Clinical trial results:
A pilot Phase I/IIa, multicentre, open proof-of-concept study on the efficacy and safety of allogeneic osteoblastic cells (ALLOB®) implantation in non-infected delayed-union fractures

Summary

EudraCT number	2012-005333-36
Trial protocol	BE GB DE
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	15 March 2020
First version publication date	15 March 2020
Summary attachment (see zip file)	ALLOB-DU1 synopsis study report (20181119_BT_ALLOB-DU1_CSR Synopsis_EudraCT.pdf)

Trial information

Trial identification

Sponsor protocol code	ALLOB-DU1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02020590
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bone Therapeutics S.A.
Sponsor organisation address	Auguste Piccard 37, Gosselies, Belgium, 6041
Public contact	Clinical Trial Information, Bone Therapeutics S.A., allob.du1@bonetherapeutics.com
Scientific contact	Clinical Trial Information, Bone Therapeutics S.A., allob.du1@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	Interim
Date of interim/final analysis	11 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the main study is to assess the safety and efficacy of ALLOB® single percutaneous implantation in healing delayed-union fractures at the end of the study period (Month 6).
Safety:
Subjects will be systematically assessed for the potential occurrence of any AE or SAE, related to the product or related to the procedure, using patient open questionnaires, physical examination, (including vital signs), and laboratory measurements.
Efficacy:
The success will be based on the percentage of treated patients (ALLOB®) not failing under treatment. A patient will be considered as failed under a treatment if, at the end of the study period (Month 6), the patient had required a rescue surgery or the Global Disease Evaluation score (VAS) as perceived by the patient has not improved by at least 25% and the TUS as assessed by CT scan has not increased by at least two points (versus baseline).

Protection of trial subjects:

For the first 16 patients, the patient recruitment was proceeded stepwise by blocks of 4. Full first 2 weeks safety data of the first block of 4 patients was analysed before the first patient of the second block of 4 patients was treated. First 48 hours safety data of the second block of 4 patients was analysed before treating the first patient of the next block. This latter scheme was repeated until the first 16 patients was treated.

A Data Safety Monitoring Board (DSMB) was established to assess the safety and efficacy when 6-month post treatment results for the first 16 assessable patients was available (i.e., interim analysis). This Board recommended to the Sponsor whether to stop the trial for efficacy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	25
EEA total number of subjects	25

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	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment period: 17 February 2014 - 30 January 2018
countries: Belgium and Germany

Pre-assignment

Screening details:

Patient diagnosed with a non-infected delayed-union fracture of a long bone of minimum 3 months and maximum 7 months (± 2 weeks)without signs of healing over the last 4 weeks at the time of screening
Modified Radiographic Union Score (mRUS) < 10
Global Disease Evaluation Score as assessed by the patients.

Period 1

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

Arms

Arm title	active treatment

Arm description:

active treatment with ALLOB single injection

Arm type	Experimental
Investigational medicinal product name	ALLOB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Percutaneous use

Dosage and administration details:

25X10^6 cell/ml (2-4 ml) administered percoutaneously into the delayed union site

Number of subjects in period 1	active treatment
Started	25
Completed	22
Not completed	3
Consent withdrawn by subject	1
Protocol deviation	2

Period 2	
Period 2 title	final efficacy analysis
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	active treatment

Arm description:

active treatment with ALLOB

Arm type	Experimental
Investigational medicinal product name	ALLOB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Percutaneous use

Dosage and administration details:

25X10^6 cell/ml (2-4 ml) administered percoutaneously into the delayed union site

Number of subjects in period 2	active treatment
Started	22
Completed	21
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	active treatment
Reporting group description:	
active treatment with ALLOB single injection	

Reporting group values	active treatment	Total	
Number of subjects	25	25	
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)	22	22	
From 65-84 years	3	3	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	16	16	

Subject analysis sets	
Subject analysis set title	per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
21 subjects were included in the per protocol population	
Subject analysis set title	safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
22 subjects were included in the safety analysis	

Reporting group values	per protocol	safety population	
Number of subjects	21	22	
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	19 2	19 3	
Gender categorical Units: Subjects			
Female Male	8 13	9 13	

End points

End points reporting groups

Reporting group title	active treatment
Reporting group description: active treatment with ALLOB single injection	
Reporting group title	active treatment
Reporting group description: active treatment with ALLOB	
Subject analysis set title	per protocol
Subject analysis set type	Per protocol
Subject analysis set description: 21 subjects were included in the per protocol population	
Subject analysis set title	safety population
Subject analysis set type	Safety analysis
Subject analysis set description: 22 subjects were included in the safety analysis	

Primary: Percentage of responders at 6 months (efficacy of ALLOB)

End point title	Percentage of responders at 6 months (efficacy of ALLOB)

End point description:

The efficacy of ALLOB® will be evaluated at Month 6. The success of the study will be based on the percentage of treated patients (ALLOB®) not failing under treatment.
A patient will be considered as failed under treatment if, at Month 6:
- He/she had a rescue surgery

Or
- The Global Disease Evaluation score (VAS) as perceived by the patient has not improved by at least 25% and the TUS as assessed by CT scan has not increased by at least two points (versus baseline).

End point type	Primary

End point timeframe:

At 6-months after treatment

End point values	active treatment	per protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: percentage	21	21		

Statistical analyses

Statistical analysis title	2-stage fleming method design

Statistical analysis description:

According to the Schoenfeld approach (Schoenfeld et al., 1980), for the efficacy analysis, the type I error rate will be increased from the usual 5% to the 10% rate. Indeed, in this pilot single arm “proof of concept” study, it is appropriate to maintain the power and increase the type I error rate. This increases the risk of erroneously concluding that the treatment is worthy of further investigation, but does not increase the risk of missing an efficacious treatment. So in this phase II study,

Comparison groups	active treatment v per protocol
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	< 5
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	One single treatment arm
Confidence interval	
level	90 %

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From ICF signature till end of long-term safety follow-up (24 months after the end of the study)

Adverse event reporting additional description:

questionnaire submitted to subjects during on site visits and phone calls

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	active treatment

Reporting group description:

active treatment with ALLOB single injection

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Display of non-serious AEs will be encoded at a later stage

Serious adverse events	active treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
angioedema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
urticaria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
implant site infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	active treatment		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 22 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 September 2017	trial prematurely stoped for efficacy reason, based on the positive results of the planned Interim Analysis.	-

Notes:

Limitations and caveats

None reported