Clinical trial results:
Autologous Stem Cells in Achilles Tendinopathy (ASCAT)- A phase II, single centre, proof of concept study

Summary

EudraCT number	2013-000966-12
Trial protocol	GB
Global end of trial date	12 September 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	12/0419

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02064062
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCL
Sponsor organisation address	Joint Research Office, UCL Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Goldberg, Royal National Orthopaedic Hospital, +44 208 3853042, andrew.goldberg@ucl.ac.uk
Scientific contact	Goldberg, Royal National Orthopaedic Hospital, +44 208 3853042, andrew.goldberg@ucl.ac.uk

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	12 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2018
Global end of trial reached?	Yes
Global end of trial date	12 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine safety by showing that there are no serious adverse reactions to autologous stem cells injected into tendon.
The secondary objectives are:
- To show that autologous bone marrow derived culture expanded MSCs can improve clinical outcomes (as measured by clinical scores).
- To gain experience in using Ultrasound Tissue Characterisation (UTC) and assess usefulness of UTC as an outcome measurement (evaluated through a comparison with convention ultrasound measures and inter-rater reliability).

Protection of trial subjects:

Analgesia and anaesthesia where appropriate

Background therapy:

No placebo arm. This was a first in man study of an active treatment.

Evidence for comparator:

N/A

Actual start date of recruitment	16 September 2015
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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was difficult due to several factors including patient population, referral restrictions and competing trials. 1st consent was 16/9/2015, last consent 26/1/2018. The 10 patients in ASCAT were based nationwide and travelled to RNOH for this treatment.

Pre-assignment

Screening details:

16 were screened: 3 were screen fails (ineligible) and 13 were enrolled. Of those 13, 3 patients didn't grow enough cells so were not treated.

Period 1

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

Arms

Arm title	Active arm - active treatment

Arm description:

There was only a single arm in which MSC were harvested and cultured. Implanted into Achilles tendon for 10 participants and then follow up at 6, 12 and 24 weeks

Arm type	Experimental
Investigational medicinal product name	Autologous bone marrow derived culture-expanded mesenchymal stem cells (MSCs)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Implantation

Dosage and administration details:

All participants received a single injection of ATIMP at a dose level of between 4-20x10e6 cells in 1ml of DMEM. IMP was supplied in a single vial, containing between 4-20x10e6 cells in 1.0ml of DMEM. The content of the vial was drawn into a syringe and injected along the length of the achilles tendon at the area of greatest degeneration starting 1cm distal to the degeneration (as deemed by ultrasound findings) and finishing 1cm proximal to normal structure under ultrasound control in the outpatient setting.

Number of subjects in period 1	Active arm - active treatment
Started	10
Completed	10

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description:

Inclusion
• Aged ≥18 and ≤ 70
• Participants with chronic midportion Achilles tendinopathy (as defined by pain in region of AT and tender swelling in mid portion of AT (no tenderness over bony attachment to heel) with symptoms for longer than 6 months who have failed conservative treatment (at least a full course of physiotherapy) and for whom surgery is being considered
• Females of CBP must be willing to use two forms of effective contraception from the time of consent to 6 months post-injection.

Exclusion
• Previous bony surgery at or in proximity to the harvest site
• Pregnancy or lactation
• Current use of steroids, anti-TNF drugs, methotrexate, or ciprofloxacin
• Positive for HBV, HCV, HIV 1 and 2, syphilis and HTLV
• Previous AT surgery on the tendon to receive MSC implantation
• Inflammatory arthritis
• Known or suspected underlying haematological malignancy
• Other active malignancy in the past 3 years
• Bovine or antibiotic allergy

Reporting group values	Treatment	Total	
Number of subjects	10	10	
Age categorical			
All subjects			
Units: Subjects			
Adults (18-64 years)	10	10	
Gender categorical Units: Subjects			
Male and female	10	10	

End points

End points reporting groups

Reporting group title	Active arm - active treatment

Reporting group description:

There was only a single arm in which MSC were harvested and cultured. Implanted into Achilles tendon for 10 participants and then follow up at 6, 12 and 24 weeks

Primary: Serious adverse reactions

End point title	Serious adverse reactions[1]

End point description:

Incidence of serious adverse reactions

End point type	Primary

End point timeframe:

Time of bone marrow harvest to 6 months post-treatment

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: No serious adverse reactions occurred in any of the subjects so there was no data to analyse for the primary endpoint

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	10[2]			
Units: Serious adverse reaction				
number (not applicable)	10			

Notes:

[2] - No serious adverse reactions occurred in any of the 10 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of success at 6 months - MOXFQ, EQ-VAS, VISA-A. VAS-pain and SAS

End point title	Incidence of success at 6 months - MOXFQ, EQ-VAS, VISA-A. VAS-pain and SAS

End point description:

Incidence of success at 6 months, where success is defined as achieving a minimally important clinical difference. These were defined for selected outcomes as:
- VISA-A: increase of 12 or more points
- VAS pain: reduction of 15 or more points (on 0-100 scale)
- MOXFQ pain: decrease of 12 or points

.
The following outcomes based on clinical scores were evaluated:
- MOXFQ
- EQ5D 5L
- EQ-VAS
- VISA-A
- VAS Pain score
- Stanmore Sporting Activity Score (SAS)

The first set of analyses of the secondary endpoints compared the changes in clinical scores from baseline to each of the subsequent time periods.The mean and standard deviation were used as summary statistics for most scores, although the median and inter-quartile range were preferred for the EQ-5d. Also reported were the mean changes in scores between timepoints, along with corresponding confidence intervals. Baseline changes to 24wk timepoint are included here.
P-values were also reported (not included here).

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post treatment

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	10[3]			
Units: Change in score from baseline to 6 month				
arithmetic mean (confidence interval 95%)				
MOXFQ walking	-30 (-43 to -16)			
MOXFQ pain	-28 (-39 to -17)			
MOXFQ social	-19 (-30 to -9)			
EQ-VAS	13 (7 to 19)			
VISA-A	22 (12 to 32)			
VAS pain	-23 (-42 to -5)			
SAS	2.0 (0.6 to 3.4)			

Notes:

[3] - 10 subjects were analysed for MOXFQ and VISA-A and VAS pain, 8 subjects for EQ_VAS and 9 for SAS

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in conventional ultrasound measurements from baseline to 24 weeks

End point title	Changes in conventional ultrasound measurements from baseline to 24 weeks

End point description:

Changes in the ultrasound variables measured on a continuous scale from baseline to each subsequent timepoint were analysed at equivalent timepoints and using equivalent methods to those described for the clinical scores. Baseline changes to 24wk timepoint are included here.

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post treatment

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Mean change				
arithmetic mean (confidence interval 95%)				
Max AP thickness of the tendon	-0.8 (-1.3 to -0.2)			
Lesion distance	10 (-15 to 34)			
% disorganised	-3 (-25 to 19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of success at 6 months - EQ-5D

End point title	Incidence of success at 6 months - EQ-5D

End point description:

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post-treatment

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Median score change: baseline to 6 month				
median (inter-quartile range (Q1-Q3))	0.16 (0.00 to 0.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in conventional ultrasound measurements from baseline to 24 weeks

End point title	Changes in conventional ultrasound measurements from baseline to 24 weeks

End point description:

Changes in the ultrasound variables measured on a continuous scale from baseline to each subsequent timepoint were analysed at equivalent timepoints and using equivalent methods to those described for the clinical scores. Baseline changes to 24wk timepoint are included here.

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post treatment

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Mean change				
median (inter-quartile range (Q1-Q3))				
Focal change	0.0 (0.0 to 0.0)			
% thickness	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in conventional ultrasound measurement of neovascularisation from baseline to 24 weeks

End point title	Changes in conventional ultrasound measurement of neovascularisation from baseline to 24 weeks

End point description:

Neovascularisation was measured on an ordinal scale, and changes from baseline were analysed using the Wilcoxon matched-pairs test.

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post treatment

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Severity				
Absent (baseline)	1			
Absent (24 weeks)	1			
Mild (baseline)	4			
Mild (24 weeks)	4			
Moderate (baseline)	0			
Moderate (24 weeks)	0			
Significant (baseline)	0			
Significant (24 weeks)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Inter-observer agreement for conventional ultrasound measurements

End point title	Inter-observer agreement for conventional ultrasound measurements

End point description:

Measurements of the conventional US parameters were made by two radiologists, and calculations of the inter-rater reliability of the US measurements were made.

The reliability of continuous measurements was evaluated using intra-class correlation (ICC). The reliability of ordinal measurements was made using the weighted kappa statistic (ie. neovascularisation). Due to the relatively small trial sample size, data from all four timepoints combined was included in each analysis.

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post treatment

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	2[4]			
Units: Mean of ICC/weighted kappa (ie.neovasc)				
arithmetic mean (confidence interval 95%)				
Max AP thickness	0.95 (0.87 to 0.98)			
Lesion distance	0.89 (0.76 to 0.95)			
Focal change	0.41 (0.00 to 0.71)			
% thickness	0.38 (0.00 to 0.69)			
Neovascularisation	0.82 (0.50 to 1.00)			

Notes:

[4] - At certain timepoints data by 1st radiologist was complete for only 2 subjects; n varies from 2 - 5.

Statistical analyses

No statistical analyses for this end point

Secondary: Association between UTC and ultrasound measurements

End point title	Association between UTC and ultrasound measurements

End point description:

The association between conventional ultrasound and UTC measurements was examined to establish the usefulness of UTC as an outcome measurement.
The final outcome related to the UTC measurements, which quantified the percentage of fibres in four different categories:

- Type 1: aligned fibrillar structure (straight fibres)
- Type 2: wavy fibres (aligned but not as aligned as type 1)
- Type 3: haphazard fibre aligned
- Type 4: amorphoric material or no fibres

Type 1 + 2 values were summed together representing 'organised' tissue, and type 3 + 4 were summed together representing 'disorganised tissue". The % disorganised tissue was analysed.

The UTC measurement analysed was the percentage of disorganised tissue. The conventional US measurements were made by two radiologists. However, there was more complete data from the second radiologist, and thus only data from this radiologist was included in these analyses.

Only the changes between baseline and each subsequent timepo

End point type	Secondary

End point timeframe:

Baseline to 24 weeks post treatment.

End point values	Active arm - active treatment			
Subject group type	Reporting group			
Number of subjects analysed	4[5]			
Units: Correlation coefficient				
number (not applicable)				
Max AP thickness (baseline to 6 weeks)	0.60			
Lesion distance (baseline to 6 weeks)	-0.15			
Focal change (baseline to 6 weeks)	-0.09			
% thickness (baseline to 6 weeks)	-0.09			
max AP thickness (baseline to 12 weeks)	0.67			
Lesion distance (baseline to 12 weeks)	0.10			
Focal change (baseline to 24 weeks)	0			
% thickness (baseline to 12 weeks)	0.41			
Max AP thickness (baseline to 24 weeks)	0.00			
Lesion distance (baseline to 24 weeks)	0.00			
Focal change (baseline to 12 weeks)	0.41			
% thickness (baseline to 24 weeks)	0			

Notes:

[5] - 6 for the baseline to 6 wk comparison, 5 for the baseline to 12 wk and 4 for the baseline to 24 wk

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were recorded from the time of the bone marrow harvest until the final follow up visit (24 weeks post treatment).

Adverse event reporting additional description:

Patient were questioned on adverse events on a telephone call 48 h after harvest and at each subsequent follow up visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	all patients treated

Reporting group description: -

Serious adverse events	all patients treated		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	all patients treated		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
Musculoskeletal and connective tissue disorders			
Injury	Additional description: Patient injured toe whilst hoovering.		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2015	Revised protocol, patient alert card and PIS Cover letter: To correct inconsistency regarding the timing of the follow up phone call to patients post treatment. Amendment to allow the trial team to send Patient Information Sheets to potential patients by post prior to their first outpatient visit. Informed consent procedure changed from; At least 24 hours will be given for consideration by the patient before consenting to take part. to Adequate time will be given for consideration by the patient before consenting to take part. Section 9 - Recording and reporting of adverse events and reactions – The AE definition has been amended and timeline for recording AEs has been changed from 'following consent' to after the bone marrow harvest'.
11 December 2015	To include dosing range for cell numbers of 4-20 x 10e6 rather than absolute value of 20 x 10e6.
26 May 2016	Updates to protocol: 1. Addition of the use of participant identification centre (PICs) 2. Addition of the use of a sports activity questionnaire 3. Dosing period changed from approx. 5 weeks to approx. 5-6 weeks Updates to protocol and PIS: 4. To document that bone marrow harvest may be done under local or general anaesthesia (rather than just local) depending on patient preference (as per routine practice). 5. Risks of general anaesthesia added. 6. To add statement that pregnancy will be assessed by self-declaration at initial screening followed by urine pregnancy tests within 7 days of bone marrow harvest and ATIMP administration. Other changes 7. Addition of the use of an advert. 8. Protocol outline created to send to PIC sites to provide information about the trial.
05 July 2017	Update to IMPD to include the option to cryopreserve cells in the event that cells grow too quickly and the surgery cannot be rescheduled for an earlier date. Cells which have not undergone more than 10 population doublings can be cryopreserved for further re-seeding and expansion closer to administration date. The protocol and PIS updated to clarify that the timing between bone harvest and implantation is an approximation (stated as approximately 5 weeks).

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.

Complex logistics to manage cell harvest, culture and implantation as well as the full gamut of clinical assessments required per patient.

Notes: