CLINICAL STUDY REPORT

Synoptic Report

Study PREOB NU3

A pivotal Phase IIb/III, multicentre, randomised, open, controlled study on the efficacy and safety of autologous osteoblastic cells (PREOB®) implantation in non-infected hypotrophic non-union fractures

Sponsor:

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Indication:	**Patients with long-bone hypotrophic non-infected non-union**
Investigational Medicinal Product	PREOB®
Control	Bone Autograft
Clinical Phase:	Pivotal Phase IIb/III
Protocol Identification:	000002/BT
EudraCT number:	2011-005584-24
Study Initiation Date (first patient enrolled):	7 March 2013 (First approval [Belgium]: 12 May 2012)
First patient treated:	18 October 2013
Last patient treated:	27 Apr 2015
Early / Premature Study Termination Date (if applicable):	*Belgium* (BE): 25 September 2017 *France* (FR): 17 July 2015 [Study termination for refusal of study extension by the French Ethical Research Committee: Comité de Protection des Personnes (CPP)] *The Netherlands* (NL): 22 August 2016
Study Completion Date (last patient completed):	23 April 2018 (24 Months long term safety follow-up)
Data Base Lock Date:	26 March 2019
Date of report:	10 May 2019

This study was performed in compliance with ICH Good Clinical Practise (GCP)

Sponsor's Responsible Medical Officer

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List of Abbreviation

Abbreviation	**Term**
AE	Adverse Event
BE	Belgium
BM	Bone Marrow
BP	Blood Pressure
BT	Bone Therapeutics
CPP	Comité de Protection des Personnes
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
FR	France
FU	Follow-Up
GCP	Good Clinical Practise
HBA1C	Hemoglobin A1c
HR	Heart Rate
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
NL	Netherlands
NU	Non-Union
PT	Preferred Term
SAE	Serious Adverse Event
SASQE	Serious Adverse Safety/Quality Event
SD	Standard Deviation
SOC	System Organ Class
T	Temperature

SYNOPTIC CLINICAL STUDY REPORT FOR STUDY PREOB NU3

TITLE OF STUDY: A pivotal Phase IIb/III, multicentre, randomised, open, controlled study on the efficacy and safety of autologous osteoblastic cells (PREOB®) implantation in non-infected hypotrophic non-union fractures

PURPOSE: This clinical study report presents results for PREOB-NU3, a prospective, multicentre, randomized, open, controlled, pivotal Phase IIb/III trial which was initiated to compare in patients with long-bone non-infected hypotrophic non-union fractures the efficacy and safety of PREOB® implantation (PREOB® Group) to Bone Autograft over 12 months. Bone Autograft (Autologous Bone graft, from iliac crest harvesting, implantation) was performed according to the standard-of-care procedures of the investigating site. Additional post-study follow-up was set-up to assess selected efficacy and safety parameters at 12 and 24 months after the end of the study.

However, the PREOB-NU3 study was terminated early (25 September 2017 (Belgium (BE) / 17 July 2015 (France (FR); Study termination for refusal of study extension by CCP) / 22 Augustus 2016 (The Netherlands (NL)) by the sponsor with <10% of planned subject enrolled because of recruitment difficulties. Additionally, new premature stop of another phase III PREOB® study in hip osteonecrosis and the decision to end the development program of PREOB® by the sponsor led to not assess the PREOB efficacy anymore.

Therefore, this final clinical study report (CSR) for PREOB-NU3 is in synoptic format presenting the safety review. Efficacy analysis was not performed.

NUMBER OF SUBJECTS: The protocol planned to enroll 176 subjects which were expected to be randomised in 2 groups, in a 1:1 ratio, as follow: 88 subjects in the Bone Autograft group and 88 subjects in PREOB® group. During this study, only 16 subjects (9% of the planned population) were screened (Patient who has dated and signed the Informed Consent Form per protocol) in 4 investigational sites in Belgium, while 7 (43.75%) subjects were randomized (Patient to whom a randomisation number has been allocated per protocol).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS: Of the 16 subjects enrolled in the study, 9 (56.25%) subjects were screen failure; out of the 7 (43.75%) subjects randomized, 5 (31.25%) subjects were treated (2 subjects in the PREOB® group and 3 subjects in the Bone Autograft group) and 2 patients were not harvested either not treated. Overall, 5 (2 PREOB® and 3 Bone autograft) of the 5 treated patients (100 %) completed the study follow-up (12 months), while 4 (2 PREOB® and 2 Bone Autograft) completed the long-term safety follow up (24months). As allowed by the study protocol, the 2 subjects in the PREOB® group withdrawn the study due to lack of efficacy assessed by PI.

All 5 treated subjects were included in the safety analysis.

Table 1: *Patient Disposition - Number of patients by site – Enrolled, screened failure and randomised patients*

Site #	Randomised Patients

	Patient Enrolled/Screened (N=16)	Screen Failure (N=9)	PREOB® (N=3)	Bone Autograft (N=4)
BE01 – Erasme	7 (43.75%)	3 (33.33%)	3 (100.00%)	1 (25.00%)
BE02 - Charleroi	3 (17.75%)	2 (22.22%)	0 (0.00%)	1 (25.00%)
BE04 - ZOL	5 (31.25%)	3 (33.33%)	0 (0.00%)	2 (50.00%)
BE06 - AZ Maria Middelares	1 (6.25%)	1 (11.11%)	0 (0.00%)	0 (0.00%)

%= (n / N) x 100

Source : Appendix document – section 1.1, Table 11.1.1 Patient Disposition – All Patients Population & Listing 12.1.1b Patient Disposition – All Patient Population

A total of 13 subjects discontinued the study: 9 subjects were screen failure due to violation of eligibility criteria (4 subjects) or to other reason (5 subjects: 2 subjects were not eligible after review of the independent radiologist; for 1 subject the fracture was considered as healed; for 1 subject the fracture was exposed to abnormal stresses; 1 subject was excluded according to exclusion criterion number 26, HBA1C = 9.3%); 1 subject in the PREOB® group discontinued for other reason, as the bone harvesting could not be done with a local anesthesia; 2 subjects withdrew the study due to lack of efficacy (PREOB® group); 1 subject withdrew the consent (Bone Autograft group). The mean reason for discontinuation at the long-term safety follow-up was lost to follow-up in 1 (6.25%) patients (PREOB® group).

Table 2: *Patient Disposition – All Patients Population*

	PREOB® (N=3)	Bone Autograft (N=4)	Not Randomised (N=9)	Overall (N=16)
Screened	3 (100.00 %)	4 (100.00 %)	9 (100.00 %)	16 (100.00 %)
Randomised	3 (100.00 %)	4 (100.00 %)	0 (0.00 %)	7 (43.75 %)
Treated	2 (66.67 %)	3 (75.00 %)	0 (0.00 %)	5 (31.25%
Reason for completion withdrawal				
Lack of Efficacy	2 (66.67%)	0 (0.00 %)	0 (0.00 %)	2 (12.50%)
Other Reason	1 (33.33%)	0 (0.00 %)	5 (55.56%)	6 (37.50%)
Withdrawn Consent	0 (0.00 %)	1 (25.00%)	0 (0.00%)	1 (6.25%)
Violation of Eligibility Criteria	0 (0.00 %)	0 (0.00 %)	4 (44.44%)	4 (25.00%)
Completed Treatment including 12 Month FU	0 (0.00 %)	3 (75.00 %)	0 (0.00 %)	3 (18.75%)
Study Population				
Safety	2 (66.67%)	3 (75.00 %)	---	5 (31.25%)
Per Protocol	1 (33.33%)	2 (50.00%)	---	3 (18.75%)
ITT	2 (66.67%)	3 (75.00 %)	---	5 (31.25%)

Source : Appendix document – section 1.1, Table 11.1.1 Patient Disposition – All Patients Population

Overall, 4 subjects of the 16 screened subjects (25.00%) had at least one major protocol deviation: 1 subject was not randomised, and 3 subjects were randomised (2 subjects in the

PREOB® group and 1 subject in the Bone Autograft group). Major protocol deviations reported for more than one subject were: "Study treatment not respected mainly due to the timelines between the visits for Bone Autograft or PREOB®", "Test/exam not done or inappropriate" and "Eligibility issues due to imaging exam or to laboratory (serology) exam not performed in accordance of the timeline".

A summary of major protocol deviations is provided in Table 3.

Table 3: *Major study protocol deviations*

	Enrolled / Screened Patients (N= 16)	**Not Randomised patient (N=9)**	**Randomised Patient**	
			PREOB® (N=3)	**Bone Autograft (N=4)**
At least one major protocol deviation				
Study Treatment not respected – Bone autograft not performed between 35 to 7 days after visit #2 for the Bone Autograft group or PREOB® implementation made >35 days +/- 2 days after visit #2	2	0	1[a]	1
Test/exam not done or inappropriate – Global disease evaluation (patient and physician) at least 2 missing answers: at Visit #1 (screening), Visit #2 (randomisation/baseline) and Visit #9 (Month 12)	1	1	0	0
Eligibility issue – X-ray not done within 14 days before visit#2 if they have not been done during Visit #1 in this same timeframe	2	0	2[a,b]	0
Eligibility issue – Serologies not done within 14 days before visit #2 if they have not been done during Visit #1 in this same timeframe	1	0	1[b]	0

([a]) Subject NUBE0104 had 2 major deviations, one linked to study treatment not respected (PREOB® implementation made >35 days +/- 2 days after visit #2) and another linked to eligibility issue (X-ray was not done within 14 days before visit#2 if they have not been done during Visit #1 in this same timeframe).

([b]) Subject NUBE0105 had 2 major deviations, both linked to eligibility criteria.

Source : Appendix document – section 1.1, Listing 12.2.2 Major Protocol Deviations – All patients Population

Intent-to-treat (ITT) population (N=5), including all randomised and treated patient per protocol, was considered for the demographic review. Treated population (N=5, same as ITT), - and the safety set (N=5) were considered for the safety review. Demographic characteristics of the ITT population are presented in Table 4.

The global mean age at treatment period (ITT population) was 42.32 years (SD: 9.40 years). Overall, 20.00% of the patients were female and 80.00 % were male. The mean height and weight at enrolment were 172.4 cm (SD: 12.20 cm) and 73.4 Kg (SD: 7.76 kg), respectively, for a mean BMI of 24.86 kg/m^2 (SD: 3.18 Kg/m2). Mean age of the PREOB® group was 37.2 years (SD: 7.3), while 45.7 years (SD: 10.3) in the Bone Autograft group. PREOB® group showed taller subjects with an average height of 180 cm (SD: 1.4) and less heavy subjects with an average weight of 70.5 kg (SD: 3.5) compared to Bone Autograft group which showed subject with a mean height of 167.3 cm (SD 14.1) and a mean weight of 75.3 kg (SD: 10.0). Mean BMI was 21.8 kg/m^2 (SD: 1.4) and 26.9 kg/m^2 (SD:1.9) for both PREOB® and Bone Autograft group respectively.

The affected bones of the treated patients were femur (N=2 (40%); 1 in PREOB® group and 1 in Bone Autograft group), Fibula (N=1 (20%); Bone Autograft group), Humerus (N=1 (20%); PREOB® group), Ulna (N=1 (20%); 1 Bone Autograft group).

Overall, mean time (days) since non-union diagnosis to date of the screening was 123.4 days (SD: 119.75). This mean time (days) was different between the two groups with a mean interval of 244 days (SD: 63.3) for PREOB® group and 43 days (SD: 49.15) Bone autograft group. Repartition of the fracture side was well harmonised globally with 2 fractures on the left side (N=1 PREOB® and N=1 Bone Autograft) and 3 fractures on the right side (N=1 PREOB® and N=2 Bone Autograft). All non-union fractures were hypotrophic as per protocol. Bone fracture was essentially closed fracture (N=4; 1 for PREOB® and 3 for Bone Autograft). One fracture was open fracture (PREOB®). The fractures were localised in the diaphysis (N=2 PREOB® and N=1 Bone Autograft), in the epiphysis (N=1 Bone Autograft) and in the metaphysis (N=1 Bone Autograft) essentially due to major trauma (N=3; 1 for PREOB® and 2 for Bone Autograft).

Table 4: *Demography – Intent-to-Treat population*

		PREOB® (N=2)	Bone Autograft (N=3)	Overall (N=5)
Age (years)	n	2	2	3
	Mean ± SD	37.2 ± 7.3	45.7 ± 10.3	42.32 ± 9.4
	Median	37.2	45.4	42.4
	Min : Max	32 : 42.4	35.6 : 56.2	32 : 56.2
	P25 : P75	32 : 42.4	35.6 : 56.2	35.6 : 45.4
Sex	Female	--- (---%)	1 (33.33%)	1 (20.00%)
	Male	2 (100%)	2 (66.67 %)	4 (80.00%)
Height (cm)	n	2	3	5
	Mean ± SD	180 ± 1.4	167.3 ± 14.1	172.4 ± 12.2
	Median	180	175	176
	Min : Max	179 : 181	151 : 176	151 : 181
	P25 : P75	179 :181	151 :176	175 : 179
Weight (Kg)	n	2	3	5
	Mean ± SD	70.5 ± 3.5	75.3 ± 10.0	73.4 ± 7.8
	Median	70.5	76	73
	Min : Max	68 :73	65 : 85	65 : 85
	P25 : P75	68 : 73	65 : 85	68 : 76
BMI (Kg/m2)	n	2	3	5
	Mean ± SD	21.8 ± 1.4	26.9 ± 1.9	24.86 ± 3.2
	Median	21.8	27.4	24.8
	Min : Max	20.8 : 22.8	24.8 : 28.5	20.8 : 28.5
	P25 : P75	20.8 : 22.8	24.8 : 28.5	22.8 : 27.4
Ethnic Group	Caucasian Whit	2 (100%)	3 (100%)	5 (100%)

BMI: Body Mass Index; SD: Standard Deviation

Source : Appendix document – section 1.1, Listing 11.1.3 Demography – Intent-to-Treat population & Listing 12.2.4.1 Demography – All Patients population

Table 5: Target fracture characteristics

		PREOB® (N=2)	Bone Autograft (N=3)	Overall (N=5)
Fracture level	Diaphysis	2 (100.00 %)	1 (33.33 %)	3 (60.00 %)
	Epiphysis	---	---	1 (20.00 %)
	Metaphysis	---	---	1 (20.00 %)
Open vs Closed fracture	Closed fracture	1 (50.00 %)	3 (100.00%)	4 (80.00 %)
	Open fracure	1 (50.00 %)	---	1 (20.00%)
Type of fracture	Commuted fracture	---	1 (33.33 %)	1 (20.00 %)
	Oblique fracture	1 (50.00%)	2 (66.67 %)	3 (60.00 %)
	Spirale fracture	1 (50.00%)	---	1 (20.00 %)
Type of non-union fracture	Hypotrophic	2 (100.00 %)	3 (100.00 %)	5 (100.00 %)
Cause of fracture	Major trauma	1 (50.00 %)	2 (66.67 %)	3 (60.00 %)
	Simple trauma	1 (50.00 %)	1 (33.33 %)	2 (40.00 %)
Type of Osteosynthesis	Internal	2 (100.00 %)	3 (100.00 %)	5 (100.00 %)
Any previous fracture	No	1 (50.00 %)	1 (33.33 %)	2 (40.00 %)
	Yes	1 (50.00 %)	2 (66.67 %)	3 (60.00 %)
Are tendon, ligament or nerve damage at the fracture sites	No	2 (100.00 %)	2 (66.67 %)	4 (80.00 %)
	Yes	---	1 (33.33 %)	1 (20.00 %)

Source : Appendix document – section 1.1, Table 11.1.5 target fracture – Intent-to-treat population

Dose of PREOB® varied from 8 x 10^6 cells (2mL) to 16 x 10^6 cells (4mL) depending on the size of the non-union interline fracture and delivered for local administration – intraosseous use - in a ready-to-use syringe / one single dose per subject. All patients treated with PREOB® underwent a core biopsy (5-mm trephine) under local or loco-regional anaesthesia combined with the implantation of PREOB® into the non-union site.

Of the 3 subjects randomised into the PREOB® group, 2 were exposed to the study treatment PREOB®. Each subject received one single dose of PREOB® (4 mL (16 x 10^6 Osteoblastic cells) and 2 mL (8 x 10^6 Osteoblastic cells)). Both subjects completed the study duration (from V#1 to V#9 [12 months]) and the long-term safety follow-up [(V#10 +12 Months] and V#11, +24 Months)] even if they were withdrawn at V#9 for lack of efficacy.

Table 6: *Volume (and number of cells) of PREOB® administered by subject in the PREOB® group*

	Volume	Number of Cells
NUBE0101	4 mL	16 x 10^6 cells
NUBE0104	2 mL	8 x 10^6 cells
NUBE0105	---	---

SUMMARY OF EFFICACY RESULTS: The PREOB-NU3 clinical study was carried out to test the efficacy and safety of the investigational medicinal product (IMP) PREOB® in the treatment of non-infected hypotrophic non-union fractures. Non-union fracture is a relatively rare condition. Bone Therapeutics estimated the incidence of non-union fractures from 1 to 4 cases per 10,000 inhabitants, based on (i) the number of osteosynthesis performed annually and (ii) the reported cases of fractures evolving to non-union (Singer et al., 1998; Crowley et al., 2007; Tressler et al., 2011; Phieffer et al., 2006). The recruitment was stopped, and the study prematurely terminated because of the difficulties faced in patients' recruitment. The premature termination of the study was declared on September 20, 2017 to Belgian competent authority by the Sponsor. The low number of subjects randomised (N=7) or treated (N=5) do not allow to perform a representative statistical analysis of the PREOB® efficacy. As a consequence, clinical study report of PREOB-NU3 is provided in a synoptic format where efficacy analyses were not performed; only demographic and safety review was considered.

SUMMARY OF SAFETY RESULTS: The safety and tolerability of the test product (PREOB®) were systematically investigated throughout the study period. Subjects were evaluated at each follow-up visit for the potential occurrence of any Adverse Event (AE) or Serious Adverse Event (SAE), related to either the product or the study procedures, and the potential occurrence of Serious Adverse Safety/Quality Event (SASQE), using the following safety criteria listed in the table 7.

Beyond the safety review presented in this report, complementary safety insight is given on the Appendices document enclosed.

Table 7: *Overview of Safety Parameters and Endpoints*

Objectives	Variables	Time Points
To evaluate the safety and tolerability of PREOB® vs. Bone Autograft	Open questionnaires	Visits #1, #2, #5, #6, #7, #8 and #9
	Physical examination	Visits #1, #2, #4, #5, #9 and in case of early discontinuation
	Vital signs (HR, BP, T°C)	Visits #1, #2, #3, #4, #5, #6, #7, #8 and #9
	Laboratory parameters • Haematology • Serum chemistry	Visits #1, #2, #3, #4, #5, #6, #7, #8 and #9
	AEs and SAEs	Visits #2, #3, #4, #5, #6, #7, #8 and #9
To evaluate the safety of the patients during the open post-treatment period	SAEs Open questionnaire (via phone call)	At 12, 24, 36 and 48 months after the end of the study.

The mean duration of follow-up for the 5 treated subjects (Safety Population) was 352 days (SD: 19.4) with comparable results between the groups; see Table 8.

From the PREOB® group two subjects completed the study duration (from V#1 to V#9 [12 months]) and the long-term safety follow-up (V#10 +12 Months and V#11, +24 Months)] even if they were withdrawn at V#9 for lack of efficacy. Additionally, it was observed that none of the subject treated by PREOB® or by Bone Autograft had a rescue surgery.

Table 8: *Treatment Exposure – Safety Population*

		PREOB® (N=2)	Bone Autograft (N=3)	Overall (N=5)
Time of treatment (days)	n	2	3	5
	Mean ± SD	359 ± 32.5	347.3 ± 11.9	352 ± 19.4
	Median	359	342	342
	Min : Max	336 : 382	339 : 361	336 : 382
	P25 : P75	336 : 382	339 : 361	339 : 361
Number of patients having rescue therapy or not	NO	2 (100.00%)	3 (100.00 %)	5 (100.00 %)
	YES	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)

Source : Appendix document – section 1.1, Table 11.3.1 Treatment Exposure – Safety Population

Treatment-emergent AE was defined as an adverse event which occurred or worsened after the bone marrow harvest procedure in PREOB® group per protocol.

An overview of the adverse events (AEs) occurring during the period from inform consent form (ICF) signature to Visit #9 (end of study) including long term safety follow-up (24 months post study follow-up), is provided in Table 9.

During the overall follow-up (study and long-term safety follow-ups), 4 (80% of the safety and treated population) subjects (N=1 PREOB® group; N=3 Bone Autograft group) experienced a total of 17 AEs (2 AEs in the PREOB® group and 15 AEs in the Bone Autograft group). Among these 4 subjects, 2 had a serious adverse event (Bone Autograft group) and 1 a treatment emergent AE (PREOB® group).

Most of these AEs were mild (7 events) or moderate (8 events) in intensity. 2 AEs were reported as severe in the Bone Autograft group only. The main reason of these severe events was due to Arthralgia (right knee pain) for one subject and to osteoarthritis (coxarthrosis left hip) for one other subject.

Only two subjects, from the Bone Autograft group, experienced a total of 8 SAEs. No events were considered related to the treatment or to the procedure in the PREOB® group. Most of these SAE were moderate (6 events) or mild (2 events).

One subject from the PREOB® group had 2 treatment emergent AE due to gastritis and plantar fasciitis.

One AE led (All population) to subject discontinuation (Withdrawal) before being treated by PREOB® due to pain during the harvesting procedure

No death was reported during the follow-up.

Table 9: *Adverse event summary – Safety Population*

	PREOB®: number of patient (N=2)		Bone Autograft: number of patient (N=3)		Overall (N=5)	
	m	**n (%)**	**m**	**n (%)**	**m**	**n (%)**
Any adverse events (AE)						
	2	1 (50.00 %)	15	3 (100 %)	17	4 (80%)
Mild	2	1 (50.00 %)	5	2 (66.67 %)	7	3 (60%)
Moderate	0	0 (00.00 %)	8	3 (66.67 %)	8	3 (60%)
Severe	0	0 (00.00 %)	2	2 (66.67 %)	2	2 (40%)
Any serious adverse events	0	0 (00.00 %)	8	2 (66.67 %)	8	2 (40%)
Any treatment emergent AE	2	1 (50.00 %)	0	0 (00.00 %)	2	1 (20%)
Any treatment emergent SAE	0	0 (00.00 %)	0	0 (00.00 %)	0	0 (0%)
Any AE leading to withdrawal	0	0 (00.00 %)	0	0 (00.00 %)	0	0 (0%)
Any SAE leading to withdrawal	0	0 (00.00 %)	0	0 (00.00 %)	0	0 (0%)
Any AE related to BM harvest	0	0 (00.00 %)	0	0 (00.00 %)	0	0 (0%)
Any AE related to PREOB®	0	0 (00.00 %)	0	0 (00.00 %)	0	0 (0%)

n: number of patients with at least one adverse event, %: (n row / N group) x 100; m: number of adverse events. A same patient can have more than one adverse event or/and serious adverse event.

Source : Appendix document – section 1.1, Table 11.3.2.1 Overall adverse event summary – Safety population & Listing 12.2.7.1.2 Adverse Events – safety population

Related to SAEs 2 Subjects experienced a total of 8 SAEs: 6 events in 1 subject and 2 events in 1 other subject in the Bone Autograft group.

All SAEs reported coded to the SOCs (summary of SAEs is presented by SOC and PT in Table 10), were “Injury, poisoning and procedural compilations” (5 SAEs by 1 subject), “Musculoskeletal and connective tissue disorders” (2 SAEs by 2 subjects) and “Medical device change / surgical and medical procedures” (1 SAE by 1 subjects). No SAEs were reported as related to the study treatment or procedure in this study.

A listing of all SAEs by patient is provided in Table 11.

Table 10: *Serious Adverse Events by System Organ Class (SOC) and Preferred Term (PT) – Safety Population*

01_SOC_T	01_PT_T	PREOB©: Number of patients (N=2)	%	Bone Autograft: Number of patients (N=3)	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	FEMUR FRACTURE	0	0.00	1	33.33
	POST-TRAUMATIC PAIN	0	0.00	1	33.33
	ROAD TRAFFIC ACCIDENT	0	0.00	1	33.33
	Subtotal per SOC	**0**	**0.00**	**1**	**33.33**
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	OSTEOARTHRITIS	0	0.00	2	66.67
	Subtotal per SOC	**0**	**0.00**	**2**	**66.67**
SURGICAL AND MEDICAL PROCEDURES	MEDICAL DEVICE CHANGE	0	0.00	1	33.33
	Subtotal per SOC	**0**	**0.00**	**1**	**33.33**

MedDRA dictionary version v21.1 and WHODD Mar 2016.

Source : Appendix document – section 1.1, Table 11.3.2.3 Serious Adverse Event by System Organ Class and Preferred Term – Safety Population

***Table 11**: Overall Serious Adverse Events, System Organ Class (SOC) and Preferred Term (PT)*

Randomisation Arm	Verbatim Preferred Term System Organ Class	StartDate Stop Date	Outcome	Intensity	Action Taken	Frequency	Where did event take place	Any medication given?	SAE	Serious Criteria
Bone Autograft group	SUPRACONDYLAR DISTAL FEMUR FRACTURE RIGHT DUE TO SECOND MOTOR BIKE ACCIDENT / FEMUR FRACTURE / INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16-MAY-2015 /18-MAY-2015	RECOVERED/RESOLVED	MODERATE	OTHER OSTEOSYNTHESIS	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 15	YES	Requires inpatient (prolongation of existaing) hospitalization
	CLOSED SPIROID FRACTURE RIGHT DISTAL TIBIA AND FIBULA DUE TO MOTOR BIKE ACCIDENT / ROAD TRAFFIC ACCIDENT / INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11-FEB-2015 /12-FEB-2015	RECOVERED/RESOLVED	MODERATE	OTHER HOSPITALISATION AND OPERATION	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 11 12 13	YES	Requires inpatient (prolongation of existaing) hospitalization
	POST-TRAUMETIC PAIN RIGHT ANKLE AND RIGHT KNEE / POST-TRAUMATIC PAIN / INJURY, POISONING AND PROCEDURAL COMPLICATIONS	03-APR-2015 /04-APR-2015	RECOVERED/RESOLVED WITH SEQUELAE PAIN HAS BEEN IMPROVED BUT NOT COMPLETELY RESOLVED	MILD	OTHER HOSPITALISATION/ REMOVAL OF HARDWARE FROM RIGHT KNEE AND RIGHT CALCANEUS	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 14	YES	Requires inpatient (prolongation of existaing) hospitalization
	POST TRAUMETIC PAIN,SUBTALAR PAIN RIGHT ANKLE CONFORM AE2 AND AE4 / POST-TRAUMATIC PAIN / INJURY, POISONING AND PROCEDURAL COMPLICATIONS	03-MAR-2016 /04-MAR-2016	RECOVERED/RESOLVED WITH SEQUELAE PAIN HAS BEEN IMPROVED BUT NOT COMPLETELY RESOLVED	MILD	OTHER HOSPITALIZED/REMOVAL OF INTERNAL FIXATION-DEBRIDEMENT	SINGLE EPISODE	OPERATING ROOM	NO	YES	Requires inpatient (prolongation of existaing) hospitalization
	ARTHROSIS RIGHT KNEE / OSTEOARTHRITIS / MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	09-JUL-2017 /14-JUL-2017	RECOVERED/RESOLVED WITH SEQUELAE PAIN HAS BEEN IMPROVED BUT IS NOT COMPLETELY RESOLVED	MODERATE	OTHER HOSPITALISATION/ TOTAL KNEE REPLACEMENT	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 18, 17	YES	Requires inpatient (prolongation of existaing) hospitalization

Randomisation Arm	Verbatim Preferred Term System Organ Class	StartDate Stop Date	Outcome	Intensity	Action Taken	Frequency	Where did event take place	Any medication given?	SAE	Serious Criteria
	POST-TRAUMETIC PAIN RIGHT ANKLE / POST-TRAUMATIC PAIN / INJURY, POISONING AND PROCEDURAL COMPLICATIONS	28-FEB-2017 /03-MAR-2017	RECOVERED/RESOLVED WITH SEQUELAE PAIN AND RESTRICTION OF MOBILITY	MODERATE	OTHER HOSPITALISATION/ ARTHRODESES RIGHT ANKLE	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 16 , 17	YES	Requires inpatient (prolongation of existaing) hospitalization
Bone Autograft group	REVISION OF THE INSERT OF THE ACETABULAR CERAMIC COMPONENT OF THE LEFT TOTAL HIP PROSTHESIS WHICH WAS BROKEN / MEDICAL DEVICE CHANGE / SURGICAL AND MEDICAL PROCEDURES	24-JUN-2016 /27-JUN-2016	RECOVERED/RESOLVED	MODERATE	OTHER REVISION TOTAL HIP PROSTHESIS	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 8 - 11	YES	Requires inpatient (prolongation of existaing) hospitalization
	COXARTHROSIS LEFT HIP / OSTEOARTHRITIS / MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	17-DEC-2015 /20-DEC-2015	RECOVERED/RESOLVED	MODERATE	OTHER OPERATION WITH TOTAL HIP REPLACEMENT	SINGLE EPISODE	OPERATING ROOM	YES - cf Concomitant Medication N°: 4,5,6,7	YES	Requires inpatient (prolongation of existaing) hospitalization

MedDRA dictionary version v21.1 and WHODD Mar 2016.

Source: Appendix 11.1 Listing 12.2.7.2 Serious Adverse Events – All Patients Population

SAFETY CONCLUSIONS: No SAEs reported following treatment with PREOB® was considered as related to PREOB®.

DISCUSSION AND OVERALL CONCLUSIONS: Although interpretation of safety results is limited by the low numbers of subjects in each treatment group, the observed incidence of deaths, serious adverse events and adverse events (not related to PREOB® treatment or procedure) was consistent with the safety findings from prior phase 2 study.

The low number of patients recruited make the confirmation of the study primary (or either its secondary efficacy) endpoint impossible as only 2 subjects were treated with IMP PREOB®. This finding does not allow to conclude a non-inferiority or not of PREOB® treatment over Bone Autograft at 12 months for non-union fractures of long bones (humerus, radius, ulna, femur, tibia, and fibula).

DATE OF REPORT : 10 May 2019

SIGNATURE PAGES FOR CLINICAL STUDY REPORT (SYNOPTIC)

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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