Clinical trial results:
Phase III, pivotal, multicentre, randomised, double-blind controlled Study to evaluate the Efficacy and Safety of Autologous Osteoblastic Cells (PREOB®) Implantation in Early Stage Non Traumatic Osteonecrosis of the Femoral Head

Summary

EudraCT number	2009-012929-11
Trial protocol	BE DE GB
Global end of trial date	04 July 2019
Results information	
Result version number	v1 (current)
This version publication date	19 July 2020
First version publication date	19 July 2020
Summary attachment (see zip file)	summary clinical study report (BT_PREOB-ON3_CSR_Final 26 JUN 2020_published on EudraCT database.pdf)

Trial information

Trial identification	
Sponsor protocol code	PREOB-ON3
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01529008
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Bone Therapeutics S.A.
Sponsor organisation address	rue Auguste Piccard, Gosselies, Belgium,
Public contact	Clinical Trial Information, Bone Therapeutics S.A., clinicaltrials@bonetherapeutics.com
Scientific contact	Clinical Trial Information, Bone Therapeutics S.A., clinicaltrials@bonetherapeutics.com

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	26 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2019
Global end of trial reached?	Yes
Global end of trial date	04 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objectives are to demonstrate that Core decompression/PREOB® implantation is superior to Core decompression/Placebo implantation in relieving clinical hip symptoms and halting (or reverting) radiological progression (to fractural stages III or higher) at 24 months.

Patients will be assessed using the Western Ontario and McMaster Universities (WOMAC®) Index. Central radiological evaluation will include conventional bilateral X-ray and MRI of the hips to assess ARCO Staging and to measure the sum of the coronal and sagittal necrotic angles.

Protection of trial subjects:

no specific trial subjects protection was in place

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	France: 23
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	67
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment between 2011 and 2018 in Belgium, Germany, France, The Netherlands andUnited Kingdom

Pre-assignment

Screening details:

Men and women, aged 18 to 70 years old, diagnosed with non-fractural (ARCO stages I or II) non traumatic osteonecrosis of the femoral head, confirmed by conventional X-ray and magnetic resonance imaging (MRI). All patients had to be symptomatic, except ARCO stage II patients.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PREOB

Arm description:

PREOB injection

Arm type	Experimental
Investigational medicinal product name	PREOB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraosseous use

Dosage and administration details:

20 X 10^6 cells in 5 ml

Arm title	Placebo

Arm description:

placebo injection

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

Dosage and administration details:

phosphate buffer saline and human serum albumine in a total volume of 5 ml

Number of subjects in period 1	PREOB	Placebo
Started	35	33
Completed	35	33

Period 2	
Period 2 title	bone marrow harvesting
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	PREOB

Arm description:
PREOB injection

Arm type	Experimental
Investigational medicinal product name	PREOB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraosseous use

Dosage and administration details:
20 X 10^6 cells in 5 ml

Arm title	Placebo

Arm description:
placebo injection

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

Dosage and administration details:
phosphate buffer saline and human serum albumine in a total volume of 5 ml

Number of subjects in period 2	PREOB	Placebo
Started	35	33
Completed	34	30
Not completed	1	3
Physician decision	1	1
Consent withdrawn by subject	-	2

Period 3	
Period 3 title	treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	PREOB

Arm description:
PREOB injection

Arm type	Experimental
Investigational medicinal product name	PREOB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraosseous use

Dosage and administration details:
20 X 10^6 cells in 5 ml

Arm title	Placebo

Arm description:
placebo injection

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

Dosage and administration details:
phosphate buffer saline and human serum albumine in a total volume of 5 ml

Number of subjects in period 3	PREOB	Placebo
Started	34	30
Completed	25	29
Not completed	9	1
Adverse event, non-fatal	6	-
not specified	3	1

Period 4	
Period 4 title	efficacy analysis
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	PREOB

Arm description:
PREOB injection

Arm type	Experimental
Investigational medicinal product name	PREOB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraosseous use

Dosage and administration details:
20 X 10^6 cells in 5 ml

Arm title	Placebo

Arm description:
placebo injection

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

Dosage and administration details:
phosphate buffer saline and human serum albumine in a total volume of 5 ml

Number of subjects in period 4	PREOB	Placebo
Started	25	29
Completed	23	26
Not completed	2	3
Consent withdrawn by subject	-	2
Physician decision	-	1
major protocol deviations	2	-

Baseline characteristics

Reporting groups	
Reporting group title	PREOB
Reporting group description:	
PREOB injection	
Reporting group title	Placebo
Reporting group description:	
placebo injection	

Reporting group values	PREOB	Placebo	Total
Number of subjects	35	33	68
Age categorical			
Units: Subjects			
Adults (18-64 years)	35	32	67
From 65-84 years	0	1	1
Gender categorical			
Units: Subjects			
Female	8	7	15
Male	27	26	53

Subject analysis sets	
Subject analysis set title	per protocol
Subject analysis set type	Full analysis

Subject analysis set description:

included all randomised and treated patients (i.e., patients with both (i) core decompression and (ii) PREOB® or Placebo implantation), with a baseline value available for both the ARCO stage and the WOMAC® pain subscale score, and at least one post-baseline value available for both the ARCO stage and the WOMAC® pain subscale score for the study treated hip and whose eligibility was confirmed after adjudication. These analyses on randomized and treated patients were performed according to the randomisation group regardless of the IMP actually received.

Reporting group values	per protocol		
Number of subjects	49		
Age categorical			
Units: Subjects			
Adults (18-64 years)	48		
From 65-84 years	1		
Gender categorical			
Units: Subjects			
Female	8		
Male	41		

End points

End points reporting groups

Reporting group title	PREOB
Reporting group description: PREOB injection	
Reporting group title	Placebo
Reporting group description: placebo injection	
Reporting group title	PREOB
Reporting group description: PREOB injection	
Reporting group title	Placebo
Reporting group description: placebo injection	
Reporting group title	PREOB
Reporting group description: PREOB injection	
Reporting group title	Placebo
Reporting group description: placebo injection	
Reporting group title	PREOB
Reporting group description: PREOB injection	
Reporting group title	Placebo
Reporting group description: placebo injection	
Subject analysis set title	per protocol
Subject analysis set type	Full analysis

Subject analysis set description:

included all randomised and treated patients (i.e., patients with both (i) core decompression and (ii) PREOB® or Placebo implantation), with a baseline value available for both the ARCO stage and the WOMAC® pain subscale score, and at least one post-baseline value available for both the ARCO stage and the WOMAC® pain subscale score for the study treated hip and whose eligibility was confirmed after adjudication. These analyses on randomized and treated patients were performed according to the randomisation group regardless of the IMP actually received.

Primary: primary endpoint

End point title	primary endpoint
End point description: Treatment Responders for the Study Treated Hip at Month 24	
End point type	Primary
End point timeframe: Month 24	

End point values	PREOB	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: patients				
number (not applicable)				
treatment responder	14	18		

Statistical analyses

Statistical analysis title	primary efficacy analysis
Statistical analysis description: Pearson’s Chi-Square test / Fisher’s exact test	
Comparison groups	PREOB v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Pearson’s Chi-Square test / Fisher’s exa
Parameter estimate	absolute difference

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were defined as treatment-emergent (TEAEs) only when they occurred following core decompression/IMP implantation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	PREOB

Reporting group description:

PREOB injection

Reporting group title	Placebo

Reporting group description:

placebo injection

Serious adverse events	PREOB	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 25 (64.00%)	18 / 29 (62.07%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 25 (4.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	7 / 25 (28.00%)	14 / 29 (48.28%)	
occurrences causally related to treatment / all	0 / 7	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis ulcerative			
subjects affected / exposed	2 / 25 (8.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	PREOB	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 25 (76.00%)	19 / 29 (65.52%)	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 25 (76.00%)	19 / 29 (65.52%)	
occurrences (all)	19	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2017	change of the statistical method

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 June 2018	manufacturing technical issuses	-

Notes:

Limitations and caveats

None reported