Clinical trial results:
Stem cells in Rapidly Evolving Active Multiple Sclerosis (STREAMS)

Summary

EudraCT number	2012-002357-35
Trial protocol	GB
Global end of trial date	31 July 2019

Results information

Result version number	v1 (current)
This version publication date	29 December 2019
First version publication date	29 December 2019

Trial information

Trial identification

Sponsor protocol code	CRO1959

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01606215
WHO universal trial number (UTN)	-
Other trial identifiers	Clinicaltrials.gov: NCT01606215

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	160 Du Cane Road Burlington Danes Building Hammersmith Campus , London, United Kingdom, W12 0NN
Public contact	Dr Paolo Muraro, Imperial College London, +44 02075946670, p.muraro@imperial.ac.uk
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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	Interim
Date of interim/final analysis	16 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2016
Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

There are two co-primary objectives.

The first is to assess the safety of intravenous therapy with autologous (derived from the individuals themselves) MSCs in MS patients. The safety of MSCs infusion will be evaluated including frequency, timing and severity of any adverse events in both MSCs and placebo treatment groups.

The second is to evaluate the activity of autologous MSCs in MS patients, quantified by the reduction in the number of new contrast-enhancing lesions on MRI scans over 24 weeks, the latter suggesting new inflammation.

Protection of trial subjects:

1. For procedures such as lumbar punctures, skin biopsy and the bone marrow harvest, local anaesthetic was used to minimise pain during the procedure

2. Patients could voluntarily withdraw at any time from the study and follow-up assessments.

3. Unblinding could be requested if the clinical situation warranted it on patient safety grounds

4. The patient’s participation in the study could also be discontinued at any time at the discretion of the investigator - justifiable reasons include dSuspected Unexpected Serious Adverse Reactions (SUSAR) or deterioration in the disease activity requiring immunomodulatory treatment

Background therapy:

N/A - the patients were not on any other treatment during the trial.

Evidence for comparator: -

Actual start date of recruitment	26 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	21
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients from the UK were recruited at Imperial College Healthcare Trust between 23 March 2013 and 26 June 2015

Pre-assignment

Screening details:

A total of 21 patients with multiple sclerosis were screened and randomised but only 13 patients completed the trial. Details: 1 patient withdrew consent after screening, 1 patient's MRI did not meet criteria after review and 6 patients failed to meet the required MSC dose after expansion

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

All subjects were randomised after verifying that they are eligible. Randomisation was carried out within a web-based system, made available to authorised researchers, by the Clinical Research Organisation (CRO) in charge.
The stem cell laboratory was made aware of the allocation (so that the order of the infusion) - both infusions were made to identical volumes and appearance - was known but the patients, investigators and data analysts were blinded to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Early MSC-treated

Arm description:

Patients receiving 1-2 x106cells/kg MSCs in the first infusion

Arm type	Experimental
Investigational medicinal product name	Mesenchymal Stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

1-2 x106 million MSC cells/kg suspended in 5% HAS/10% DMSO

Arm title	Placebo

Arm description:

placebo Drug Product comprising 5% HAS/10% DMSO is prepared - only lacks the MSCs that are present in the active arm

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

equal volume of 5% HAS/10% DMSO

Number of subjects in period 1	Early MSC-treated	Placebo
Started	10	11
Completed	6	7
Not completed	4	4
Consent withdrawn by subject	1	-
mscs did not expand	3	-
mri on re-review did not meet criteria	-	1
mscs failed to expand	-	3

Period 2	
Period 2 title	Crossover
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	MSCs after placebo

Arm description:

Patients receiving 1-2 x106cells/kg MSCs in the first infusion

Arm type	Experimental
Investigational medicinal product name	Mesenchymal Stem cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

1-2 x106 million MSC cells/kg suspended in 5% HAS/10% DMSO

Arm title	Placebo after treatment

Arm description:

placebo Drug Product comprising 5% HAS/10% DMSO is prepared - only lacks the MSCs that are present in the active arm

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

equal volume of 5% HAS/10% DMSO

Number of subjects in period 2	MSCs after placebo	Placebo after treatment
Started	7	6
Completed	7	6

Baseline characteristics

Reporting groups

Reporting group title	Randomisation

Reporting group description: -

Reporting group values	Randomisation	Total	
Number of subjects	21	21	
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)	21	21	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	38		
full range (min-max)	25 to 50	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	6	6	
Ethnic group Units: Subjects			
Caucasian	20	20	
Afro-Caribbean	0	0	
Middle Eastern	1	1	
Disease duration Units: years			
arithmetic mean	5.49		
full range (min-max)	0.5 to 9.83	-	
baseline EDSS Units: units			
arithmetic mean	3.85		
full range (min-max)	2.0 to 6.0	-	
relapses in 18 months pre-trial Units: n/a			
arithmetic mean	2.23		
full range (min-max)	1 to 4	-	
no of gadolinium enhancing lesions on MRI at baseline Units: number			
arithmetic mean	1.38		

full range (min-max)	1 to 3	-	

Subject analysis sets

Subject analysis set title	early msc treated completed
Subject analysis set type	Sub-group analysis

Subject analysis set description:

early msc treated period 1 pts who completed treatment

Subject analysis set title	delayed MSC group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

pts receiving MSCs at Week 24 having received placebo at Week 0

Reporting group values	early msc treated completed	delayed MSC group	
Number of subjects	6	7	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	6	7	
Age continuous Units: years			
arithmetic mean	41.7	32.1	
full range (min-max)	30 to 50	25 to 43	
Gender categorical Units: Subjects			
Female	4	5	
Male	2	2	
Ethnic group Units: Subjects			
Caucasian	6	6	
Afro-Caribbean			
Middle Eastern		1	
Disease duration Units: years			
arithmetic mean			
full range (min-max)			
baseline EDSS Units: units			
arithmetic mean			
full range (min-max)			

relapses in 18 months pre-trial Units: n/a arithmetic mean full range (min-max)			
no of gadolinium enhancing lesions on MRI at baseline Units: number arithmetic mean full range (min-max)			

End points

End points reporting groups

Reporting group title	Early MSC-treated
Reporting group description:	
Patients receiving 1-2 x106cells/kg MSCs in the first infusion	
Reporting group title	Placebo
Reporting group description:	
placebo Drug Product comprising 5% HAS/10% DMSO is prepared - only lacks the MSCs that are present in the active arm	
Reporting group title	MSCs after placebo
Reporting group description:	
Patients receiving 1-2 x106cells/kg MSCs in the first infusion	
Reporting group title	Placebo after treatment
Reporting group description:	
placebo Drug Product comprising 5% HAS/10% DMSO is prepared - only lacks the MSCs that are present in the active arm	
Subject analysis set title	early msc treated completed
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
early msc treated period 1 pts who completed treatment	
Subject analysis set title	delayed MSC group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
pts receiving MSCs at Week 24 having received placebo at Week 0	

Primary: number of adverse events

End point title	number of adverse events[1][2]
End point description:	
End point type	Primary
End point timeframe:	
24 week period in each half of the trial	

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: numbers too small

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: numbers too small

End point values	Placebo	early msc treated completed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	7	6		
Units: number				
number (not applicable)	4	5		

Statistical analyses

No statistical analyses for this end point

Secondary: number of relapses in first period

End point title	number of relapses in first period

End point description:

total number of relapses in MSC treated periods vs sham periods

End point type	Secondary

End point timeframe:

12 months

End point values	Early MSC-treated	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: number				
number (not applicable)	2	10		

Statistical analyses

No statistical analyses for this end point

Secondary: total number of relapses in second period

End point title	total number of relapses in second period

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	MSCs after placebo	Placebo after treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: number				
number (not applicable)	4	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4
Reporting groups	
Reporting group title	msc treated
Reporting group description: 13 patients receiving MSCs either at Week 0 or Week 24 11 total AEs in 7 pts	
Reporting group title	placebo group
Reporting group description: 13 patients given sham infusion either at week 0 or at week 24 4 adverse events in total in 3 patients	

Serious adverse events	msc treated	placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	msc treated	placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 13 (53.85%)	3 / 13 (23.08%)	
Vascular disorders			
DVT	Additional description: unrelated to infusion - flight and family history		
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
headache			
subjects affected / exposed	0 / 13 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	3 / 13 (23.08%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Urinary tract infection bacterial			
subjects affected / exposed	2 / 13 (15.38%)	1 / 13 (7.69%)	
occurrences (all)	4	1	
upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
loss of appetite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2013	requesting additional blood samples and inserting an additional mantoux test
03 January 2014	1.The inclusion criterion "Disease duration 2-10 years from diagnosis" was changed to "Disease duration 0-10 years from diagnosis". T 2. The inclusion criterion "EDSS 3.0 - 6.5 at screening evaluation" was changed to "EDSS 2.0 - 6.5 at screening evaluation" 3.inclusion criterion "≥1GEL on MRI within 3 months prior to harvesting" was changed to "≥1GEL on MRI within 6 months prior to harvesting"
02 April 2014	to allow a dose range of 1-2 x106 cells/kg rather than stipulate 2 x 106 cells/kg
14 January 2015	to allow second phase of recruitment into streams

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.

small study but double blind and randomised

Notes: