SYNOPSIS

Name of Sponsor	Bone Therapeutics S.A.
Name of Product	ALLOB®
Name of Active Ingredient	Allogeneic osteoblastic cells
Indication (phase)	Treatment of delayed-union fractures of long bones (Phase I/IIa)
Title of Study	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
REPORT PARTICULARS	
Report date	19 November 2018
Period of study	17 February 2014 to 30 January 2018 (Visit #6)
OBJECTIVES	
The primary objective of the study was 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).	

METHODOLOGY	
Study Design	Prospective, multicentre, open, non-controlled study
Treatments	ALLOB® is an allogeneic osteoblastic cell product falling under the scope of the European Regulation 1394/2007/EC and the Directive 2001/83/EC, manufactured by Bone Therapeutics S.A.
Treatment Duration	Single administration
Study Drug and Formulation	ALLOB® is composed of viable human *ex-vivo* cultured (non-genetically modified) osteoprogenitor cells derived from bone marrow mesenchymal stromal cells of healthy adult donors. ALLOB® is provided as a cell suspension in pre-filled syringes at a concentration of 25 x 10^6 cells/ml. ALLOB® must be kept at 2-8°C and must be administered within 96 hours of preparation.
Dose and Route of Administration	ALLOB® was given percutaneously, as a single administration of a suspension solution at a concentration of 25 x 10^6 cells/ml, into the delayed-union site using a trephine. The volume administered was based on the size of the delayed-union gap and determined as follows: • Fracture interline < 0.5 cm: 2 ml of suspension solution • Fracture interline ≥ 0.5 – ≤ 1 cm: 3 ml of suspension solution • Fracture interline > 1 – ≤ 2.5 cm: 4 ml of suspension solution If implantation using 2 surgical sites was judged to be the best approach by the Investigator, a total of up to 4 ml of solution was administered.
Concomitant and Excluded Therapy	No drugs/procedures were pre-defined in the protocol as prohibited during the study.

SUBJECT POPULATION	
Number Planned; Number Analysed	Up to 35 patients were to be enrolled to provide 32 assessable patients if the study recruitment were not stopped after interim analysis following a 2-stage Fleming design. The study enrollment was stopped after the 25th patient, since analysis of the 16 patients having completed the 6-month visit indicated pre-defined efficacy criterion had been reached. Of the 25 patients enrolled, 22 patients were treated and included in the Safety population and 21 patients were included in the Per Protocol (PP) population.
Major Inclusion Criteria	Men and women, aged 18 to 80 years old, diagnosed with a non-infected delayed-union fracture of a long bone (femur, tibia, fibula, humerus, ulna or radius) of minimum 3 and maximum 7 months (± 2 weeks) duration at the time of inclusion.
ASSESSMENTS	
Safety	In addition to standard pharmacovigilance requirements, particular attention was given to adverse events (AEs) indicative of allogeneic-induced reactions. All severe AEs potentially related to the Investigational Medicinal Product (IMP) and in particular those potentially related to allogeneic reactions were managed by the Safety Monitoring Committee (SMC) who analysed and reported these events in a timely manner consistent with the safety of patient recruitment scheme.
Efficacy	The following clinical and radiological criteria were used: • Clinical: Global disease evaluation (GDE) score as assessed by the patient and Investigator using a Visual Analogue Scale (VAS); Pain using a VAS; Weight-bearing score using a Likert scale • Radiological healing progression as assessed by CT scan and by conventional X-ray using the Tomographic Union Score (TUS) and modified Radiological Union Score (mRUS), respectively

STATISTICAL METHODS AND ANALYSIS	
Safety	The safety of ALLOB® was evaluated throughout the study period. Patients were 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 efficacy of ALLOB® was evaluated at 6 months. The success was based on the percentage of responders. A treated patient was considered as responding if, at the end of the study (6 months): • He/she had not required rescue surgery *and* • The GDE score as perceived by the patient had improved by at least 25% *or* the TUS as assessed by CT scan had increased by at least 2 points. The other endpoints evaluated were: • Evolution from baseline to each time point of the GDE score (VAS) as perceived by the patient and physician • Evolution from baseline to each time point of the TUS as assessed by CT scan • Evolution from baseline to each time point of Pain VAS at rest or during activities as assessed by the patient, and at palpation as assessed by the physician • Evolution from baseline to each time point of Weight-Bearing score • Evolution from baseline to each time point of the mRUS assessed by conventional X-ray • Evolution of the biodistribution of the ALLOB® cells up to 72 hours post-implantation • Evolution from baseline to each time point of the biomarkers
STUDY POPULATION RESULTS	
Demographics	The mean age at enrolment of the 22 patients who received treatment was 47.3 years (SD: 13.96 years), with most patients < 65 years of age. Overall, 59.1% of the patients were male and all were Caucasian/White.
Treatment Terminations	All 22 treated patients received the entire volume prescribed. 8 (36.4%) patients received 2 ml, 1 (4.5%) patient received 3 ml and 13 (59.1%) patients received 4 ml.
SAFETY RESULTS	
Extent of Exposure	All 22 treated patients completed to the Month 6 follow-up visit.

All AEs	During the follow-up period, 18 (81.8%) patients experienced a total of 56 Treatment Emergent AEs (TEAEs). Most of the TEAEs were mild (41 events) or moderate (13 events) in intensity. Two TEAEs were reported as severe. The most frequent event overall was procedural pain, experienced by 5 (22.7%) patients. Pain was reported as related to the procedure and not related to the IMP. Three (13.6%) patients experienced 3 TEAEs for which the relationship to the IMP was reported as unknown by the Investigator but which were considered to be related to the IMP for analysis. These were: • oedema peripheral, which was moderate in intensity. The event lasted approximately 3 months, then resolved without treatment. • arthralgia ("knee pain"), which was moderate in intensity. The event lasted 3 days and resolved without treatment. • pruritus reported as occurring on the left leg (i.e., corresponding to the location of the fractured tibia) and moderate in intensity. The event was ongoing at the end of the 6-month follow-up.
Deaths and Other Serious AEs	No death was reported during the follow-up. Two (9.1%) patients experienced 3 serious TEAEs: implant site infection for one patient and angioedema and urticaria for a second patient. All events resolved. Although all events were considered as not related to ALLOB® by the Investigator, the Sponsor chose to report angioedema and urticaria as SUSARs as a precautionary measure.
Laboratory Results	Among the patients with normal values at baseline, clinically significant abnormal values were observed in at least 2 patients during the post-implantation visits (Week 2 to Month 6 visits) for: • AST, ALP, CRP (standard assay), total cholesterol, potassium, calcium and phosphate. • haematocrit, lymphocytes and eosinophils. • PT and APTT.
Vital Signs and Physical Findings	Vital signs remained stable over the course of follow-up; 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. All treatment-emergent findings at physical examination were reported as TEAEs.
Special Safety Assessments	Before implantation, anti-HLA Class I/II antibodies were detected in 8 (36.4%) patients. After implantation, anti-HLA Class I/II antibodies could be detected in 14 (63.6%) patients. No lytic anti-HLA antibodies were detected before implantation whereas after implantation, donor-specific lytic anti-HLA antibodies were detected for 9 (40.9%) patients.

EFFICACY RESULTS	
Primary Variable	The response rate at Month 6 for the 21 patients in the PP population was 100% (90% CI: 86.71 - 100%). None of the treated patients required rescue surgery. An improvement of GDE score of at least 25% was reported for 16 (76.2%) patients. An increase in TUS of at least 2 points was reported for 16 (76.2%) patients; all patients met at least one of these two criteria.
Secondary Variable(s)	Following treatment: • There was a statistically significant improvement in global health, as shown by the difference in GDE score from pre- to post-treatment. Improvement was observed by the patient and by the physician. An effect was shown at Week 2 which persisted to Month 6. • There was a statistically significant decrease in pain at rest, pain during activities and pain at palpation, based on VAS scores. An effect was shown at Week 2 which persisted to Month 6. • There was a marked improvement in weight bearing score for patients with fractures of the lower extremity and for patients with fractures of the upper extremity. The weight bearing score increased over time. • There was a statistically significant evolution in bone healing, as shown by the total TUS and the mRUS. The effect of treatment which was apparent at Month 1 for the total TUS and at Month 3 for the mRUS increased with time to Month 6. The analysis of biodistribution was performed in 2 patients. In both patients, the kinetics observed were consistent with published data when mesenchymal stem cells are injected into the blood stream.
CONCLUSIONS	
Safety	ALLOB® was shown to be well tolerated without biological or clinical AEs of clinical relevance. No immediate hypersensitivity reactions were attributed to the IMP. In one patient, a hypersensitivity reaction without an established causal relationship to ALLOB® was reported 4 weeks after administration, with full recovery. Approximately one-half of the patients contained donor-specific antibodies, either pre-existing or developed after administration.
Efficacy	At six months post-administration, 100% of the patients met the primary endpoint, defined as the absence of a rescue surgery together with an increase of at least 2 points on the TUS or an improvement of at least 25% of the GDE score. From a clinical perspective, a statistically significant improvement in global health and in pain (at rest, at palpation and during activities) was observed at Week 2, which persisted to Month 6. From a radiological perspective, a significant evolution in bone healing was observed which increased with time. All together these data provide preliminary data of ALLOB® potential effectiveness in delayed-union fracture indication.
Conclusion	The results from the present study indicate that ALLOB® was well tolerated and provide preliminary evidence for potential effectiveness of ALLOB® in the treatment of delayed-union fractures suggesting further clinical development in this indication is warranted.