Synopsis zum Ergebnisbericht nach ICH E3

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

EudraCT-Nr.: 2015-001820-51
Study Code: BMC2012 Phase II

1. Name of Sponsor:
   Prof. Dr. Josef M. Pfeilschifter (former Dean of the Medical Faculty)
   Johann-Wolfgang-Goethe-University Frankfurt

2. Name of Finished Product:
   BMC2012

3. Name of Active Ingredient:
   BMC2012- bone marrow-derived mononuclear cells

4. Individual Study Table: Referring to Part of the Dossier (Version 6.0, Page 11)

5. Title of Study:
   BMC2012, Cell based therapy by implanted bone marrow-derived mononuclear cells (BMC) for bone augmentation of plate-stabilized proximal humeral fractures - an open, randomized, multicenter phase IIa study

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   Last Version 6.0 of May 16th 2019

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8. Publication (reference):

Seebach C, Henrich D, Scherzed A, Alini M, Marzi I. "Early "endothelial progenitor cells on ß-Tricalcium Phosphate scaffold under osteogenic conditions are useful for vascularisation in Bone tissue engineering.European Cells and Materials. 2007;13(2):51.

Seebach C, Henrich D, Schaible A, Relja B, Jugold M, Bönig H, Marzi I.Cell based therapy by implanted humane bone marrow-derived mononuclear cells (BMC) improved bone healing of large bone defects in rats. Tissue Eng Part A. 2015;21(9-10):1565-78.

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Seebach C, Henrich D, Meier S, Nau C, Bonig H, Marzi I. Safety and feasibility of cell-based therapy of autologous bone marrow-derived mononuclear cells in plate-stabilized proximal humeral fractures in humans. J Transl Med. 2016 Nov 15;14(1):314. PubMed PMID: 27846890; PubMed Central PMCID: PMC5111224.

Henrich D, Nau C, Kraft SB, Zollfrank M, Kontradowitz K, Oppermann E, Schultheiss J, Meier S, Frank J, Marzi I, Seebach C. Effect of the harvest procedure and tissue site on the osteogenic function of and gene expression in human mesenchymal stem cells

9. Studied period (years): date of first enrolment, date of last completed

   02.07.2016 - 06.06.2019

   An interim analysis after the planned completion time – and approved by the ethical committee - showed that there is no significant difference between the two treatments with regard to the primary outcome parameter (secondary dislocation). The study was terminated after review and evaluation of the data by a statistician. For ethical reasons it was recommended to terminate the study, as it would not have been possible to achieve a significant difference even if the remaining patients would have been recruited.
   The study was therefore completed within the scheduled time, but with fewer patients (57 instead of 94) than planned.
   It has to be stated, that no negative medical aspects were associated with the treatment of the autologous BMC preparation.

10. Phase of development:

    Clinical trial phase-IIa

11. Objectives:

    Efficacy and side effects (tolerability) of the cell based therapy by BMC to improve bone repair and regeneration in large bone defects of subcapital humeral fractures.

    Main objectives

    a) Osseous healing of fracture after 12 weeks by radiological evaluation:
       - Frequency of secondary dislocation of result of reposition (varus dislocation of ≥ 20° of head/shaft angle α, $\Delta\alpha$)

    Secondary objectives

    a) Osseous healing of fracture
       - osseous healing of fracture (consolidation, necrosis)
       - secondary perforation of bone screw
       - quantitative evaluation of $\Delta\alpha$
    b) With regards to tolerability / side effects:
       - extraction morbidity
       - local infection / side effects (inflammation, wound healing disorder)
       - systemic infection / side effects (BB, CRP, IL-6, PCT)
       - Fever (>38,5 °C) longer than 2 days
    c) Shoulder function: DASH-Score (12 weeks post-op)
    d) Registration of concomitant medication (visits 0-5) and adverse events (visits 2-5)

12. Methodology:

47 patients of the verum group should have received the cell-based therapy with implantation of BMC2012 in the surgical treatment of subcapital humerus fractures.
47 patients in the control group should have received only the cell-free bone graft substitute ß-TCP. A 24h-online randomization was performed after enrollment of the patients.
Each study site was randomized separately.

A total of six visits were conducted during the course of the study.
- V0: Patient identification, screening, study inclusion, randomization
- V1: preoperative day (up to a maximum of 48 hours before surgery):
Obtaining autologous BMC by iliac crest puncture (verum group).
Production of the investigational preparation and blood collection for autologous serum, infectious serology and safety laboratory (control group only safety laboratory).
- V2: Surgery on day 0, implantation of the investigational product (verum group), collection of the safety laboratory, questioning of the concomitant medication and AEs, x-ray (x-ray is not a study act, but a clinical control).
- V3: post-operative in the 1st week (day 1-7) after the start of the study medication, collection of the safety laboratory, interview of the concomitant medication and AEs, x-ray (x-ray is not a study act, but clinical control).
- V4: 6 weeks (±1 week) postoperatively; withdrawal of the safety laboratory, interview of the concomitant medication and AEs, x-ray (x-ray is not a study act, but clinical control).
- V5: 12 weeks (±2 weeks) postoperatively after the start of the study medication ("end-of-study-visit"); collection of the safety laboratory, interview of the concomitant medication and AEsx-ray image (x-ray is not a study act, but clinical control), determination of the DASH score, study completion.

13. Number of patients (planned and analysed):

94 patients were planned.
57 patients were included and analysed, 1 drop-out and 1 screening failure occurred.

14. Diagnosis and main criteria:

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 ≥45° between the fragments and/or
- Dislocation of the tubercle majus from ≥5 mm
- negative pregnancy test in premenopausal women
- ability to understand the nature, scope and significance of the clinical trial
- signed consent form for the operation and study participation

Exclusion criteria:

- Contraindications against the administration of the investigational product are pregnancy and lactation
- Luxation fracture
- known mental illness, which makes cooperation considerably more difficult (e.g. dementia, schizophrenia, severe depression)
- incapacitated patients
- pathological fractures caused by other underlying diseases
- fracture-related nerve damage
- Tumour disease with adjuvant therapy or treatment within the last 3 months (e.g. chemotherapy, radiotherapy), untreated tumour diseases
- Participation in a clinical trial within the last 3 months before inclusion in this trial

15. Test product, dose and mode of administration, batch number:

The investigational product bone marrow-derived mononuclear cells (BMC) consisted of 16x10E6 ± 20% nucleated blood cells (white blood cells, WBCs) in 12 ml X-Vivo 10 medium with 20% autologous serum, was isolated from the patient's own bone marrow aspirate preoperatively and was injected intraoperatively into the bone defect at a concentration of 1.33x10E6 WBCs/ml X-Vivo 10 medium and was seeded with 20% autologous serum on 1 ml ß-tricalcium phosphate (TCP, Chronos®, Synthes, Switzerland), which already filled the fracture gap in situ.

16. Duration of treatment:

12 weeks observation time after implantation of BMC into bone defect.

17. Reference therapy, dose and mode of administration, batch number:

cell-free bone graft substitute ß-tricalciumphosphate (TCP,Chronos®,Synthes Switzerland); intrafractural gap

18. Criteria for evaluation:

Primary outcome parameter:
The phase IIa clinical trial was designed to evaluate the efficacy and tolerability of the cell-based therapy with BMC2012 in subcapital humeral fractures to improve bone healing.

The primary outcome parameter was the frequency of secondary loss of the reduction result after 12 weeks, which was defined as varus dislocation of ≥ 20° of the head-shaft angle in the true a.p. radiograph compared to the primary reduction result.

Secondary outcome parameter:

a) The analysis of fracture healing as well as the analysis of the secondary perforation of screws was done radiologically by evaluating the bony superstructure in the true a.p. and the outlet x-ray. The x-rays were also taken to determine the fracture position and implant location and to detect screw breakage, osteonecrosis and implant failure (loosening or fracture). To detect secondary varus dislocation, the head-shaft angle was measured in the true a.p. radiograph. To detect secondary screw perforation/cut out, the distance between the screw tip and the joint surface was measured for the screw closest to the surface.

b) Specifically for the compatibility of BMC2012 was under review:
- extraction morbidity,
- local infection/side effect (inflammation, wound healing disorder),
- systemic infection/side effects (BB, CRP, IL-6, PCT),
- Fever (>38.5 °C) for more than 2 days.

c) Function of the shoulder: DASH score (12 weeks postoperative)
It is a "self report" questionnaire in which the patient answered 30 questions about his current condition, which record the global function of the upper extremity. The DASH-Score allows a statement regarding function, symptoms and special activity (sportsmen, musicians).
d) Registration of concomitant medication (V0-5) and AEs (V2-5)

19. Statistical methods:

Primary outcome parameter:

The Chi-Square test was used for statistical evaluation of the primary dichotomous examination variable. The frequency of occurrence of secondary dislocations (> 20°) in the treatment groups (BMC2012+ß-TCP, ß-TCP only) was compared.

For all statistical analyses of the secondary objectives, a probability of error of $p<0.05$ was considered a statistically significant difference. Frequency distributions were analysed using the Chi-Square test, physical measures (e.g. mediators in serum) were analysed quantitatively using the nonparametric Wilcoxon test.

Secondary outcome parameter:

a) - Fracture healing (consolidation, necrosis): Frequencies in the experimental groups were analyzed using the Chi-Square test.
- secondary perforation of screws: frequencies in the experimental groups were analyzed using the Chi-Square test.
- quantitative evaluation of both experimental groups: In this case the comparison was made with the non-parametric Wilcoxon test.

b) - extraction morbidity,
- local infection/side effect (inflammation, wound healing disorder),
- systemic infection/side effects (BB, CRP, IL-6, PCT),
- Fever (>38.5 °C) for more than 2 days.

Frequencies of occurrence in the treatment groups of the above mentioned parameters were analysed. The statistical evaluation was also carried out using the Chi-Square test.
In addition, the parameters describing systemic inflammation (BB, CRP, IL-6; Procalcitonin) were statistically evaluated quantitatively using the nonparametric Wilcoxon test.

c) A DASH score of 0 corresponds to a result with optimal function without disability.
A DASH score of 100 corresponds to a maximum disability.
The DASH score was statistically evaluated quantitatively using the nonparametric Wilcoxon test.

d) Registration of concomitant medication (V0-5) and AEs (V2-5).
Frequencies of concomitant medications in the treatment groups were analyzed using the Chi-Square test.

20. Summary – Conclusions: Efficacy Results, Safety Results, Conclusion

A two-armed, randomized, placebo-controlled Phase IIa clinical trial was conducted. The aim was to demonstrate a positive clinical effect of local transplantation of the autologous cell product BMC2012 into the bone defect on the complication rate in patients with proximal humerus fracture. Over a period of 42 months, 59 patients were enrolled in the study at the two participating study centers and of these 57 were considered for evaluation. The dropout rate was one in the placebo group. There was one screening failure.

Median values are presented in the following result presentation. The first-mentioned value refers to the placebo group, the second-mentioned value to the verum group. Statistical comparisons were performed using the nonparametric Wilcoxon-Mann-Whitney U-test, and a two-sided $p<0.05$ was considered a significant difference.

The primary outcome parameter was the incidence of complications, defined as an increase in the angle difference $\Delta\alpha$ >20° between postoperative status and after 12 weeks of healing. The assumed frequency of this complication, based on literature references and own preliminary work, was 30%. The central hypothesis was that the frequency of these complications is significantly lower in the verum group. After evaluation of the data, this hypothesis cannot be answered unequivocally. No complications (angle difference $\Delta\alpha$ >20°) occurred in either group.

Therefore, the originally planned statistical analysis of the frequency distribution was not performed. The direct statistical comparison of the measured angles α between the placebo and verum group resulted in significantly higher values directly postoperatively (round 3) in the placebo group (139° vs 131°, $p<0.05$, median values), but not at round 5, 12 weeks after surgery (133° vs 125°, $p=0.09$). A statistically significant reduction in the angle α between rounds 3 (postoperative) and rounds 5 (12 weeks postoperative) was observed in both the control group (β-TCP only) and the verum group (β-TCP+BMC2012) (placebo, V3: 139° vs V5: 133°, $p<0.05$; verum, V3: 131° vs V5: 125°, $p<0.05$). The extent of the decrease (angle difference $\Delta\alpha$) did not differ between placebo and verum group , this was 6° for placebo and 6° for the verum grou0kk respectively ($p=0.326$, figure 1).

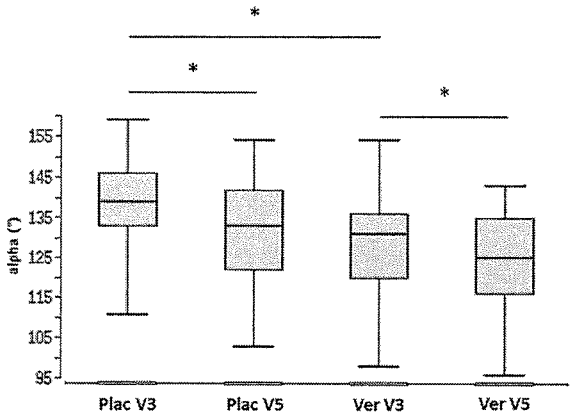


Figure 1: Angle α in the placebo (Plac) and verum (Ver) group immediately after surgical treatment of the fracture and implantation of the cell preparation (V3) and after 12 weeks healing time (V5). *=p<0.05

Functional analysis using the Dash Score also showed no significant differences between the two groups (55.8 points vs. 58.3 points, p=0.96).

Safety aspects:

No severe adverse events (SAE) were observed. Analysis of serum samples did not show significant differences in inflammatory parameters (IL-6, PCT, CRP, leukocytes) between both groups preoperatively, postoperatively and to the follow-up rounds V4 and V5 (see also table).

Time point	Parameter	Placebo	Verum	p-value
V2	IL-6 [pg/mL]	10.6	9.0	0.863
V2	PCT [µg/L]	0.03	0.04	0.503
V2	CRP [µg/mL]	1.42	1.88	0.667
V2	Leukocytes/nL	6.02	5.55	0.327
V3	IL-6 [pg/mL]	11.8	10.2	0.477
V3	PCT	0.05	0.05	0.808
V3	CRP	3.4	3.1	0.908
V3	Leukocytes/nL	7.66	7.05	0.263
V4	IL-6[pg/mL]	3.4	3.2	0.867
V4	PCT	0.03	0.03	0.730
V4	CRP	0.21	0.11	0.224
V4	Leukocytes/nL	7.07	6.77	0.825

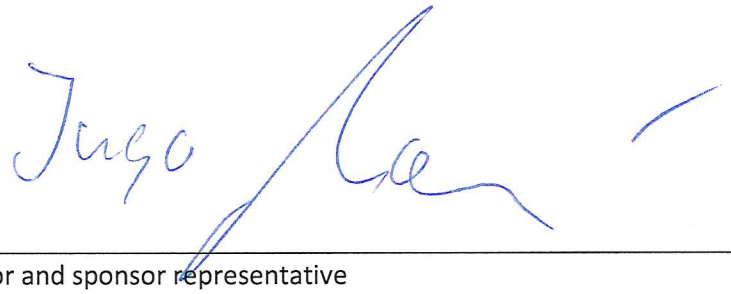
Table: Inflammation parameters intraoperative (V2), postoperative (V3) and 6 weeks postoperative (V4). Values preoperatively and 12 weeks postoperatively (round 5) are not listed and also did not differ significantly. Median values are given, statistics: Wilcoxon-Mann-Whitney-U-Test.

Conclusions:

In conclusion, it could not be clearly established whether cell therapy of proximal humerus fracture with BMC2012 can significantly reduce the complication rate, defined as angular difference $\Delta\alpha$ >20° after 12 weeks healing time, because the angular differences in both groups remained below this threshold. The observed reduction in the angle difference in both groups is more indicative of a bony consolidation of the fracture, a finding that could be equally confirmed radiologically for both groups. Based on the data available, it can be concluded that BMC2012 did not have any negative effect on bone healing.

The absence of SAEs, as well as the inconspicuous course of the inflammation parameters, demonstrate the good tolerability of autologous cell therapy with BMC2012.

21. Date of report
    November 2, 2020



November 2, 2020

Date, signature of the author and sponsor representative