Clinical trial results:
Evaluation of the Safety of Cell Bandage in the Treatment of Meniscal Tears

Summary

EudraCT number	2010-024162-22
Trial protocol	GB
Global end of trial date	26 November 2020

Results information

Result version number	v1 (current)
This version publication date	04 August 2022
First version publication date	04 August 2022

Trial information

Trial identification

Sponsor protocol code	ACTL-P001-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Azellon Ltd (a subsidiary of NTL Biologica)
Sponsor organisation address	Boston House, 2a Boston Road , Henley on Thames, Oxon, United Kingdom, RG9 1DY
Public contact	Executive Chairman, Azellon Ltd (a subsidiary of NTL Biologica), +44 7484631765, igraney@ntlbiologica.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	01 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2020
Global end of trial reached?	Yes
Global end of trial date	26 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was:
- To evaluate the safety of the Cell Bandage.

The secondary objective of the trial was:
- To evaluate the clinical outcome of the use of Cell Bandage.

Protection of trial subjects:

The study was conducted in accordance with the principles set forth in the Declaration of Helsinki as amended in 2013 (Brazil), the Guidelines of the International Conference on Harmonisation (ICH) on Good Clinical Practice (GCP) (CPMP/ICH/135/95), as well as the requirements of the European Union Data Protection Directive 95/46/EC, and other applicable regulatory requirements.

Background therapy:

The menisci are fibrocartilaginous structures in the knee. There is one on each side of the joint, the medial and lateral menisci. The medial meniscus is approximately "C" shaped and the lateral meniscus is almost circular, they are both triangular in cross section. The menisci have a role in the load distribution, stability, lubrication and nutrition in the knee. Loss of meniscal tissue predisposes to osteoarthritis. Injury to the meniscal cartilage is one of the most common knee injuries and the most common indication for knee surgery.

There are two broad groups of meniscal tears, those in the younger adult, which tend to be traumatic in nature and those in the older adult that occur partly due to the increased stiffness of the meniscus that occurs with ageing and degeneration. Traumatic lesions are more commonly associated with longitudinal tears and vertical, transverse or radial tears. Degenerative tears are more commonly horizontal tears or complex tears. Other patterns of tears that occur, such as flap and horn are variations of the above patterns.

The standard treatment of meniscal tears in the adult is to remove the damaged portion of the cartilage when there is pain, locking or giving way of the knee. When the tear is located purely in the outer third of the cartilage where the blood supply is retained (red-red zone), a relatively rare injury, there is the option to repair the cartilage with sutures. The red-red zone is fully vascular and therefore has an excellent healing prognosis. The red white zone is at the border of vascular supply and has a generally good healing prognosis. The white white zone is relatively avascular and has a poor prognosis for healing.

Evidence for comparator:

Not applicable - no comparator used.

Actual start date of recruitment	10 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study recruitment was undertaken in the United Kingdom. The recruitment process began in September 2012 and concluded in November 2012. 13 patients were deemed eligible, of which 5 patients were treated. Of the 5 patients who were treated, only 1 patient completed all 7 year follow up assessments.

Pre-assignment

Screening details:

Patients were screened to the inclusion/exclusion criteria of the protocol. The following assessments were performed: Informed consent, Medical History, Physical Exam including knee exam, Demographics, ECG, Vital Signs and Safety Laboratory Testing/Urinalysis, MRI & specific markers of pain/inflammation measured through questionnaires and testing.

Pre-assignment period milestones

Number of subjects started	15[1]
Number of subjects completed	5

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No Cell Bandage available: 2
Reason: Number of subjects	Meniscal Tear not suitable: 2
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	No Cell Bandage released: 1
Reason: Number of subjects	Clotting Issues with Samples: 3
Reason: Number of subjects	Screen Fail at Pre-Operative Assessment: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects assigned to the pre-assignment period is indicative of the number of subjects initially screened for participation in the study. The subsequent number of enrolled subjects reflects those who were screened and enrolled into the study. Of the 15 subjects who initially screened, only 5 were subsequently enrolled onto the study and received treatment.

Period 1

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

Blinding implementation details:

N/A - this study was open label.

Arms

Arm title	Overall Treated Patient Population

Arm description:

This subject analysis set corresponds to the 5 enrolled patients who were treated with implantation of the cell bandage. This analysis set will be utilised to report data in relation to all endpoints within the study. Patients enrolled were followed up for a period of up to 7-years post-operative implantation of cell bandage. Of the 5 patients who were treated, only 1 patient completed all 7 year follow up assessments.

Arm type	Experimental

Investigational medicinal product name	Cell Bandage
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Intracartilaginous use

Dosage and administration details:

Single dose (single implantation) of Cell Bandage: product contains 1 million cells/sq cm of autologous mesenchymal stem cells. Implantation occurred on the baseline visit with follow up assessments carried out at the following milestones: 1 week post-op, 1 month post-op, 3 months post-op, 6 months post-op, 1 year post-op, 2 years post-op, 3 years post-op, 4 years post-op, 5 years post-op, 6 years post-op & 7 years post-op.

Number of subjects in period 1	Overall Treated Patient Population
Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	5	5	
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)	5	5	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	35.0		
standard deviation	± 3.74	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	4	4	
Height Units: centimetre			
arithmetic mean	177.3		
standard deviation	± 8.34	-	
Weight Units: kilogram(s)			
arithmetic mean	81.48		
standard deviation	± 8.90	-	

End points

End points reporting groups

Reporting group title	Overall Treated Patient Population

Reporting group description:

This subject analysis set corresponds to the 5 enrolled patients who were treated with implantation of the cell bandage. This analysis set will be utilised to report data in relation to all endpoints within the study. Patients enrolled were followed up for a period of up to 7-years post-operative implantation of cell bandage. Of the 5 patients who were treated, only 1 patient completed all 7 year follow up assessments.

Primary: Treatment Emergent Adverse Events

End point title	Treatment Emergent Adverse Events[1]

End point description:

This primary endpoint relates to the number of subjects who reported a treatment emergent adverse event (TEAEs) during the study. Forty (40) TEAEs were reported in the 7 year post operative period by 5 patients who received the Cell Bandage.

Three (3) patients reported SAEs during the study. At 2 years post operative, 2 patients had undergone partial or full meniscectomy in the affected knee (after implantation of the Cell Bandage) for SAEs of severe, definitely related meniscus injury and severe definitely related joint swelling, arthralgia and joint lock. A third patient reported an SAE of moderate, possibly related post operative wound complication. Another patient also underwent partial meniscectomy (SAE) in the contralateral knee (no implantation with Cell Bandage) for severe not related arthralgia and meniscal injury.

With exception of joint lock (catching), breast mass and meniscal injury, arthralgia and joint swelling, all TEAEs resolved.

End point type	Primary

End point timeframe:

Collection of treatment emergent adverse events occurred from the point of implantation of the cell bandage until completion of the 7-year post-operative assessment.

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: Treatment Emergent Adverse Events were listed as descriptive statistics with no statistical analyses conducted.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	5			

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy - Percentage of patients that have partial or full meniscectomy during or after the initial procedure.

End point title	Efficacy - Percentage of patients that have partial or full meniscectomy during or after the initial procedure.[2]

End point description:

This primary endpoint will report the number of subjects who underwent a partial or full meniscectomy during or after the initial procedure within the study follow-up period.

At 2 year post operative, 2 patients had undergone partial or full meniscectomy in the affected knee (after implantation of the Cell Bandage) as a result of SAEs and 1 patient had undergone partial meniscectomy in the contralateral knee as a result of severe meniscal injury. All fully recovered after surgery.

End point type	Primary

End point timeframe:

Implantation to end of 2 year initial study.

Notes:

[2] - 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: Efficacy endpoints were listed as descriptive statistics with no statistical analyses conducted.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of post-treatment meniscectomies	2			

Statistical analyses

No statistical analyses for this end point

Primary: Laboratory Parameters

End point title	Laboratory Parameters[3]

End point description:

This primary endpoint will report the number of subjects who had out of range results for any of the Laboratory Parameters (biochemistry, haematology & urinalysis).

This endpoint will only report number of subjects who had out of range results from Day 1 onwards following implantation of the cell bandage until the completion of the 2 year post-operative study assessment visit.

There were no clinically significant biochemistry, haematology or urinalysis results during the study.

End point type	Primary

End point timeframe:

Laboratory Parameters (biochemistry, haematology and urinalysis) were measured at set time points from the baseline visit until the 2 year post-operative study assessment visit.

Notes:

[3] - 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: Laboratory Parameters were listed as descriptive statistics with no statistical analyses conducted.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	4			

Statistical analyses

No statistical analyses for this end point

Primary: Post-Surgical Complications

End point title	Post-Surgical Complications[4]

End point description:

This primary endpoint will report the number of subjects who reported a post-operative surgical complication following implantation of the cell bandage.

There were no post surgical complications following implantation of the Cell Bandage (chronic pain, arthrofibrosis, damage to the neurovasculature, osteonecrosis, post surgical inflammation, infection, bleeding and deep vein thrombosis), although 1 patient did require prolonged hospitalisation (> 72 h) following implantation for pain.

End point type	Primary

End point timeframe:

Post-Surgical Complications were evaluated at set time points from the baseline visit until the 7 year post-operative study assessment visit.

Notes:

[4] - 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: Post-Surgical Complications were listed as descriptive statistics with no statistical analyses conducted.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Current Knee Function - Daily Living Scores

End point title	Summary of Current Knee Function - Daily Living Scores

End point description:

The IKDC scores were measured on a scale of 0-10 with measures scored as follows:
Pain Frequency: 0 = constant pain, 10 = never
Pain Severity: 0 = worst pain, 10 = no pain

Overall, current function of the knee (daily living activities) improved in patients who received the Cell Bandage. In the majority of patients, activity levels and current function of the knee had improved at 3 and 6 months post operative when compared to pre operative (mean scores 6 and 8 vs 4, respectively.

One patient saw a slight reduction in current function of the knee at 3 months post operative, although function had improved by 6 months post operative. One patient saw no change in current function of the knee at 3 months post operative, although function had improved by 6 months post operative. In all patients, activity levels and current function of the knee at their final visit remained higher than that observed pre operative.

End point type	Secondary

End point timeframe:

Time points for evaluation of Daily Living Scores (IKDC) were as follows: Baseline, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years and 7 years post-operative from implantation of the cell bandage.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	5			

Attachments (see zip file)	Summary of Daily Living Scores Data/RD652.25378

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Operative Medication Use

End point title	Post-Operative Medication Use

End point description:

Following cell bandage implantation, post operative pain medication included paracetamol (taken by 4 patients), ibuprofen (taken by 3 patients), codeine phosphate (taken by 4 patients), tramadol (taken by 3 patients) and diclofenac (taken by 5 patients) each taken for between 1 day and 2 months. Two (2) patients also required short term morphine taken for between 2-4 days. One patient also received paracetamol for post operative pain and pain that started prior to the operation (January 2013) and continued post-operatively (June 2013).

End point type	Secondary

End point timeframe:

Time points for evaluation of Post-Operative Medication Use were as follows: Baseline, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years and 7 years post-operative from implantation of the cell bandage.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of VAS Pain Scores

End point title	Summary of VAS Pain Scores

End point description:

The VAS pain scale was measured on a scale of 0-10 with measured scored as follows:

Pain Frequency: 0 = constant pain, 10 = never
Pain Severity: 0 = worst pain, 10 = no pain

Overall, the frequency and intensity of knee pain reduced in patients who received the Cell Bandage with reduction in pain observed from the 1 week post-operative assessment.

in all patients, the frequency of pain was greatly reduced at 3 and 6 months post operative when compared to pre operative (mean scores of 8 and 9 vs 4, respectively) and with the exception of one patient (who experienced a slight worsening of pain severity at 3 months post operative), all patients were also in less severe pain at these time points (mean scores of 7 and 8 vs 5, respectively).

All patients remained in less frequent and less intense pain at their final visit, with 2 patients reporting no pain at the final visit.

End point type	Secondary

End point timeframe:

Time points for evaluation of VAS Pain Scores were as follows: Baseline, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years and 7 years post-operative from implantation of the cell bandage.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	5			

Attachments (see zip file)	Summary of VAS Pain Scores Data/RD652.25378 (ACTL_P001-

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Range of Motion

End point title	Summary of Range of Motion

End point description:

Overall, the range of motion of the affected knee improved in all patients who received the Cell Bandage. In the majority of patients, the range of motion of the affected knee (active and passive) had improved at 3 and 6 months post operative when compared to pre operative (mean change from baseline; active 4.4 and 6.4 degrees, respectively; passive 5.2 and 4.4 degrees, respectively. One patient saw no change in passive range of motion of the affected knee at 3 and 6 months post operative, although active range of motion had improved by 6 months post operative. One patient saw a reduction in range of motion (active and passive) at these time points, although range of motion had improved by 1 year post operative. In all patients, the range of motion in affected knee (active and passive) at their final visit remained higher than that observed pre operative.

End point type	Secondary

End point timeframe:

Time points for evaluation of Range of Motion were as follows: Baseline, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years and 7 years post-operative from implantation of the cell bandage.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Subjects	5			

Attachments (see zip file)	Summary of Range of Motion Data/RD652.25378 (ACTL_P001-

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Tegener Questionnaire Results

End point title	Summary of Tegener Questionnaire Results

End point description:

For the majority of patients, there was little difference in the work and sporting activities that they were able to participate in following implantation of the Cell Bandage.

Review of individual patient data did, however, demonstrate that for 1 patient, the ability to participate in work and sporting activities improved from being "on sick leave or disability because of knees" to being able to participate in competitive sports: Soccer lower divisions, ice hockey, wrestling and/or gymnastics" within a 1 year period, an activity level that was sustained when assessed at the 2 and 4 (final) year visit.

It should also be noted that all patients indicated difficulty with work and sporting activities 1 month post operative, with 4 being "on sick leave or disability because of knees" and 1 only able to participate in "sedentary work or walking on even ground". This probably reflects the fact that the knee was swollen and recovering from surgery during this period.

End point type	Secondary

End point timeframe:

Time points for evaluation of Tegner Questionnaire Results were as follows: Baseline, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years and 7 years post-operative from implantation of the cell bandage.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	5			

Attachments (see zip file)	Summary of Tegner Questionnaire Data/RD652.25378

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Lysholm Questionnaire Results

End point title	Summary of Lysholm Questionnaire Results

End point description:

Overall, the frequency of common complaints associated with knee problems was reduced in patients who received the Cell Bandage. In all patients, the frequency of 1 or more common complaints (“limp”, knee "locking" and "catching", "instability", "pain", “swelling”, "climbing stairs" and "squatting") was reduced at 3 and 6 months post operative when compared to pre operative. In all patients, the frequency of knee complaints at their final visit remained lower than that observed pre operative.

A worsening of knee complaints was observed in two patients at 1 year post operative and one patient at 2 years and 6 years post operative when compared to the previous visit and is likely a reflection of deterioration in knee function during this these periods that resulted in surgical and medical action.

End point type	Secondary

End point timeframe:

Time points for evaluation of Lysholm Questionnaire Results were as follows: Baseline, 1 week, 1 month, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years and 7 years post-operative from implantation of the cell bandage.

End point values	Overall Treated Patient Population			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of Patients	5			

Attachments (see zip file)	Summary of Lysholm Questionnaire Data/RD652.25378

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time of signing informed consent until completion of the 7-year post-operative study visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Adverse Event Safety Population

Reporting group description:

This reporting groups corresponds to the 5 enrolled patients in the study for whom adverse events were reported throughout the study.

Serious adverse events	Adverse Event Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Meniscus injury	Additional description: Of the 3 reported SAEs, 2 of the patients re-tore the meniscus in the treated knee. The third patient tore the meniscus in the untreated knee i.e., this SAE was unrelated to treatment.		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Meniscus removal	Additional description: Of the 3 reported SAEs, 2 of the patients underwent meniscectomy related to the treated knee. A third patient underwent meniscectomy of the untreated knee i.e., this SAE was unrelated to treatment.		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Arthroscopy	Additional description: Of the 3 reported SAEs, 2 of the patients underwent meniscectomy related to the treated knee. A third patient underwent meniscectomy of the untreated knee i.e., this SAE was unrelated to treatment.		
subjects affected / exposed	3 / 5 (60.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Adverse Event Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Postoperative wound complication			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Musculoskeletal and connective tissue disorders Joint lock subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 2 / 5 (40.00%) 2 3 / 5 (60.00%) 6 3 / 5 (60.00%) 4 1 / 5 (20.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	 3 / 5 (60.00%) 4 1 / 5 (20.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2012	Substantial Amendment 01 - The amendment was issued to change the CRO details from Factory CRO to Simbec. The amended protocol (version 2.5, 10 May 2012) (Appendix 16.1.1.3), and associated documents were approved by the REC on 24 May 2012. The protocol was updated to version 2.5, 10 May 2012 and submitted for REC approval, but the protocol footers were not updated in error. As a result, the REC approval document states approval for version 2.4, 21 April 2012. When the error was noted a non substantial amendment was issued to confirm the correct version of the amended protocol approved on 24 May 2012, was version 2.5, 10 May 2012.
03 August 2012	Substantial Amendment 02 - The amendment was issued to include additional urine pregnancy tests (on day of stem cell harvest and at the 3 month and 1 year post operative visits), correction of typographical errors in synopsis, update contact telephone numbers and modify the age range for inclusion in the study from 18 35 to 18 55 years old. The protocol was initially updated to version 2.6, 13 July 2012 (to include additional urine pregnancy tests (on day of stem cell harvest and at the 3 month and 1 year post operative visits), correction of typographical errors in synopsis and update contact telephone numbers), and together with associated documents submitted for REC approval, but before REC review, the protocol was updated again to version 2.7, 3 August 2012) (Appendix 16.1.1.4) and re submitted together with associated documents, in order to modify the age range for inclusion in the study from 18 35 to 18 55 years old. The amended protocol (version 2.7, 3 August 2012) and associated documents were approved by the REC on 15 August 2012.
10 February 2014	AZ/CTA/01-004 - The amendment was issued to add an additional MRI scan at the 1 year post operative visit. The protocol was updated to version 2.9, 10 February 2014 (Appendix 16.1.1.6), and together with associated documents submitted for REC approval. The amended protocol (version 2.9, 10 February 2014) and associated documents were approved by the REC on 23 April 2014.
15 August 2017	AZ/CTA/01 005 - The amendment was issued to add an additional MRI scan at the 5 year post operative visit. The protocol was updated to version 3.0, 15 August 2017 (Appendix 16.1.1.7), and together with associated documents submitted for REC approval. The amended protocol (version 3.0, 15 August 2017) and associated documents were approved by the REC on 03 October 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 October 2012	During the cell culture of bone marrow aspirates from the first three patients, a membrane appeared on the surface of the cultures which had not been observed during process validation. The decision was made to temporarily halt the trial so that this could be thoroughly investigated.	23 November 2012

Notes:

Limitations and caveats

None reported