CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I.REACTION INFORMATION

1.PATIENT INITIALS (first, last)	1a.COUNTRY	2.DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year
PRIVACY	ES			1938	80	Male	19	DEC	2018

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☒ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☒ OTHER MEDICALLY IMPORTANT CONDITION

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data)

TRANSIENT AND RECURRENT ATRIOVENTRICULAR DISSOCIATION (Atrioventricular dissociation (10069571), Atrioventricular dissociation (10069571)) - Recovered/resolved
Protocol relatedness:
As per reporter: Study medication
As per company: Other

Case level outcome :Recovered/resolved

Case ID: Cx611-201812-35

Initial report received on 20/Dec/2018 and Fup#1 received on 09 and 15/Jan/2019 from the SEPCELL study (A phase Ib/IIa, randomized, double blind, parallel group, placebo controlled, multicenter study to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the intravenous

Cont...

II.SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

1) Cx611(INVESTIGATIONAL DRUG)(Suspension for infusion)
2) Placebo for Cx611(PLACEBO)(Solution for infusion)

Cont...

20.DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
1) 160 x 10^6 cell 2)

16. ROUTE(S) OF ADMINISTRATION
1) Intravenous drip 2) Intravenous drip

17. INDICATION(S) FOR USE
1) SEVERE COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA[10010120 - Community acquired pneumonia]
2) SEVERE COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA[10010120 - Community acquired pneumonia]

21.DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
1) 17/DEC/2018 2) 17/DEC/2018

19. THERAPY DURATION
1) 24 Minutes 2) 24 Minutes

III.CONCOMITANT DRUG(S) AND HISTORY

22.CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

ULCER PEPCID PROPHYLAXIS(MAGNESIUM CARBONATE, ALUMINIUM HYDROXIDE GEL, DRIED) 17/DEC/2018 - (40 Milligram,1)

Cont...

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

Concurrent Disease:
HYPERTENSION ARTERIAL[10020775 - Hypertension arterial] (//1998 -) (Continuing: Yes)
PAROXYSMAL ATRIAL FIBRILLATION[10034039 - Paroxysmal atrial fibrillation] (//2003 -) (Continuing: Yes)

Cont...

IV.MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Tigenix SAU
C/ Marconi 1, Parque Tecnológico de Madrid
Madrid, Tres Cantos 287660 SPAIN

Initial Reporter:
SPAIN

EudraCT no : 2015-002994-39
Study no : Cx611-0204
Center no : 220
Cont...

24b. MFR. CONTROL NO.
CX611-201812-35(1)

24c. DATE RECEIVED BY MANUFACTURER
09/JAN/2019

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☐ AUTHORITY
☒ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT
17/JAN/2019

25a. REPORT TYPE
☐ INITIAL ☒ FOLLOW UP

Cont... = Continuation attached sheet(s)

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Continuation Sheet for CIOMS report   Mfr. Control No. :CX611-201812-35(1)

Reaction Information (Cont...)

Seq. No.	:	1
Reaction	:	TRANSIENT AND RECURRENT ATRIOVENTRICULAR DISSOCIATION (Atrioventricular dissociation (10069571), Atrioventricular dissociation (10069571))
Start Date	:	19/Dec/2018;18:30
Stop Date	:	20/Dec/2018
Duration	:	5 Hours

Describe Reaction(s)(Include relevant test/lab data) (Cont...)

treatment of adult patients with severe community-acquired bacterial pneumonia and admitted to the intensive care unit), arising from Spain.

Subject was a 80-year-old male (subject ID: 22004), weight 90 kg, height 165 cm, diagnosed with severe community-acquired bacterial pneumonia (sACBP).

Previous medical history included arterial hypertension (ongoing since 1998), paroxysmal atrial fibrillation (ongoing since 2003), stage 2 acute kidney injury (ongoing since 16/Dec/2018) and chronic bronchopathy, and ex-smoker since unknown date.

Concomitant medications at the time of event onset included ceftriaxone and levofloxacin for CABP peptic ulcer prophylaxis (unknown drug), , enoxaparin, amiodarone for paroxysmal atrial fibrillation medical history (150mg/OD, i.v) that was increased to 900mg/continuous, i.v.) on 18/Dec/2018 and stopped on 19/Dec/2019 for atrial fibrillation with rapid ventricular response, and erythromycin among others, which included fluid-therapy, mineral supplements, antipyretics and sedoanalgesia support..

Subjects were to be randomized to receive either Cx611 (160 million cells, 2 million cells/ mL, total volume 80 mL) each day or Placebo. Cx611/Placebo was to be administered as an intravenous infusion on Day 1 and Day 3.

First infusion (Dose 1) was administered on 17/Dec/2018 (start 12:55; stop 13:19).
Second infusion (Dose 2) was administered on 19/Dec/2018, (start 14:05; stop 14:30).

An ECG obtained on 17/Dec/2018 at 19:05 (post-dose) showed sinus tachycardia, supraventricular extrasystole, left bundle branch block, QT=360 msec, QRS=120 msec and heart rate 135 bpm.

On 19/Dec/2018, at 18:30h (4 hours after ending 2nd dose administration) the patient developed transient and recurrent (self-limited) atrioventricular dissociation with hemodynamic instability. ECG performed (20:23) showed left bundle branch block, PR normal, and sinus rhythm. The condition required increase in norepinephrine intravenous infusion that caused worsening of the patient’s existing condition of acute kidney injury.

The laboratory tests performed on 19/Dec/2018 (to be clarified if pre or post-dosing) showed, among others the following abnormal results: C-reactive protein (CRP) 35.8 mg/dL (range 0.1 – 0.5); aPTT 45 sec (range 22.5-33.5); D-Dimer 4930 ng/mL (range 0.1 - 500); renal function tests showed urea increased (108 mg/dL; range 15-50) as well as creatinine 2.29 mg/dL (range 0.67 – 1.17) and GFR 25.9mL/min (range 60-140). Cardiac enzymes showed troponin I 0.16 ng/mL (range 0.001 – 0.05) and cardiac CK fraction of 9.8 ng/mL (range 0.1-5). Ionogram showed results within normal values except for Ca++ (7.4mg/dL; range 8.5-10.5), and

Lab tests performed on 20/Dec/2018 showed similar results for CRP, aPTT, urea, troponin I, Ca++, among others (see lab results in Lab Tests) but worsened data on D-Dimer (12821 ng/mL), CK (606 IU/L; range 1-190) and its cardiac fraction (CK-MB 16.9 mg/dL). Urinalysis performed that day was positive for RBC and hyaline casts.

The patient had 2 episodes of ventricular dissociation, self–limited and transient, with mild increasing serum urea and creatinine. No further episodes were seen.

No action was taken with the Cx611/Placebo due to the event.
As per reporter, the event stopped on 20/Dec/2018 although the outcome of the event at the time of the report was considered not recovered/not resolved (to be clarified by the reporter).
This case is linked to Case ID Cx-611-2019-01-38
:::-
::::::::::::::::::::::::::::::
Case narrative as per reporter; all critical information is summarized above
Follow-up #1 information received on 09 & 15/Jan/2019:
Additional details about the event, concomitant medications, medical history, ECG results and final outcome and end date were provided.
INVESTIGATOR’S ASSESSMENT:
In the Investigator’s opinion, the event of transient and recurrent atrioventricular dissociation is possibly related to the blinded IMP and not related to the IMP procedure administration. Severity of the event was severe. Seriousness criteria were: life-threatening, hospitalisation/prolongation, and medically important. According to Investigator, the event was also possibly due to worsening of the following pre-existing conditions: left bundle branch block, paroxysmal atrial flutter and fibrillation, and left ventricular (septal mostly) hypertrophy.

SPONSOR’S ASSESSMENT:

1.- Transient and recurrent atrioventricular dissociation (PT: Atrioventricular dissociation)
•Temporal relationship: plausible
•Risk factors: age, previous history of paroxysmal atrial fibrillation since more than 15 years; pneumonia; left bundle branch block, paroxysmal atrial flutter and fibrillation, left ventricular (mostly septal) hypertrophy not reported in medical history but described in the current hospitalization in a critical and fragile patient which leads to presume that were diagnosed following the hospitalization in critical conditions; concomitant medication with erythromycin and amiodarone used for atrial fibrillation with rapid ventricular response prior to the reported event onset cannot be ruled out
•Transient and recurrent atrioventricular dissociation (PT: Atrioventricular dissociation) is not expected in the RSI contained in the IB in force at the time of event onset (IB.v.11.0)

SPONSOR’S CAUSALITY ASSESSMENT:

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Although temporal relationship is plausible, risk factors (age, patient's medical history, pneumonia, and the worsening of cardiovascular comorbidities explain plausible relationship with the development of transient and recurrent (self-limited) atrioventricular dissociation; in special the development of branch block and other risk factors that are presumed to be developed before the event onset. Concomitant medications cannot be ruled out. The patient presented cardiac abnormalities (troponin I, CK MB increase) which could explain a prior cardiac ischemia leading to the event (to be clarified by the reporter). Causal relationship with the IMP seems to be unlikely; no other report has been previously reported.

Suspect Drugs (Cont...)

Product-Reaction level

Seq.No. : 1
Drug : Cx611(INVESTIGATIONAL DRUG)(Suspension for infusion)
Daily Dose : 2) 160 x 10^6 cell
Route of Admin : 1) Intravenous drip
2) Intravenous drip
Therapy Dates/Duration : 1) 17/DEC/2018;12:55 - 17/DEC/2018;13:19
2) 19/DEC/2018;14:05 - 19/DEC/2018;14:30 (25 Minutes)

Causality

1) TRANSIENT AND RECURRENT ATRIOVENTRICULAR DISSOCIATION (Atrioventricular dissociation (10069571), Atrioventricular dissociation (10069571))
Action(s) taken with drug : No action taken
Causality as per reporter (Drug/Vaccine) : Possible
Causality as per Mfr.(Drug/Vaccine) : Unlikely
Dechallenge : Not Applicable
Rechallenge : Not Applicable

Seq.No. : 2
Drug : Placebo for Cx611(PLACEBO)(Solution for infusion)
Route of Admin : 1) Intravenous drip
2) Intravenous drip
Therapy Dates/Duration : 1) 17/DEC/2018;12:55 - 17/DEC/2018;13:19
2) 19/DEC/2018;14:05 - 19/DEC/2018;14:30 (25 Minutes)

Causality

1) TRANSIENT AND RECURRENT ATRIOVENTRICULAR DISSOCIATION (Atrioventricular dissociation (10069571), Atrioventricular dissociation (10069571))
Action(s) taken with drug : No action taken
Causality as per reporter (Drug/Vaccine) : Possible
Causality as per Mfr.(Drug/Vaccine) : Unlikely
Dechallenge : Not Applicable
Rechallenge : Not Applicable

Concomitant drugs (Cont...)

Seq.No. : 1
Drug : ULCER PEPCID PROPHYLAXIS(MAGNESIUM CARBONATE, ALUMINIUM HYDROXIDE GEL, DRIED)
Route of Admin : 1) Intravenous
Indication for use : 1) PROPHYLAXIS[10064084 - Gastroesophageal reflux prophylaxis]

Seq.No. : 2
Drug : METOCLOPRAMIDE(METOCLOPRAMIDE)
Daily Dose : 1) 40 Milligram (10 Milligram,4 in 1 Days)
Route of Admin : 1) Intravenous
Indication for use : 1) PROPHYLAXIS[10064084 - Gastroesophageal reflux prophylaxis]
Therapy Dates/Duration : 1) 18/DEC/2018 -

Seq.No. : 3
Drug : LACTULOSE(LACTULOSE)
Daily Dose : 1) 20 Gram (10 Gram,2 in 1 Days)
Route of Admin : 1) Oral
Indication for use : 1) CONSTIPATION PROPHYLAXIS[10052933 - Constipation prophylaxis]
Therapy Dates/Duration : 1) 19/DEC/2018 -

Seq.No. : 4
Drug : PHYTOMENADIONE(PHYTOMENADIONE)
Daily Dose : 1) (10 Milligram,Once)
Route of Admin : 1) Intravenous

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Indication for use	:	1) CABP[10010120 - Community acquired pneumonia]
Therapy Dates/Duration	:	1) 17/DEC/2018 - 17/DEC/2018 (1 Days)

Seq.No.	:	5
Drug	:	CALCIUM CHLORIDE(CALCIUM CHLORIDE)
Daily Dose	:	1) (1000 Milligram,Once) 2) (1000 Milligram,Once)
Route of Admin	:	1) Intravenous 2) Intravenous
Indication for use	:	1) MINERAL SUPPLEMENTATION[10053963 - Mineral supplementation]
Therapy Dates/Duration	:	1) 17/DEC/2018 - 17/DEC/2018 (1 Days) 2) 19/DEC/2018 - 19/DEC/2018 (1 Days)

Seq.No.	:	6
Drug	:	ENOXAPARIN(ENOXAPARIN)
Daily Dose	:	1) 40 Milligram (40 Milligram,1 in 1 Days)
Route of Admin	:	1) Subcutaneous
Indication for use	:	1) PROPHYLAXIS[10036898 - Prophylaxis]
Therapy Dates/Duration	:	1) 17/DEC/2018 - 20/DEC/2018 (4 Days)

Seq.No.	:	7
Drug	:	AMIODARONE(AMIODARONE)
Daily Dose	:	1) (150 Milligram,Once)
Route of Admin	:	1) Intravenous
Indication for use	:	1) PAROXYSMAL ATRIAL FIBRILLATION[10034039 - Paroxysmal atrial fibrillation]
Therapy Dates/Duration	:	1) 17/DEC/2018 - 17/DEC/2018 (1 Days)

Seq.No.	:	8
Drug	:	FUROSEMIDE(FUROSEMIDE)
Daily Dose	:	1) 1 gm continuous
Route of Admin	:	1) Intravenous
Indication for use	:	1) STAGE 2 ACUTE KIDNEY INJURY[10080269 - Stage 2 acute kidney injury]
Therapy Dates/Duration	:	1) 19/DEC/2018 - 19/DEC/2018 (1 Days)

Seq.No.	:	9
Drug	:	CEFTRIAXONE(CEFTRIAXONE)
Daily Dose	:	1) 2 Gram (2 Gram,1 in 1 Days)
Route of Admin	:	1) Intravenous
Indication for use	:	1) CABP[10010120 - Community acquired pneumonia]
Therapy Dates/Duration	:	1) 16/DEC/2018 -

Seq.No.	:	10
Drug	:	ALBUMIN 20%(ALBUMIN HUMAN)
Daily Dose	:	1) (50 ml,Once)
Route of Admin	:	1) Intravenous
Indication for use	:	1) FLUID CHALLENGE[10016804 - Fluid replacement NOS]
Therapy Dates/Duration	:	1) 18/DEC/2018 - 18/DEC/2018 (1 Days)

Seq.No.	:	11
Drug	:	ERYTHROMYCIN(ERYTHROMYCIN)
Daily Dose	:	1) 1000 Milligram (250 Milligram,4 in 1 Days)
Route of Admin	:	1) Intravenous
Indication for use	:	1) PROKINETICS TO IMPROVE FEEDING TOLERANCE
Therapy Dates/Duration	:	1) 17/DEC/2018 - 21/DEC/2018 (5 Days)

Seq.No.	:	12
Drug	:	LEVOFLOXACIN(LEVOFLOXACIN)
Daily Dose	:	1) 1000 Milligram (500 Milligram,2 in 1 Days)
Route of Admin	:	1) Intravenous
Indication for use	:	1) CABP[10010120 - Community acquired pneumonia]
Therapy Dates/Duration	:	1) 16/DEC/2018 - 19/DEC/2018 (4 Days)

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Seq.No. : 13
Drug : METAMIZOL MAGNESIUM(METAMIZOLE MAGNESIUM)
Daily Dose : 1) 8 Gram (2 Gram,4 in 1 Days)
Route of Admin : 1) Intravenous
Indication for use : 1) CABP[10010120 - Community acquired pneumonia]
Therapy Dates/Duration : 1) 17/DEC/2018 -

Seq.No. : 14
Drug : PARACETAMOL(PARACETAMOL)
Daily Dose : 1) 4000 Milligram (1000 Milligram,4 in 1 Days)
Indication for use : 1) CABP[10010120 - Community acquired pneumonia]
Therapy Dates/Duration : 1) 17/DEC/2018 -

Seq.No. : 15
Drug : REMIFENTANIL(REMIFENTANIL)
Daily Dose : 1) 2 MG CONTINOUS
Route of Admin : 1) Intravenous
Indication for use : 1) SEDOANALGESIA[10002182 - Analgesia]
Therapy Dates/Duration : 1) 16/DEC/2018 - 20/DEC/2018 (5 Days)

Other relevant history (Cont...)

ACUTE KIDNEY INJURY 2[10080269 - Stage 2 acute kidney injury] (16/Dec/2018 -) (Continuing: Yes)
SEVERE COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA[10010120 - Community acquired pneumonia] (Continuing: Yes)
EX-SMOKER[10015572 - Ex-smoker] (Continuing: Yes)
CHRONIC BRONCHOPATHY[10064914 - Bronchopathy] (Continuing: Yes)

Clinical Trial Identification (Cont...)

Patient no : 22004
Study identification for EudraCT: 2015-002994-39#SEPCELL study

Additional information (continuation)

Lab Result :

Test name	Test date	Test result	Normal value	Classification
APTT	19/Dec/2018	45 sec	22.5 - 33.5	
BODY HEIGHT		165 cm		
C-REACTIVE PROTEIN	19/Dec/2018	35.8 mg/dL	0.1 - 0.5	
	19/Dec/2018	35.8 mg/dL	0.1 - 0.5	
	20/Dec/2018	39.5 mg/dL	0.1 - 0.5	
CK	20/Dec/2018	606 IU/L	1 - 190	
CK-MB	20/Dec/2018	16.9 mg/dL		
CREATININE	19/Dec/2018	2.29 mg/dL	0.67 - 1.17	
	20/Dec/2018	3.18 mg/dL	0.67 - 1.17	
EKG	17/Dec/2018	sinus tachycardia, supraventricular extrasystole, left bundle branch block, QT=360 msec, QRS=120 msec and heart rate 135 bpm		
	19/Dec/2018	Left bundle branch block, PR normal, and sinus rhythm		
EOSINOPHILS	19/Dec/2018	0.6 %	1 - 7	
	20/Dec/2018	0.9 %	1 - 7	
FIBRIN D DIMER	19/Dec/2018	4930 ng/dL	0.1 - 500	
	20/Dec/2018	12821 ng/dL	0.1 - 500	
GFR	19/Dec/2018	25.9 mL/min	60 - 140	

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HEMOGLOBIN	19/Dec/2018	13.1 g/dL	13.5 - 18
	20/Dec/2018	12.6 g/dL	13.5 - 18
LYMPHOCYTES	19/Dec/2018	4.8 %	15 - 50
	20/Dec/2018	8.1 %	15 - 50
NEUTROPHILS	19/Dec/2018	86.7 %	40 - 74
	20/Dec/2018	82 %	40 - 74
TROPONIN	19/Dec/2018	0.16 ng/mL	0.001 - 0.05
	20/Dec/2018	0.13 ng/mL	0.001 - 0.05
UREA	19/Dec/2018	108 mg/dL	15 - 50
urea increased			
WEIGHT		90 kg	