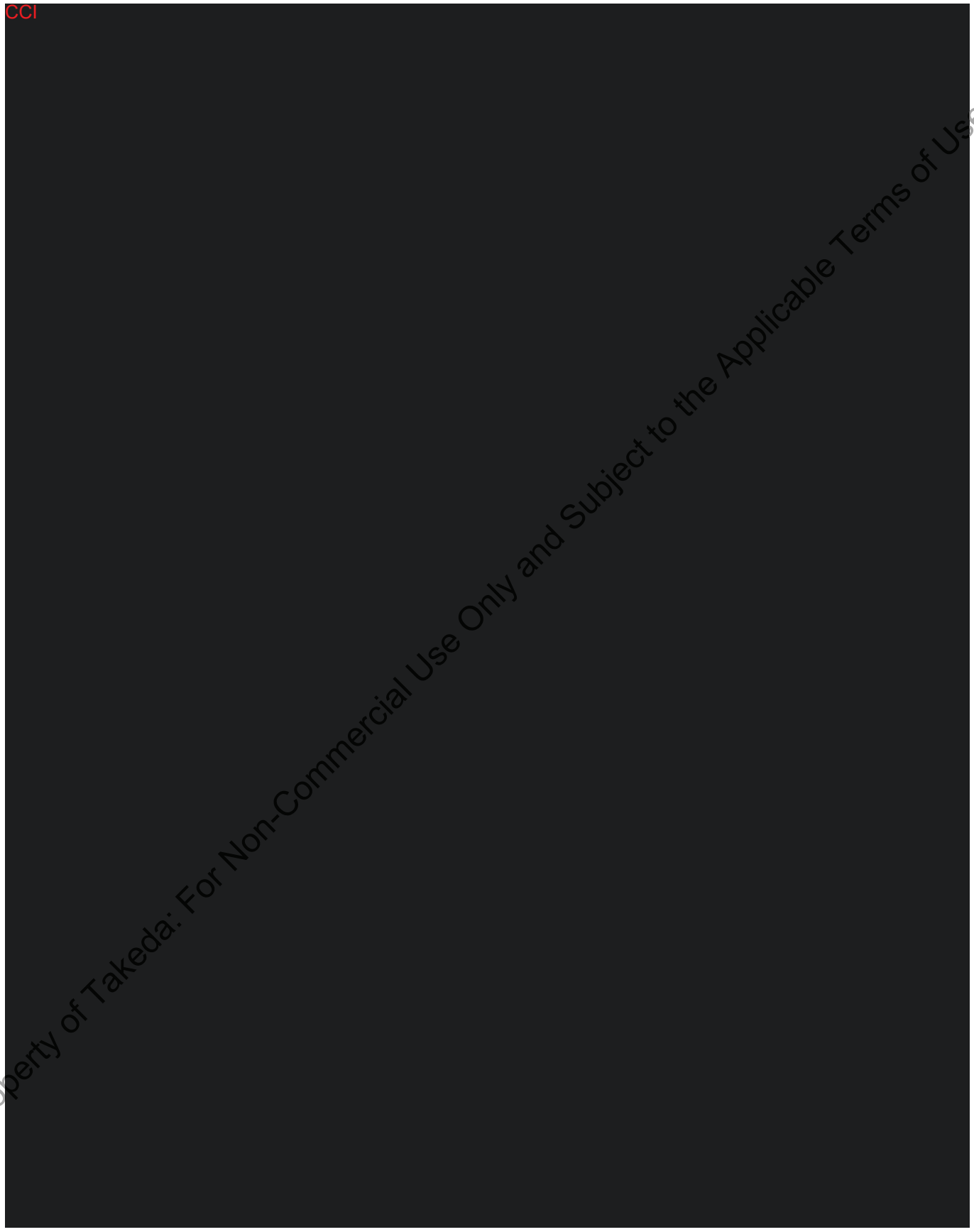

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