Clinical trial results:
A Phase II Efficacy Study of Intracerebral CTX0E03 DP In Patients with Stable Paresis of the Arm Following an Ischaemic Stroke.

Summary

EudraCT number	2012-003482-18
Trial protocol	GB
Global end of trial date	16 August 2017

Results information

Result version number	v1 (current)
This version publication date	06 November 2019
First version publication date	06 November 2019

Trial information

Trial identification

Sponsor protocol code	RN01-CP-0002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02117635
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ReNeuron Ltd.
Sponsor organisation address	Pencoed Business Park,Pencoed,, Bridgend, United Kingdom, CF35 5HY
Public contact	Shaun Stapleton, ReNeuron Ltd., +44 2038198400, shaun-stapleton@reneuron.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2017
Global end of trial reached?	Yes
Global end of trial date	16 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To determine whether a sufficient proportion of patients experience response of their paretic arm following treatment with CTX0E03 DP at a dose level of 20 million cells to justify a subsequent randomised study.
o Response will be defined as a minimum improvement of 2 points in test number 2 of the Action Research Arm Test (Grasp a 2.5 cm^3 block and move it from the starting position to the target end position) in the affected arm 3 months after injection of CTX0E03 DP. This would represent an improvement from a pre-treatment state in which the patient was unable to grasp and reposition the block as required to a post-treatment state in which the patient could accomplish the task as specified within 60 seconds and would represent recovery of useful function in a previously paretic arm.

Protection of trial subjects:

The study protocol, the patient information sheet (PIS) and consent form and all amendments were submitted to all relevant Competent Authorities (CA) and Research Ethics Committees (REC) in accordance with local regulations. Approval was obtained from the REC and regulatory agency prior to study initiation.

This study was conducted in accordance with Good Clinical Practice (GCP) as defined by the International Council for Harmonization (ICH), the ethical principles that have their origin in the Declaration of Helsinki and its amendments, and all applicable national and international laws.

Prior to enrolment and any screening activities, the study procedures and any known or likely risks were explained to the patients in lay language by the Investigator or designee. Patients were provided with a written PIS and informed consent form (ICF) and were given ample opportunity to enquire about the study. Once the Investigator was assured that the patient understood the commitments of participating in the study, the patient was asked to sign and personally date the ICF in the presence of the Investigator or Sub-investigator. If the patient was not physically able to sign the form, a witness may have signed the consent form on their behalf. Each patient’s consent form was also signed and dated by the Investigator or Subinvestigator. No protocol-specific tests or procedures, that were not part of routine care, were performed prior to informed consent being obtained. All active patients signed an updated ICF if revisions that affected the patients’ safety or decision to participate were made to the ICF during the course of the study.

This study was guided by a Data Safety Monitoring Board (DSMB) which included a minimum of one clinician expert in the management of stroke, one neurosurgeon and one medical statistician. The DSMB reviewed all safety data at predetermined intervals during the course of the study.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	01 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason, Safety
Long term follow-up duration	100 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 41 patients were enrolled from 8 different clinical sites in the UK. Out of the 41 patients enrolled, 23 patients were treated. The first patient was enrolled on 31 July 2014. The last patient visit took place on 16 August 2017.

Pre-assignment

Screening details:

Of the 41 patients screened, 23 passed screening and were treated in the study. The reasons for screen failure were as follows, in order of importance: Test positive for Human Leucocyte Antigens (HLA) expressed on the CTX0E03 cell line; Withdrawal of consent; Did not meet the entry criteria; Missing record; Other.

Period 1

Period 1 title	D365 Final Analysis (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	CTX0E03 DP
Investigational medicinal product code	CTX0E03 DP
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intracerebral use

Dosage and administration details:

CTX0E03 DP is a formulation containing a human neural stem cell line developed by ReNeuron. CTX0E03 DP is an off-white, opaque, sterile suspension.

The treatment in this study was an intracerebral implantation of 400 µL CTX0E03 DP at a nominal dose level of 20x10^6 cells in sterile suspension on a single occasion.

Number of subjects in period 1	Treatment arm
Started	23
D90	23
Completed	20
Not completed	3
Death	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	D365 Final Analysis
Reporting group description:	
All treated subjects	

Reporting group values	D365 Final Analysis	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	62.39		
standard deviation	± 10.77	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	13	13	

Subject analysis sets	
Subject analysis set title	Day 365
Subject analysis set type	Full analysis
Subject analysis set description: All treated subjects at Day 365	
Subject analysis set title	Day 90
Subject analysis set type	Full analysis
Subject analysis set description: All treated subjects at Day 90	
Subject analysis set title	NIHSS UL < 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects with a baseline NIHSS Upper Limb Score of less than 4	
Subject analysis set title	NIHSS UL = 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects with a baseline NIHSS Upper Limb score of 4	

Reporting group values	Day 365	Day 90	NIHSS UL < 4
Number of subjects	23	23	14
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	11	9
From 65-84 years	12	12	5
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	62.39	62.39	57.57
standard deviation	± 10.77	± 10.77	± 9.43
Gender categorical			
Units: Subjects			
Female	10	10	8
Male	13	13	6

Reporting group values	NIHSS UL = 4		
Number of subjects	9		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	2		
From 65-84 years	7		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	69.89		
standard deviation	± 8.39		
Gender categorical			
Units: Subjects			
Female	2		
Male	7		

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description: -	
Subject analysis set title	Day 365
Subject analysis set type	Full analysis
Subject analysis set description: All treated subjects at Day 365	
Subject analysis set title	Day 90
Subject analysis set type	Full analysis
Subject analysis set description: All treated subjects at Day 90	
Subject analysis set title	NIHSS UL < 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects with a baseline NIHSS Upper Limb Score of less than 4	
Subject analysis set title	NIHSS UL = 4
Subject analysis set type	Sub-group analysis
Subject analysis set description: All subjects with a baseline NIHSS Upper Limb score of 4	

Primary: Action Research Arm Test 2 - Minimum improvement of 2 points

End point title	Action Research Arm Test 2 - Minimum improvement of 2 points[1]

End point description:

The primary efficacy endpoint, correlating to useful recovery of function, was defined as the ability to use the previously paretic arm to pick up a 2.5cm^3 block from a table top, lift it and reposition it on a higher surface. This is Action Research Arm Test number 2.

A responder is defined as having a minimum improvement of 2 points in test number 2 from baseline.

Results are also displayed per baseline NIHSS Upper Limb Score.

The % of subjects is presented to the nearest whole number.

End point type	Primary

End point timeframe:

90 Days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The system does not allow for statistical analysis for studies with a single treatment arm.

End point values	Treatment arm	NIHSS UL < 4	NIHSS UL = 4	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	14	9	
Units: % of subjects				
number (not applicable)				
Day 90	4	7	0	
Day 365	15	25	0	

Statistical analyses

No statistical analyses for this end point

Secondary: National Institutes of Health Stroke Scale - Minimum improvement of 10 points

End point title	National Institutes of Health Stroke Scale - Minimum improvement of 10 points

End point description:

This endpoint is to assess the efficacy of intracranial CTX0E03 DP in restoring function following an ischaemic stroke using the National Institutes of Health Stroke Scale (NIHSS).

The NIHSS comprises 11 items, each scored from 0-2/3/4 giving a total of 0 - 42 where lower numbers correspond to better neurological impairment outcomes.

A responder is defined as having a minimum improvement of 10 points from baseline.

End point type	Secondary

End point timeframe:

90 Days; 365 Days

End point values	Day 365	Day 90		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	23		
Units: No. of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Barthel Index - Minimum improvement of 9 points

End point title	Barthel Index - Minimum improvement of 9 points

End point description:

This endpoint is to assess the efficacy of intracerebral CTX0E03 DP in improving patient’s ability to execute activities of daily living following an ischaemic stroke using the Barthel Index (BI).

The BI comprises 10 items, each scored from 0-10 or 0-15 in intervals of 5 points giving a total of 0 - 100 where higher numbers correspond to better functional outcomes.

A responder is defined as having a minimum improvement of 9-points from baseline.

Results are also displayed per baseline NIHSS Upper Limb score.

The % of subjects is presented to the nearest whole number.

End point type	Secondary

End point timeframe:

90 Days; 365 Days

End point values	Treatment arm	NIHSS UL < 4	NIHSS UL = 4	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	14	9	
Units: % of subjects				
number (not applicable)				
Day 90	35	21	56	
Day 365	40	25	63	

Statistical analyses

No statistical analyses for this end point

Secondary: Fugl-Meyer Assessment - Minimum improvement of 10 points

End point title	Fugl-Meyer Assessment - Minimum improvement of 10 points

End point description:

This endpoint is to assess the efficacy of intracerebral CTX0E03 DP in sensorimotor recovery of the affected limb restoring function following an ischaemic stroke using the Fugl-Meyer Assessment (FMA).

FMA comprises motor assessments for upper extremities (33 tests), lower extremities (17 tests), and sensory assessments (12 tests), giving a total motor and sensory score of 0 - 124, where higher numbers correspond to a better medical outcome.

A responder is defined as having a minimum improvement of 10 points from baseline on either Motor Function Upper Extremity Score or Motor Function Lower Extremity Score.

The % of subjects is presented to the nearest whole number.

End point type	Secondary

End point timeframe:

90 Days; 365 Days

End point values	Day 365	Day 90		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: % of subjects				
number (not applicable)	30	40		

Statistical analyses

No statistical analyses for this end point

Secondary: modified Rankin Score - Minimum improvement of 1 Grade

End point title	modified Rankin Score - Minimum improvement of 1 Grade

End point description:

The modified Rankin Score (mRS) assessment is a hierarchical score of disability graded from 0-6 where 0 represents no symptoms
and 6 represents death. Lower numbers correspond to better disability outcomes. A score of ≤2 is generally accepted to represent functional independence and a score of ≤3 signifies independence in walking. The Focused Assessment tool is a structured interview that improves inter-observer agreement on assigning mRS grades.

A responder is defined as a minimum improvement of 1 grade from baseline

Results are also displayed per baseline NIHSS Upper Limb score.

The % of subjects is presented to the nearest whole number.

End point type	Secondary

End point timeframe:

Day 90; Day 365

End point values	Treatment arm	NIHSS UL < 4	NIHSS UL = 4	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	14	9	
Units: % of subjects				
number (not applicable)				
Day 90	30	43	11	
Day 365	35	50	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Action Research Arm Test Total Score - Minimum improvement of 6 points

End point title	Action Research Arm Test Total Score - Minimum improvement of 6 points

End point description:

This endpoint was to assess overall improvement in Action Research Arm Test (ARAT) total score. The ARAT comprises 19 test items, each scored from 0-3 giving a total of 0 - 57 where higher numbers correspond to better functional outcomes.

A responder is defined as a minimum improvement of ARAT total score of 6 points from baseline.

Results are also displayed per baseline NIHSS Upper Limb score.

The % of subjects is presented to the nearest whole number.

End point type	Secondary

End point timeframe:

Day 90; Day 365

End point values	Treatment arm	NIHSS UL < 4	NIHSS UL = 4	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	23	14	9	
Units: % of subjects				
number (not applicable)				
Day 90	13	21	0	
Day 365	25	42	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 365

Adverse event reporting additional description:

This report provides safety data for all 23 treated patients. Safety data are available through the completion of the Day 365 study completion visit for 20/23 (86.96%) patients. One patient died (sepsis of unknown origin), and so was withdrawn from the study prematurely and 2 patients were lost-to follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Treatment Group

Reporting group description: -

Serious adverse events	Treatment Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Investigations			
HLA marker study positive			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Ischaemic cerebral infarction			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertonia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 23 (91.30%)		
Injury, poisoning and procedural complications			

Procedural hypotension subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3		
Fall subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 4		
Procedural headache subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Wound complication subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Wound secretion subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Joint injury subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	6 / 23 (26.09%) 7		
Aphasia subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Balance disorder subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Migraine with aura subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 6		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2 4 / 23 (17.39%) 4		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3		
Renal and urinary disorders Hypertonic bladder subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3 2 / 23 (8.70%) 2 1 / 23 (4.35%) 2		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2014	Protocol version 4.0, dated 09 Jul 2014. Changes to inclusion/exclusion criteria and trial evaluation schedule.
26 November 2014	Protocol version 6.0, dated 21-Nov-2014 Clarification regarding the use of antiplatelet and anticoagulant therapy prior to surgery. Expanding the definition of exclusion criterion #8 (relating to patients with cardiovascular events prior to the planned injection of CTX0E03 DP).
15 May 2015	Protocol version 7.0, dated 15-Apr-2015 Changes to qualifying stroke functional assessments Changes to inclusion/exclusion criteria Re-screening of potential eligible subjects added to protocol
11 April 2016	Protocol version 8.0, dated 09-Mar-2016 Timing of primary endpoint brought forward Additional efficacy measure is proposed as a secondary endpoint - Fugl-Meyer Assessment (FMA) Study design modification to a single cohort design Include females of childbearing potential Revised AE/SAE, follow-up and pregnancy reporting wording

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

NA

Notes: