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			1967	51	Male	08	JAN	2019

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

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

RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep vein thrombosis (10051055), Deep vein thrombosis (10051055)) - Not recovered/not resolved
Protocol relatedness:
As per reporter: Study medication
As per company: Other

RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Popliteal vein thrombosis (10062589), Deep vein thrombosis (10051055)) - Not recovered/not resolved
Protocol relatedness:
As per reporter:
As per company:

RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep venous thrombosis femoral (10049916), Deep vein thrombosis (10051055)) - Not recovered/not resolved

Cont...

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

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 cells 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) 03/JAN/2019 2) 03/JAN/2019

19. THERAPY DURATION
1) 30 Minutes 2) 30 Minutes

III.CONCOMITANT DRUG(S) AND HISTORY

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

No concomitants reported

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

Concurrent Disease:
COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA[10010120 - Community acquired pneumonia] (Continuing: Yes)

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.
CX611-201901-40(0)

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

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

DATE OF THIS REPORT
22/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. :CX611-201901-40(0)**

Reaction Information (Cont...)

Seq. No.	:	1
Reaction	:	RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep vein thrombosis (10051055), Deep vein thrombosis (10051055))
Start Date	:	08/Jan/2019;12:00
Seq. No.	:	2
Reaction	:	RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Popliteal vein thrombosis (10062589), Deep vein thrombosis (10051055))
Start Date	:	08/Jan/2019;12:00
Seq. No.	:	3
Reaction	:	RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep venous thrombosis femoral (10049916), Deep vein thrombosis (10051055))
Start Date	:	08/Jan/2019;12:00

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

Protocol relatedness:
As per reporter:
As per company:

Case level outcome :Not recovered/not resolved

Case ID: Cx611-201901-40

Initial report received on 09/Jan/2019 and on 16/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 treatment of adult patients with severe community-acquired bacterial pneumonia and admitted to the intensive care unit), arising from Spain.

Subject was a 51-year-old male (subject ID: 22006), weight 70 kg, height 175 cm, diagnosed with severe community-acquired bacterial pneumonia (sACBP).

Neither medical history nor concomitant treatments were reported at the time of event onset, but the investigator informed that a multi-organ failure consisting of: 1. Acute Respiratory Failure (Pa/Fi < 100), Acure Kidney Injury (serum Creatinine 2,8 mg/dl), Septic shock (noradrenalin > 0,1 mcg/kg/min) and septic encephalopaty (GCS 14) had occurred previous to the ICU admission.

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 03/Jan/2019.
Second infusion (Dose 2) was administered on 05/Jan/2019.

On 08/Jan/2019 (Day+ 4 following the last IMP administration), the patient underwent lower limb compression US, as per protocol, and right popliteal vein and left femoral and popliteal veins deep venous thromboses were found. As stated by the reported, no signs of thrombophlebitis were present and platelets and coagulation laboratory results showed no significant alterations (no data provided).

Pneumatic compression stockings were used as corrective treatment.

No action was taken with the Cx611/Placebo due to the event.
The outcome of the event was reported as not recovered at the time of the report.

INVESTIGATOR'S ASSESSMENT:
In the Investigator's opinion, the events of right popliteal vein and left femoral and popliteal veins deep venous thromboses were possibly related to the Cx611/Placebo and not related to the procedure administration. Severity of the events was moderate. The events were considered Adverse Events of Special Interest (as per protocol) and serious (hospitalization/prolongation of hospitalization).
According to the Investigator's opinion, the events were considered the worsening of pre-existing condition of a critically ill patient with community acquired pneumonia with multi-organ failure; no data on multi-organ failure were reported. The investigator stated that deep vein thrombosis is a relatively frequent complication in critically ill patients.

SPONSOR'S ASSESSMENT:

1.- Right popliteal vein and left femoral and popliteal veins deep venous thrombosis (LLT: Deep vein thrombosis; PT: Deep vein thrombosis)
2.- Right popliteal vein and left femoral and popliteal veins deep venous thrombosis (LLT: Popliteal vein thrombosis; PT: Deep vein thrombosis)
3.- Right popliteal vein and left femoral and popliteal veins deep venous thrombosis (LLT: Deep venous thrombosis femoral; PT: Deep vein thrombosis)

For the all three events:

•Temporal relationship: Plausible
•Risk factors: Severe sepsis, critically ill patient, in-bed patient
•Right popliteal vein and left femoral and popliteal veins deep venous thromboses (PT: Deep vein thrombosis

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Continuation Sheet for CIOMS report

Mfr. Control No. :CX611-201901-40(0)

for all the three events) 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:

51-year male critically ill patient. Received dosing with IMP/Placebo on days 03 and 05 January 2019. Except that he was critically ill with multi-organ failure, very sparse information is provided and has been requested. The bilateral deep vein leg thrombosis was detected on 08 January-2018.

Comment: Even if the thrombosis occurred after IMP/Placebo, a causal relationship is unlikely with IMP or administration procedure. Although thromboembolic events are AESI, this mainly refers to pulmonary embolism and peripheral thrombi are not expected events from IMP or administration procedures but common complications in ICU bedridden critically ill patients with multi-organ failure such as in this case. Therefore, the association with the IMP/Placebo is unlikely.

Suspect Drugs (Cont...)

Product-Reaction level

Seq.No. : 1
Drug : Cx611(INVESTIGATIONAL DRUG)(Suspension for infusion)
Daily Dose : 2) 160 x 10^6 cells
Route of Admin : 1) Intravenous drip
2) Intravenous drip
Therapy Dates/Duration : 1) 03/JAN/2019;21:39 - 03/JAN/2019;22:09
2) 05/JAN/2019;21:35 - 05/JAN/2019;22:06 (31 Minutes)

Causality

1) RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep vein thrombosis (10051055), Deep vein thrombosis (10051055))
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
2) RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Popliteal vein thrombosis (10062589), Deep vein thrombosis (10051055))
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
3) RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep venous thrombosis femoral (10049916), Deep vein thrombosis (10051055))
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) 03/JAN/2019;21:39 - 03/JAN/2019;22:09
2) 05/JAN/2019;21:35 - 05/JAN/2019;22:06 (31 Minutes)

Causality

1) RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep vein thrombosis (10051055), Deep vein thrombosis (10051055))
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
2) RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Popliteal vein thrombosis (10062589), Deep vein thrombosis (10051055))
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
3) RIGHT POPLITEAL VEIN AND LEFT FEMORAL AND POPLITEALS VEINS DEEP VENOUS THROMBOSIS (Deep venous thrombosis femoral (10049916), Deep vein thrombosis (10051055))
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

Clinical Trial Identification (Cont...)

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Continuation Sheet for CIOMS report **Mfr. Control No. :CX611-201901-40(0)**

Patient no : 22006
Study identification for EudraCT: 2015-002994-39#SEPCELL study

Additional information (continuation)

Lab Result :

Test name	Test date	Test result	Normal value	Classification
BODY HEIGHT		175 cm		
COAGULATION TEST		no significant alteration		
LOWER LIMB ULTRASOUND				
PLATELET COUNT		no significant alteration		
WEIGHT		70 kg		