



Clinical trial results:

BMC2012, Cell based therapy by implanted bone marrow-derived mononuclear cells (BMC) for bone augmentation of plate-stabilized proximal humeral fractures - a randomized, open, multicentric study - phase IIa

Summary

EudraCT number	2015-001820-51
Trial protocol	DE
Global end of trial date	07 January 2020

Results information

Result version number	v1 (current)
This version publication date	08 September 2021
First version publication date	08 September 2021
Summary attachment (see zip file)	Synopsis BMC2012 phase II (BMC2012_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	BMC2012-PhaseII
-----------------------	-----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02803177
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Klinik für Unfall-, Hand- und Wiederherstellungschirurgie, Universitätsklinikum Frankfurt
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt/Main, Germany, 60590
Public contact	Prof. Dr. Ingo Marzi, Klinik für Unfall-, Hand- und Wiederherstellungschirurgie, Universitätsklinikum Frankfurt, Goethe-Un, +49 6963016123, marzi@trauma.uni-frankfurt.de
Scientific contact	Prof. Dirk Henrich, Klinik für Unfall-, Hand- und Wiederherstellungschirurgie, Universitätsklinikum Frankfurt, +49 6963017110, d.henrich@trauma.uni-frankfurt.de

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	17 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 January 2020
Global end of trial reached?	Yes
Global end of trial date	07 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Osseous healing of fracture after 12 weeks by radiological evaluation:

- Frequency of secondary dislocation of result of reposition (varus dislocation of $\geq 20^\circ$ of head/shaft angle α , $\Delta\alpha$)

Protection of trial subjects:

Novalgine 500 mg p.o.
Paracetamol 1g/ 100 ml i.v.
Enoxaparin 20 mg s.c.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2016
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	Germany: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	15
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

date of first enrolment, date of last completed:
02.07.2016 - 06.06.2019

Frankfurt, Germany

Pre-assignment

Screening details:

Main criteria for inclusion:

- patients between the ages of ≥ 50 and ≤ 90 with a proximal humerus fracture
 - Indication for an open reduction and internal stabilization with a proximal fixed-angle plate of the humerus (PHILOS®, Synthes, Oberdorf, Switzerland)
 - 2, 3 or 4 fragment Neer fracture
- Dislocation of ≥ 10 mm between the fragments and/or

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Main Inclusion criteria:

- patients between the ages of ≥ 50 and ≤ 90 with a proximal humerus fracture
- Indication for an open reduction and internal stabilization with a proximal fixed-angle plate of the humerus (PHILOS®, Synthes, Oberdorf, Switzerland)
- 2, 3 or 4 fragment Neer fracture
- Dislocation of ≥ 10 mm between the fragments and/or
- angle of $\geq 45^\circ$ between the fragments and/or
- Dislocation of the tubercle majus from ≥ 5 mm

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description:

verum group should have received the cell-based therapy with implantation of BMC2012 in the surgical treatment of subcapital humerus fractures

Arm type	Experimental
Investigational medicinal product name	BMC2012- bone marrow-derived mononuclear cells
Investigational medicinal product code	
Other name	BMC2012- bone marrow-derived mononuclear cells
Pharmaceutical forms	Matrix for implantation matrix
Routes of administration	Not mentioned

Dosage and administration details:

Local Implantation of ex-vivo concentrated, washed and filtrated human bone marrow-derived mononuclear cells (BMC) seeded onto β -tricalciumphosphate(TCP) 1.3×10^6 autologous BMC/ml/ml β -TCP

Arm title	Control
------------------	---------

Arm description:

patients in the control group should have received only the cell-free bone graft substitute β -TCP

Arm type	only the cell-free bone graft substitute β -TCP
----------	---

Investigational medicinal product name	only the cell-free bone graft substitute β -TCP
Investigational medicinal product code	
Other name	only the cell-free bone graft substitute β -TCP
Pharmaceutical forms	Matrix for implantation matrix
Routes of administration	Not mentioned

Dosage and administration details:

Local Implantation of β -tricalciumphosphate (TCP)

Investigational medicinal product name	BMC2012- bone marrow-derived mononuclear cells
Investigational medicinal product code	
Other name	BMC2012- bone marrow-derived mononuclear cells
Pharmaceutical forms	Matrix for implantation matrix
Routes of administration	Not mentioned

Dosage and administration details:

Local Implantation of ex-vivo concentrated, washed and filtrated human bone marrow-derived mononuclear cells (BMC) seeded onto β -tricalciumphosphate(TCP) 1.3×10^6 autologous BMC/ml/ml β -TCP

Number of subjects in period 1	Verum	Control
Started	29	28
Completed	29	28

Baseline characteristics

Reporting groups

Reporting group title	Verum
-----------------------	-------

Reporting group description:

verum group should have received the cell-based therapy with implantation of BMC2012 in the surgical treatment of subcapital humerus fractures

Reporting group title	Control
-----------------------	---------

Reporting group description:

patients in the control group should have received only the cell-free bone graft substitute β -TCP

Reporting group values	Verum	Control	Total
Number of subjects	29	28	57
Age categorical			
42 subjects are in the age categorie between 65-84. 15 subjects are in the age categories between 18-64.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	12	23
From 65-84 years	18	16	34
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	21	20	41
Male	8	8	16

End points

End points reporting groups

Reporting group title	Verum
Reporting group description: verum group should have received the cell-based therapy with implantation of BMC2012 in the surgical treatment of subcapital humerus fractures	
Reporting group title	Control
Reporting group description: patients in the control group should have received only the cell-free bone graft substitute β -TCP	

Primary: Osseous healing of fracture

End point title	Osseous healing of fracture
End point description: Osseous healing of fracture after 12 weeks by radiological evaluation: Frequency of secondary dislocation of result of reposition (varus dislocation of $\geq 20^\circ$ of head/shaft angle α , $\Delta\alpha$)	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Verum	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: grad				
number (not applicable)	29	28		

Attachments (see zip file)	Data BMCII/Studiendaten BMC2012 IIa - Report EMA.pdf
-----------------------------------	--

Statistical analyses

Statistical analysis title	primary test statistic
Statistical analysis description: The primary outcome parameter is the incidence of secondary loss of reduction result at 12 weeks, which is defined as varus dislocation of $\geq 20^\circ$ of head-shaft angle in the true a.p. radiograph compared with the primary reduction result. For the statistical evaluation of the primary dichotomous study variable, the chi-square test is applied. The frequency of occurrence of secondary dislocations ($> 20^\circ$) in the treatment groups (BMC2012+ β -TCP, β -TCP only) is compared.	
Comparison groups	Verum v Control

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Frequency distribution

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	no dictionary used
-----------------	--------------------

Dictionary version	0
--------------------	---

Reporting groups

Reporting group title	Verum
-----------------------	-------

Reporting group description:

patients of the verum group received the cell-based therapy with implantation of BMC2012 in the surgical treatment of subcapital humerus fractures.

Reporting group title	control
-----------------------	---------

Reporting group description:

patients in the control group received only the cell-free bone graft substitute β -TCP

Serious adverse events	Verum	control	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	5 / 28 (17.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Aortic insufficiency			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertensive derailment			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
NSTEMI, cardiac decompensation			

subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrethmia with know atrial fibrillation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute renale insufficiency			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Inlay erosion hip			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intraarticular screw perforation			

subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection triggered COPD			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Verum	control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 29 (24.14%)	4 / 28 (14.29%)	
Gastrointestinal disorders			
stomach problems			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Exanthema subitum			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Melanoma recurrent			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
blood in urine			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

lumbago			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Infections and infestations			
cold			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
chills			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
circulatory problems			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 May 2016	Test plan version 3 from 18.02.2016 conditioned by PEI deficiency letter from 21.12.2015
04 October 2016	SV Change Schmidt-Horlohé -> Wincheringer; incl. CTA for changes Non Subst.02 (address FhG; protocol V3.1)
17 July 2017	Protocol V4.0 from 04.05.2017 (AEs and UAEs and administrative changes)
23 August 2017	Message PZ Prof. Hansen (HT Kliniken)
26 February 2018	PP V5.0 from 22.01.2018, ICF V3.0 from 23.01.2018
02 July 2018	ICF V3.1 (DSGVO)
16 April 2019	SV Wechsel Wincheringer Albrecht-Schoeck;
24 June 2019	Fisher test is replaced by the chi-square test. Originally, the evaluation was planned with the Fisher exact test. However, this test does not fully exploit the significance level and is therefore considered unnecessarily conservative. > Interim analysis to be performed after 56 patients or 60% of patients have reached study visit 5.
20 August 2019	IB V3 (neue Lit.), DSUR No. 3

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported