SYNOPSIS

Name of Sponsor	Bone Therapeutics S.A.
Name of Product	PREOB®
Name of Active Ingredient	Human autologous bone marrow-derived osteoblastic cells
Indication (phase)	Treatment of non-traumatic early stage (ARCO I or II) osteonecrosis of the femoral head (Pivotal Phase III trial)
Title of Study	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
REPORT PARTICULARS	
Report date	26 June 2020 (Version 1.0)
Period of study	14 December 2011 to 13 February 2019
OBJECTIVES	
The main objective of the study was to demonstrate that Core decompression/PREOB® implantation into necrotic lesion was superior to Core decompression/Placebo implantation in relieving hip symptoms and halting (or reverting) radiological progression to fractural stages (ARCO III or higher) in patients with non-traumatic early stage osteonecrosis of the femoral head, at 24 months.	
METHODOLOGY	
Study Design	Multicentre, Randomised, Double-blind Controlled Phase III Study
Treatments	PREOB® or placebo
Treatment Duration	Single administration

Study Drug and Formulation

PREOB® was a fresh – non-cryopreserved - cell suspension, consisting in human autologous bone marrow-derived osteoblastic cells in suspension, provided in a single dose ready-to-use syringe.

Components	Description	Dosages
Osteoblastic cells	Active substance	$20x10^6$
Phosphate buffer saline (ml)	Excipient	3.75
Human Serum Albumin 20% (ml)	Excipient	1.25
Total Volume		**5ml**

Placebo had the same composition as PREOB®, but contained no cells. It was provided in a single dose ready-to-use syringe.

Components	Description	Dosages
Phosphate buffer saline (ml)	Excipient	3.75
Human Serum Albumin 20% (ml)	Excipient	1.25
Total Volume		**5ml**

Lot Numbers released

The lot number was unique to each patient and identical to the patient's ID.

Dose and Route of Administration

	PREOB	Placebo
Single Dose	5 ml – 20×10^6 cells	5ml
Procedure/Route of administration	Core decompression and intra-osseous implantation with trephine	
Dosage Schedule	One single dose per patient on Visit 3 (Day 0)	

Concomitant and Excluded Therapy

Prior and concomitant drugs/procedures considered as rendering the subject ineligible for participation in the study were listed in the study exclusion criteria. No drugs/procedures were pre-defined in the protocol as prohibited during the study

SUBJECT POPULATION

Number Planned; Number Analysed

Number Planned

118 patients randomised in 1:1 ratio

- 59 patients in the control group
- 59 patients in the PREOB® group

Number Analysed:

Interim analysis

- FAS: 44 patients

	Final analysis - Extended SAF: 64 patients - SAF: 54 patients - FAS: 49 patients - PP Set: 48 patients
Major Inclusion Criteria	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, with a combined coronal and sagittal necrotic angular sum superior to 190°.
ASSESSMENTS	
Efficacy	**Clinical Evaluation** The WOMAC® VA3.1 (Visual Analogue Scale) pain subscale was selected as primary efficacy outcome. The total WOMAC® Index (including composite pain, stiffness, and function subscales) was used as a secondary efficacy endpoint. Post study long term follow-up (phone call visits) was performed using the WOMAC® LK3.1 (Likert) scale. **Radiological Evaluation** Patients were assessed using both conventional X-ray and magnetic resonance imaging (MRI) of the hips, which are well established imaging tools for both diagnosis and staging (according to ARCO Classification) of femoral head osteonecrosis, achieving excellent sensitivity and specificity. CT scan of the hips was also performed once during the trial (during the Screening Period only), for additional diagnostic and exploratory purposes.
Safety	From the beginning to the end of the main study period at Month 24, patients were to be systematically assessed for the potential occurrence of any AE or SAE, related to the product or related to the procedure by patient interview, physical examination (including body mass index and vital signs), and laboratory measurements. A long-term follow-up was planned to be performed via phone calls (conventional X-ray to be performed only when the patient still felt pain on the treated hip) at 36 and 48 months after IMP implantation. This included assessment of hip symptoms (pain, stiffness, and function) using WOMAC® LK3.1 (Likert Scale) and the potential occurrence of any AEs and SAEs (patient open questionnaire, including any changes in health status and need for total hip arthroplasty).

STATISTICAL METHODS AND ANALYSIS	
Efficacy	**Interim Analysis** A formal pre-planned unblinded interim efficacy analysis was planned in this study in order to assess the efficacy of PREOB® versus Placebo with the intent to stop the study early if there was overwhelming evidence of treatment benefit or futility or if any safety issues were identified. The interim analysis was to be performed when the complete data set on 12-month post-treatment follow-up was available for approximately 40% of the initial target number of 110 patients, *i.e.*, 44 patients. The DSMB was responsible for reviewing accumulated efficacy and safety data and evaluating the results of the interim efficacy analysis (primary and selected secondary endpoints, as described for the analysis at Month 24). The DSMB was to provide a recommendation to the Sponsor on whether to continue, modify or stop the clinical trial. **Final Analysis** The efficacy of PREOB® was evaluated at 24 months. The success was based on the percentage of responders. A treated patient was considered as responding if, at the end of the study (24 months): • the WOMAC® VA3.1 pain subscale score of the study treated hip improved from baseline by at least the MCID (set at 10 mm) and • the study treated hip did not progress to fractural stages (ARCO III or higher), as assessed by conventional X-ray. Secondary and exploratory efficacy endpoints were defined but were not analysed, as the study was stopped for futility. The endpoints are listed in Section 5.5.4 and Section 5.5.5, respectively.
Safety	Occurrence of any AEs and serious adverse events (SAEs), related or not to the product or the procedure, using patient open questionnaire, physical examination (including vital signs), laboratory measurements, BMI and concomitant medications over the study period.
STUDY POPULATION RESULTS	
Demographics	Of the 68 randomised patients, 64 (94.1%) underwent (sham) bone marrow harvest and were included in the Extended Safety Set; of these, 54 (79.4%) underwent core decompression/IMP implantation (25 [71.4%] of the 35 patients randomised to the PREOB® group and 29 [87.9%] of the 33 patients randomised to the Placebo group) and were included in the Safety Set. The mean age at screening for the 64 patients in the Extended Safety Set was 45.9 years (SD: 9.7 years; range 30 - 68 years). Overall, the majority (82.8%) of the patients were male. The ethnic origin of the majority of patients (92.2%) was reported as Caucasian/White.

Treatment Terminations	Of the 34 patients in the PREOB® group for whom bone marrow harvest had been performed, 6 did not undergo core decompression and IMP implantation due to quality issues with the cell preparation (which consisted of a lower than anticipated number of cells at either Day 14 or Day 21 of culture). 3 patients in the PREOB® group and 1 patient in the Placebo group were not treated for other reasons. Overall, 44 (81.5%) of the 54 treated patients were followed up for 12 months post-implantation and 35 (64.8%) patients were followed up for 18 months. A total of 23 (42.6%) patients (11 [44.0%] of the 25 patients treated with PREOB® and 12 [41.4%] of the 29 patients who received placebo) completed the study to Month 24. A total of 31 (57.4%) of the 54 treated patients discontinued the study before Month 24.

EFFICACY RESULTS	
Primary Variable	**Interim analysis** The interim analysis, which included efficacy and safety data up to Month 12, was conducted as planned. The DSMB met on 05 November 2018 to review the efficacy results of the interim analysis and to provide recommendations regarding study continuation. At the time of the interim analysis, 48 patients had undergone (sham) harvest and core decompression/IMP implantation. Of these, 44 patients (21 treated with PREOB® and 23 treated with Placebo) were considered as eligible for inclusion in the FAS. In patients treated with PREOB®, the proportion of treatment responders at Month 12 was 66.7% (95% CI: 43.0 ; 85.4), compared with 65.2% (95% CI: 42.7 ; 83.6) in the Placebo group. The difference in proportions between the PREOB® and the Placebo groups was -0.01 (95% CI: -0.29 ; 0.27), which was not statistically significant. Treatment groups were also compared with respect to clinical response and radiological response, which are the 2 composites of the treatment response. The difference between treatment groups was not statistically significant for either parameter. The difference between treatment groups in the proportion of clinical responders was -0.11 (95% CI: -0.37 ; 0.14) and the difference between treatment groups in the proportion of radiological responders was 0.02 (95% CI: -0.23 ; 0.27). **Final analysis** The results of the final analysis at Month 24 were similar to those of the interim analysis, showing no statistically significant difference between the treatment response of the PREOB® group and the Placebo group. In patients treated with PREOB®, the proportion of treatment responders at Month 24 was 60.9% (95% CI: 38.5 ; 80.3), compared with 69.2% (95% CI: 48.2 ; 85.7) in the Placebo group. The difference in proportions between the PREOB® and the Placebo groups was -0.08 (-0.35 ; 0.18).
Secondary Variable(s)	As the trial was stopped for futility, the secondary efficacy endpoints were not assessed.
SAFETY RESULTS	
Extent of Exposure	The mean duration of post-treatment follow-up was 17.0 months (SD: 7.7; range 0 - 26 months) for patients in the PREOB® group and 17.6 months (SD: 6.9; range 3 - 24 months) for patients in the Placebo group. The median duration of follow-up was 22 months in both groups.

All AEs	**AEs following (sham) bone marrow extraction** Nine AEs were reported by 7 patients in the PREOB® group following bone marrow extraction; six AEs were reported by 5 patients in the Placebo group. **AEs following IMP implantation** In the Safety Set (N=54), a total of 24/25 (96.0%) patients in the PREOB® group and 26/29 (89.7%) patients in the Placebo group reported at least 1 TEAE. Five patients reported TEAEs considered related to the IMP: 1 (4.0%) patient in the PREOB® group (systemic inflammatory response syndrome) and 4 (13.8%) patients in the Placebo group (2 cases of systemic inflammatory response syndrome, 1 case of decrease in lactate dehydrogenase, and 1 case of joint stiffness). Most of the TEAEs were mild (130 [75.6%] events in the PREOB® group and 68 [58.6%] in the Placebo group) or moderate (37 [21.5%] events in the PREOB® group and 34 [29.3%] in the Placebo group) in intensity. Most events (114 [66.3%] events in the PREOB® group and 75 [64.7%] in the Placebo group) had resolved without sequelae by the end of follow-up. The most frequent TEAE for patients in both groups was arthralgia, reported by 12 (48.0%) patients in the PREOB® group and 13 (44.8%) patients in the Placebo group. The second most frequent event was disease progression, reported by 7 (28.0%) patients in the PREOB® group and 12 (41.4%) patients in the Placebo group; osteonecrosis was reported by 4 (16.0%) patients in the PREOB® group and 1 (3.4%) patient in the Placebo group. None of the frequent TEAEs was considered as related to IMP. One TEAE (systemic inflammatory response syndrome) was reported as related to the IMP in the PREOB® group. This event occurred 2 days following core decompression/IMP implantation and lasted for 33 days. The patient recovered without treatment. Four TEAEs were reported as related to the IMP in the Placebo group: these included 2 cases of systemic inflammatory response syndrome, both of which occurred 2 days following core decompression/IMP implantation and lasted respectively 26 days and 82 days. Both patients recovered without treatment. Other events considered as related to the IMP in this group were a decrease in lactate dehydrogenase, which was initially reported 27 days after core decompression/IMP implantation which was ongoing at the time the patient withdrew from the study and joint stiffness which was reported on the day after core decompression/IMP implantation and was ongoing at the time the patient withdrew from the study.

Deaths and Other Serious AEs	A total of 70 TEAEs were reported as SAEs; 38 events for 16 (47.1%) patients in the PREOB® group and 32 events for 18 (60.0%) patients in the Placebo group. No death was reported during the follow-up. The most frequently reported SAE was disease progression, reported for 7 (20.6%) patients in the PREOB® group and 14 (46.7%) patients in the Placebo group. With the exception of ulcerative colitis which was reported for 2 (5.9%) patients in the PREOB® group, chest pain and fall which were reported each for 1 (2.9%) patient in the PREOB® group and 1 (3.3%) patient in the Placebo group, all other events were reported by a single patient. No SAEs were considered related to the IMP. One SAE (procedural pain) reported by 1 patient in the PREOB® group was considered related to bone marrow aspiration/other study procedure.
Laboratory Results	In the Extended Safety Set, abnormal haematology laboratory values (from Visit 3/Day 1 [Implantation] to study end) were considered as clinically significant for 2 (5.9%) of 34 patients in the PREOB® group and 4 (13.3%) of 30 patients in the Placebo group. For 5 patients (1 in the PREOB® group and 4 in the Placebo group), clinically abnormal values were only observed at Visit 3; for the remaining patient in the PREOB® group, abnormal values for leukocyte count, neutrophil count, and monocyte count were reported throughout the follow-up. The investigator reported mild hyperleukocytosis as an adverse event for this patient; hyperleukocytosis was reported as not related to IMP, bone marrow aspiration, or a procedure. For one patient, the investigator reported moderate biological inflammatory syndrome with neutrophil and C-reactive protein increase; the event was reported as related to IMP and study procedures, but not related to sham marrow aspiration. Abnormal biochemistry laboratory values (from Visit 1 [Screening] to study end) were considered as clinically significant in 14 (41.2%) of 34 patients in the PREOB® group and 12 (40.0%) out of 30 patients in the Placebo group. With the exception of blood lipid values (i.e. total cholesterol, LDL cholesterol, triglycerides), most abnormal values in patients in both groups were sporadic. For 14 patients (8 [23.5%] patients in the PREOB® group and 6 [20.0%] patients in the Placebo group), out of range laboratory values were reported as adverse events, most of which were considered as not related to IMP, (sham) bone marrow aspiration or study procedures.
Vital Signs and Physical Findings	Vital signs remained stable over the course of follow-up in both the PREOB® and Placebo groups; no clinically relevant changes from Baseline in any parameter were observed. Individual patient values were in line with what could be expected in this population. None of the treatment-emergent findings at physical examination were reported as TEAEs related to the IMP.
Special Safety Assessments	No special safety assessments were performed.

CONCLUSIONS	
Efficacy	The interim analyses at Month 12 showed no statistically significant difference between the PREOB® group and the Placebo group for the primary efficacy endpoint (treatment responders) nor for the secondary efficacy endpoints of clinical and radiological responses. Conditional power regarding the probability of the trial to be successful at the final analysis at Month 24 was estimated to be close to 0. Given the low percentage difference of responders between the treatment groups, added to the low recruitment rates (the study had been ongoing for 7 years at the time of the interim analysis), the DMSB considered that the probably of reaching statistically significant results in favour of PREOB® by including more patients was negligible and therefore, recommended that the study be stopped for futility. The results of the final analysis at Month 24 were similar to those of the interim analysis, showing no significant difference between the treatment response of the PREOB® group and the Placebo group.
Safety	PREOB® cells were shown to be well tolerated, with a safety profile which was similar to that of Placebo.
Conclusion	Although the results from the present study indicate that PREOB® cells were well tolerated, there was no benefit of PREOB® treatment in combination with core decompression with respect to core decompression alone. The primary efficacy endpoint of improvement in WOMAC pain scale and non-progression of fractural stages was not reached when PREOB® was compared against placebo.