

CLINICAL INVESTIGATION PLAN

PERFORMANCE AND SAFETY OF THE RESORBABLE COLLAGEN MEMBRANE “EZ CURE™” IN GUIDED TISSUE REGENERATION AND GUIDED BONE REGENERATION PROCEDURES

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PROTOCOL FOR RESEARCH INVOLVING HUMAN PARTICIPANTS

(Category 3 – Non-interventional study)

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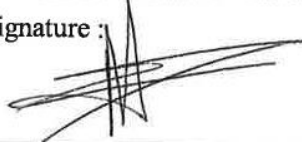
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PROTOCOL AMENDMENT HISTORY

<u>VERSION</u>	<u>DATE</u>	<u>DESCRIPTION OF THE MODIFICATION</u>
N° 1.0	13/02/2019	First validated version presented to the Ethical Committee

VALIDATION AND SIGNATURES

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CLINICAL CENTERS

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ARS	regional health agency
CAL	Clinical Attachment Level
CFR	Code of Federal Regulations
CI	Confidence Interval
CPP	Committee for Protection of Persons
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DDS	Doctor of Dental Surgery
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
GBR	Guided Bone Regeneration
GTR	Guided Tissue Regeneration
MD	Mean Difference
MedDRA	Medical Dictionary for Regulatory Activities
NNT	Number Needed to Treat
OFD	Open Flap Debridement
PP	Per-Protocol
PPD	Probing Pocket Depth
PT	Preferred Term
RCM	Resorbable Collagen Membrane
RR	Risk Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-Emergent Adverse Events

I. SYNOPSIS OF THE STUDY

Title	Performance and safety of the Resorbable Collagen Membrane “EZ CURE™” in Guided Tissue Regeneration and Guided Bone Regeneration procedures.	
Sponsor	BIOMATLANTE SA	
Coordinating investigator	Dr. Saïd KIMAKHE	
ANSM identification	2018-A03202-53	
Justification / context	<p>The evaluation of the clinical data has demonstrated the conformity of the Resorbable Collagen Membrane (RCM), EZ Cure™, with the relevant essential requirements for its use in periodontal applications. The RCM is intended for Guided Tissue Regeneration (GTR) and Guided Bone Regeneration (GBR) procedures. It acts as a barrier against the migration of epithelial cells within the bone defect (performance) and thus complies with several surgical indications in the treatment of maxillofacial bone defects. It has been concluded that the risks associated with the use of this device are acceptable when weighted against the benefits to the patients.</p> <p>In order to improve the clinical data on the RCM, the manufacturer, Biomatlante, decided to assess that the performance and safety of the device are maintained until the reaching of its intended use. In this objective, the goal of this study will be to observe the following parameters:</p> <ol style="list-style-type: none"> 1. Tissue regeneration (mucosa health on the site of implantation) 2. Safety (report of any adverse event) 3. Radiographic analysis of periodontal tissues 	
Studied disease	<p>Oral maxillofacial and periodontal defects requiring Guided Tissue Regeneration.</p> <p>Alveolar dental defects after tooth/teeth extraction.</p>	
Puopose of the device	<input checked="" type="checkbox"/> Treatment <input type="checkbox"/> Diagnostic <input type="checkbox"/> Supportive care <input type="checkbox"/> Prevention	<input type="checkbox"/> Screening <input type="checkbox"/> Health services Research <input type="checkbox"/> Basic science <input type="checkbox"/> Other
Study model	<input checked="" type="checkbox"/> Single groupe <input type="checkbox"/> Parallel	<input type="checkbox"/> Crossover <input type="checkbox"/> Factorial
Type of data	<input type="checkbox"/> Safety <input checked="" type="checkbox"/> Safety/Efficacy <input type="checkbox"/> Efficacy <input type="checkbox"/> Bio-equivalence	<input type="checkbox"/> Bio-availability <input type="checkbox"/> Pharmacokinetics <input type="checkbox"/> Pharmacokinetics/dynamics <input type="checkbox"/> Pharmacodynamics
Number of arms	1	
Medical device used	EZ Cure™ Resorbable Collagen Membrane (CE 0123)	
Studied component	<input type="checkbox"/> Drug (including placebo) <input type="checkbox"/> Radiation <input checked="" type="checkbox"/> Device <input type="checkbox"/> Behavioral	<input type="checkbox"/> Biological / vaccine <input type="checkbox"/> Genetic <input type="checkbox"/> Procédure / surgery <input type="checkbox"/> Dietary supplement

	<input type="checkbox"/> Other
Classification of the study	<p>Category 3 : Non-interventional study.</p> <p>This clinical investigation is prospective, multicentric and non-comparative. The study is classified as category 3 according to the Jardé Law (French Law relative to the Clinical Research Involving Human Persons) and thus is qualified as “non-interventional”.</p> <p>Indeed, according to the terms of the protocol established in collaboration with the stakeholders, this research will be carried out on a CE-marked device (CE 0123) and does not involve any risk or constraint since all the procedures will be performed and the products used in a usual way, without any additional or unusual diagnostic, treatment or monitoring action.</p>
Intervention description	<p>Covering oral-maxillofacial or a periodontal defects with the Resorbable Collagen Membrane in order to avoid epithelial cell infiltration and to promote periodontal tissues healing.</p> <p>Covering alveolar bone defects after tooth-teeth extraction.</p>
Surgical technique	Covering oral-maxillofacial or periodontal or alveolar bone defects with a RCM after filling or not the defect with a bone filling material.
Primary outcome measure	Evaluation of performance of the RCM in terms of periodontal tissue regeneration by the observation of mucosa health in terms of swelling, wound closure and colour of the implantation site.
Time points at which primary outcome measure is assessed	<ul style="list-style-type: none"> - 1 week post-surgery (± 2 days) - 2 weeks post-surgery (± 2 days) - 12 weeks post-surgery (± 1 week)
Secondary outcomes measures	<ul style="list-style-type: none"> - Evaluation of safety of the RCM by the record of any adverse event during follow-up, especially the one mentioned in the Instructions For Use (IFU) such as post-operative infections, discomfort, irritation, fever, inflammatory reaction and allergy. - Radiographic examination of periodontal tissues.
Time points at which the secondary outcomes measures are assessed	<p><u>Safety data:</u></p> <p>From screening through visit at 12 weeks (± 1 week).</p> <p><u>X-Rays measurements:</u></p> <ul style="list-style-type: none"> - Pre-surgery - 12 weeks post-surgery (± 1 week)
Inclusion criteria	<ul style="list-style-type: none"> - Male or female aged from 18 to 70 - Periodontal defects (e.g. cyst, bone tumour, crest augmentation...) - Alveolar bone defect after tooth (teeth) extraction - Non Opposition form (consent of the patient) - Patients affiliated to the French social security - Patients not under guardianship or judicial protection
Exclusion criteria	<ul style="list-style-type: none"> - Pregnancy or breastfeeding women - Severe smoker (>10 cigarettes per day) [13] - Acute infections - Allergies to the material (if an allergy of any kind is suspected, adequate exams must be carried out in advance) - Refusal of the patient to adhere to surgical follow-up and to the limit in

	<p>activity level</p> <ul style="list-style-type: none"> - Fever and/or local inflammation - HIV positive known - History of uncontrolled diabetes (untreated or not stabilized by treatment) - History of treatments for previous corticosteroids, long-term (more than 6 months) and interrupted for less than 3 months - History of chemotherapy in progress or during the last three months - History of cervico-facial radiotherapy - History of bone disease with disorders of blood circulation which is defined as Albers-Schönberg disease or Paget's disease - Known severe hyperparathyroidism - History of severe immune deficiency
Study size	<p>A sample size of 50 patients would give with 95% confidence interval a precision of $\pm 8.3\%$.</p> <p>Accounting for a maximum of 10% of dropouts or missing data, 56 patients should be recruited in the cohort.</p>
Duration of the research	<ul style="list-style-type: none"> - Duration of the inclusion period: 18 months - Duration of follow-up per participant: 12 weeks (± 1 weeks) - Total duration of the research project: 22 months
Statistical analysis of the data	<p>A Statistical Analysis Plan (SAP) will be written by the Biostatistician of the CRO in charge of the study. This document will be approved and signed by the Sponsor, the Coordinating Investigator and the clinical expert before the first database lock.</p> <p>All data will be presented using descriptive statistics.</p> <p>An interim analysis is planned in this study protocol in order to obtain the first results for December 2019.</p> <p>Quantitative or ordinal variables will be described by the number of values entered, the number of missing data, the mean, the standard deviation, 95% confidence interval (CI) of the mean, the median, the 1st and 3rd quartiles, the minimum and the maximum.</p> <p>Qualitative variables will be described by the number of data filled in, the number of missing data, the frequency and the percentage of each modality. The 95% CIs of the percentages will be performed using exact confidence limits method.</p> <p>The medical and surgical histories and adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).</p> <p>The primary efficacy endpoint is the mucosa aspects reported by swelling, wound closure and colour. The composite primary endpoint will be described using descriptive statistics. Sensitivity will be analysed using different analyses sets and missing data handling as described in section "Missing values / dropouts". The Per-Protocol (PP) analysis will be considered as confirmatory analysis.</p>

	<p>Adverse Events (AEs) will be classified according to period of occurrence: pre-treatment AEs, Treatment-emergent Emergent AEs (TEAEs).</p> <p>TEAEs will be summarized and detailed by:</p> <ul style="list-style-type: none"> - seriousness, - intensity, - action taken with trial medication, - other action taken, - relationship to study treatment, - severity according to the relationship with patient identifications <p>The number/frequency of patients with each TEAE will be displayed by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA classification.</p> <p>All serious adverse events (SAEs) will be listed separately with the same information that the TEAE.</p> <p>All individual data will be presented in listings.</p> <p>The statistical analysis will be performed using SAS® or equivalent software.</p> <p>No sub-group analysis is planned.</p> <p>The radiographic analysis of periodontal tissues will be reviewed and analyzed by the clinical expert and the coordinating investigator. These data will be recorded in the electronic case report form (eCRF). The description of the radiographic analyses and the presentation of these results will be in a separate document from the statistical report produced by the CRO.</p>
Expected impacts	<p>This study will confirm the ability of the RCM, EZ Cure™, to promote Guided Tissue Regeneration within 12 weeks in oral maxillo facial and periodontal defects, alveolar pockets after tooth (teeth) extraction and its acceptable benefit/risk balance.</p>
Keywords	<p>Periodontal defects, alveolar bone preservation, collagen membrane, mucosa healing</p>

II. SCIENTIFIC JUSTIFICATION

II.1. INTRODUCTION

Collagen membranes have been used worldwide for 20 years in different periodontal applications. Their biocompatibility has been proven thanks to in vitro, in vivo and long lasting use in clinical cases. They have been well described in Guided Bone Regeneration (GBR) and Guided Tissue Regeneration (GTR) procedures and their resorption properties lead to good tissue healing in periodontal surgery. These collagen membranes are safe when following manufacturers' instructions for use.

The Resorbable Collagen Membrane (RCM), manufactured by BIOMATLANTE SA, is an improvement of the generation of collagen membrane used in soft tissue wound healing management during GTR and GBR procedures. Its performance and safety were already assessed in GTR and GBR procedures in the case of periodontal and oral/maxillofacial bone defects. The clinical evidence demonstrates conformity of the RCM (EZ Cure™ – CE0123) with the relevant essential requirements.

In order to improve the clinical data on the device, the manufacturer decided to assess the performance and safety of its RCM during the post-market phase in the same indications and for the same intended use.

II.2. CURRENT STATE OF KNOWLEDGE

One review from Cochrane Library analysed the main strategies currently used to address the issue of guided tissue regeneration GTR or GBR in periodontal defects:

“Guided tissue regeneration for periodontal infra-bony defects”. Review Intervention

Ian Needleman, Helen V Worthington, Elaine Giedrys-Leeper, Richard Tucker

Cochrane Oral Health Group. DOI: 10.1002/14651858.CD001724.pub2View/save citation

Background

Restoration of large bone defects remains a great issue due to the insufficient supply of horizontal and/or vertical bone at implant sites [1,9]. Meanwhile, the infiltration of non-osteogenic tissue at those sites also hinders bone regeneration process [6]. To overcome these obstacles, different approaches, including bone-grafting techniques, alveolar distraction, and guided bone regeneration have been implemented to allow the implant to be fully integrated and maintained during functional loading [2, 4, 16]. Among them, utilization of materials to prevent the entry of non-osteogenic tissue and allow exclusively osteogenic cells to repopulate the defect is one of the most commonly used strategies [7, 15].

A barrier membrane needs to be biocompatible and acts as temporary matrice to facilitate cell proliferation, vascularization, and extracellular matrix deposition in addition to transport nutrition, enable bone cell penetration and support bone tissue formation [8, 14, 19]. The device should also possess adequate mechanical properties such as sufficient rigidity to endure the compression of overlying soft tissue while maintaining a certain degree of plasticity to adapt to the shape of defective site. Barrier membrane can be classified into two types including non-resorbable and resorbable membranes [9]. Comparing these two types, bioresorbable membranes are more advantageous since no second surgery for membrane removal is required, the cost-effectiveness profil is suitable and the patient morbidity is reduced [7].

Conventional treatment of destructive periodontal (gum) disease arrests the disease but does not usually allow the recovery of the bone support or connective tissue lost in the disease process. Guided Tissue Regeneration (GTR) is a surgical procedure that specifically aims to regenerate the periodontal tissues when the disease is advanced and could overcome some of the limitations of conventional therapy. In addition of the evaluation of mucosa healing (clinical observation, mucosa attachment, inflammation etc...), the height of the alveolar crest (in periodontal disease comparison of the depth of the pocket before surgery and after several months) was also measured [21]. Same measurment was realized for alveolar socket after tooth (teeth) extraction.

Search methods

We conducted an electronic search of the Cochrane Oral Health Group Trials Register, MEDLINE and EMBASE up to April 2004. Handsearching included Journal of Periodontology, Journal of Clinical Periodontology, Journal of Periodontal Research and bibliographies of all relevant papers and review articles up to April 2004. In addition, we contacted dental surgeons and experts/groups/companies involved in surgical research to find other trials or unpublished material or to clarify ambiguous or missing data and posted requests for data on two periodontal electronic discussion groups.

Selection criteria

Patients with periodontal defects, tooth (teeth) extraction or other maxillofacial bone defects (e.g. cyst, bone tumour, crest augmentation...) requiring a Guided Tissue Regeneration (mucosa and bone) with a membrane. Patients having good oral hygiene, and accepting the standard post-operative survey. The standard surgical procedure is open flap debridement for the treatment of periodontal infra-bony defects. Furcation involvements and studies specifically treating aggressive periodontitis were excluded.

Data collection and analysis

Screening of possible studies and data extraction was conducted independently. The methodological quality of studies was assessed in duplicate using individual components and agreement determined by Kappa scores. Methodological quality was used in sensitivity analyses to test the robustness of the conclusions. The Cochrane Collaboration statistical guidelines were followed and the results expressed as mean differences (MD and 95% CI) for continuous outcomes and risk ratio (RR and 95% CI) for dichotomous outcomes calculated using random-effects models. Any heterogeneity was investigated.

In complement, the sub group (membrane used alone), has been analyzed and compared to the second sub group (membrane and bone void filler used together).

Main results

The search produced 626 titles, of these 596 were clearly not relevant to the review. The full texts of 32 studies of possible relevance were obtained and 15 studies were excluded. Therefore, 17 studies were included in this review, 16 studies testing GTR alone and two testing GTR with bone substitutes (one study had both test treatment arms).

No tooth loss was reported in any study although these data are incomplete where patient follow up was not complete. For attachment level change, the mean difference between GTR and Open Flap Debridement (OFD) was 1.22 mm (95% CI Random Effects: 0.80 to 1.64, Chi2 for heterogeneity 69.1 (df = 15), $P < 0.001$, $I^2 = 78\%$) and for GTR with bone substitutes was 1.25 mm (95% CI 0.89 to 1.61, Chi2 for heterogeneity 0.01 (df = 1), $P = 0.91$). GTR showed a significant benefit when comparing the numbers of sites failing to gain 2 mm attachment with risk ratio 0.54 (95% CI Random Effects: 0.31 to 0.96, Chi2 for heterogeneity 8.9 (df = 5), $P = 0.11$). The number needed to treat (NNT) for GTR to achieve one extra site gaining 2 mm or more attachment over OFD was therefore 8 (95% CI 5 to 33), based on an incidence of 28% of sites in the control group failing to gain 2 mm or more of attachment. For baseline incidences in the range of the control groups of 3% and 55% the NNTs are 71 and 4.

Probing depth reduction was greater for GTR than OFD: 1.21 mm (95% CI 0.53 to 1.88, Chi2 for heterogeneity 62.9 (df = 10), $P < 0.001$, $I^2 = 84\%$) or GTR with bone substitutes, weighted mean difference 1.24 mm (95% CI 0.89 to 1.59, Chi2 for heterogeneity 0.03 (df = 1), $P = 0.85$).

For gingival recession, a statistically significant difference between GTR and OFD controls was evident (mean difference 0.26 mm (95% CI Random Effects: 0.08, 0.43, Chi2 for heterogeneity 2.7 (df = 8), $P = 0.95$), with a greater change in recession from baseline for the control group.

Regarding hard tissue probing at surgical re-entry, a statistically significant greater gain was found for GTR compared with OFD. This amounted to a weighted mean difference of 1.39 mm (95% CI 1.08 to 1.71, Chi2 for heterogeneity 0.85 (df = 2), P = 0.65). For GTR with bone substitutes the difference was greater, with mean difference 3.37 mm (95% CI 3.14 to 3.61).

Adverse effects were generally minor although with an increased treatment time for tissues regeneration. Exposure of the barrier membrane was frequently reported with a lack of evidence of an effect on healing.

Concerning more specifically the rate of failure in GTR, clinical publications concerning the use of resorbable membrane, generally in association with bone substitute grafting for filling the defect, can be cited. Merli et al [12] report an analysis of 65 full text articles: they report only one publication with 396 patients and all the others concerned limited sample size studies. All these studies report successful results for tissue regeneration at implant dehiscences and fenestration with membranes for GTR.

Several articles specifically report a failure in tissue regeneration, with RCM covering the defect to assure barrier effect, cells of bacterial infiltration, promoting the mucosa regeneration and protecting the bone ingrowth under the membrane. The following studies report similar success :

Publication	Percentage of soft tissue healing
<i>Wessing et al [20]</i>	100 %
<i>De Angelis et al [3]</i>	88.5 %
<i>Felice et al [5]</i>	100 %
<i>Merli et al [11]</i>	100 %
<i>Taschieri et al [17]</i>	81.2 %
<i>Taschieri et al [18]</i>	89.5 %
<i>Meloni et al [10]</i>	87 %

Table 1 Justification of the percentage of soft tissue healing

Authors' conclusions

GTR has a greater effect on probing measures of periodontal treatment than OFD, including improved attachment gain, reduced pocket depth, less increase in gingival recession and more gain in hard tissue probing at re-entry surgery. However there is marked variability between studies and the clinical relevance of these changes is unknown.

There is therefore little value in future research repeating simple, small efficacy studies. The priority should be to identify factors associated with improved outcomes as well as investigating outcomes relevant to patients. Types of research might include large observational studies to generate hypotheses for testing in clinical trials, qualitative studies on patient-centred outcomes and trials exploring innovative analytic methods such as multilevel modelling. Open flap surgery should remain the control comparison in these studies.

Methological issues

1. The aim of main studies was to evaluate the efficacy of the whole procedure of tissue reconstruction in periodontal surgery: surgery strategy + bone substitute + collagen membrane. Thus, it is quite difficult to certify that the obtained results can be extended to the collagen membrane alone: the success is charged to the whole procedure in which the collagen membrane takes its part. Knowing this limitation, all studies were used for the performance analysis.
2. The articles were analyzed only if the use of a collagen membrane in these strategies was clearly indicated. Even if the final outcome was not to assess safety the collagen membrane per se, the absence of complications related to the strategy can be extended to the use of the collagen membrane as well. Thus, all studies were kept in the safety analysis.
3. The minimal clinical follow up taking into account soft tissue healing was 3 months to have reliable data.
4. Most of the studies have been conducted following the best required methodology (prospective randomized study, or prospective comparative study) to assess performance and safety of a product (level I). The other prospective and retrospective (clinical cases) studies (level II & III) are less appropriate because of the lack of methodological design (no comparison) and only descriptive statistics (or unique case), but the most interesting informations were kept in the clinical review.
5. Split mouth approach was often used to compare different approaches within the same patient and to increase the number of cases in the same study.
6. Moreover, in periodontal applications, main results concern radiological and histological assessments that are not clinical outcomes; it is the most usual way to address this question in these indications.

II.3.STUDY HYPOTHESES

Based upon previous data collected in the literature [3, 5, 10, 11, 17, 18] and previous experience with the Biomatlante RCM, the hypothesis that justifies this research is that 90% of the patients who will undergo GTR and/or GBR involving the RCM in oral/maxillofacial defects will show tissue regeneration at 12 weeks after surgery, as assessed by observation of :

- Tissue regeneration (mucosa health on the implantation site)
- Safety report on any adverse event
- Height preservation of the alveolar crest

II.4.JUSTIFICATION OF METHODOLOGY CHOICES

Regarding:

- the number of RCM units commercialized,
- the ability of the centers to recruit and appropriately record follow-up data,
- the previous data about the principal criterion,
- the follow-up duration of the patients

The sponsor expects that a prospective observational study will allow gathering the data required in terms of performance, and safety in a 22 months delay.

II.5.EXPECTED IMPACTS

This study will confirm the performance and safety of the RCM in periodontal defects and its acceptable benefit/risk balance.

III. OBJECTIVES

III.1. MAIN OBJECTIVE

The main objective of this study is to observe performance of the RCM in terms of periodontal tissue regeneration by the observation of mucosa health in terms of swelling, wound closure and colour of the implantation site

III.2. SECONDARY OBJECTIVES

The secondary objectives are:

- Evaluation of the safety of RCM by recording all the adverse events during the follow-up
- Evaluation of the radiographic analysis of periodontal tissues

IV. STUDY DESIGN

IV.1. CLASSIFICATION OF THE STUDY

This clinical investigation is prospective, multicentric, single arm and non-comparative.

The study is classified as category 3 according to the Jardé Law (French Law relative to the Clinical Research Involving Human Persons) and thus is qualified as “non-interventional”.

Indeed, according to the terms of the protocol established in collaboration with the stakeholders, this research will be carried out on a CE-marked device (CE 0123) and does not involve any risk or constraint since all the procedures will be performed and the products used in a usual way, without any additional or unusual diagnostic, treatment or monitoring action.

IV.2. RESEARCH PROJECT AGENDA

- Duration of the inclusion period: 18 months
- Duration of follow-up per participant: 12 weeks (± 1 week)
- Total duration of the research project: 22 months

IV.3. SUMMARY TABLE OF PARTICIPANT FOLLOW-UP

	Pre-inclusion V -1	Inclusion V 0	Visit V 1 At 1 week	Visit V 2 At 2 weeks	Visit V 3 At 12 weeks
	-1 month to Day 0	Day 0	± 2 days	± 2 days	± 1 week
Full information and non-opposition	✓				
Inclusion / Exclusion criteria	✓				
Demographic data ^(a)	✓				
Life habits (smoker)	✓				
Relevant medical and surgical histories	✓				
Periodontal clinical examination ^(b)	✓				
PROCEDURE					
Batch		✓			
Clinical indication		✓			
Usability		✓			
CLINICAL EXAM					
Control of tissue regeneration ^(c)		✓	✓	✓	✓
Membrane performance ^(d)			✓	✓	✓
SAFETY					

	Pre-inclusion V -1	Inclusion V 0	Visit V 1 At 1 week	Visit V 2 At 2 weeks	Visit V 3 At 12 weeks
	-1 month to Day 0	Day 0	± 2 days	± 2 days	± 1 week
Adverse events recording	✓ <-----> ✓				
X-RAY					
Probing Pocket Depth (PPD)	✓*	✓*			✓
Clinical Attachment Level (CAL)	✓*	✓*			✓

(a) Demographic data: age, sex

(b) Periodontal clinical examination: in accordance with the current practice (e.g. Probing Pocket Depth (PPD) using sensor and search for gingival inflammatory signs)

(c) Control of tissue regeneration: swelling, wound closure, colour of the implantation site

(d) Membrane performance: barrier effect, membrane exposition

* X-Ray performed at pre-inclusion or inclusion visit (before the surgery)

IV.4. INFORMATION TO PARTICIPANTS

During pre-inclusion visit, the Investigator (a qualified individual) will ask the participant and/or the legal guardians/legal representative to participate in the research project and provide him/her/them with information regarding:

- The objective, the description of the surgery and,
- The automatic processing of participant-related data that will be collected during the research project, and shall also specify the participant's right to access, object to, or rectify the data.

The Investigator will also ensure that the eligibility criteria are met. If a person agrees to participate, he or she will sign the consent form included at the end of the patient information sheet. His or her non-opposition to data use will be recorded and stored in his or her medical file. The participant may, at any moment, oppose the use of his or her data as part of the research.

IV.5. FOLLOW-UP VISITS

- V -1, pre-inclusion visit (-1 month to Day 0):
 - Signature of the written consent
 - Inclusion / Exclusion criteria
 - Demographic data
 - Life habits: smoker
 - Relevant medical and surgical histories
 - X-Ray

- Periodontal clinical examination
- V 0, inclusion visit:
 - X-Ray (Pre-surgery, if not performed at pre-inclusion visit)
 - Periodontal surgery, tooth extraction, alveolar filling
 - Evaluation of product stability and usability
 - Safety evaluation by the record of any adverse event
- V 1 and V 2 at 1, 2 weeks post-surgery (± 2 days):
 - Control of soft tissue regeneration
 - Membrane performance
 - Safety evaluation by the record of any adverse event

IV.6. END OF RESEARCH PROJECT VISIT

- V 3 at 12 weeks (± 1 week):
 - Control of soft tissue regeneration
 - Membrane performance
 - X-Ray
 - Safety evaluation by the record of any adverse event

V. STUDY POPULATION

V.1.INCLUSION CRITERIA

- Male or female aged 18 to 70
- Periodontal defects (e.g. cyst, bone tumour, crest augmentation...)
- Alveolar bone defect after tooth (teeth) extraction
- Non Opposition form (consent of the patient)
- Patients affiliated to the French social security
- Patients not under guardianship or judicial protection

V.2.EXCLUSION CRITERIA

- Pregnancy or breastfeeding women
- Severe smoker (>10 cigarettes per day)

- Acute infections.
- Allergies to the material (if an allergy of any kind is suspected, adequate exams must be carried out in advance)
- Refusal of the patient to adhere to surgical follow-up and to the limit in activity level
- Fever and/or local inflammation
- HIV positive known
- History of uncontrolled diabetes (untreated or not stabilized by treatment)
- History of treatments for previous corticosteroids, long-term (more than 6 months) and interrupted for less than 3 months
- History of chemotherapy in progress or during the last three months
- History of cervico-facial radiotherapy
- History of bone disease with disorders of blood circulation which is defined as Albers-Schönberg disease or Paget's disease
- Known severe hyperparathyroidism
- History of severe immune deficiency

V.3. FEASIBILITY AND RECRUITMENT PROCEDURES

Coordinating Investigator

Dr. Said Kimakhe, PhD, Doctor of Dental Surgery (DDS) Associate professor Dental Faculty Nantes University Hospital, France.

Other Investigators

- Dr. Xavier Struillou, PhD, DDS, Associate professor Dental Faculty Nantes University Hospital, France.
- Dr. Philippe Lesclois, PUPH, PhD, DDS, Dental Faculty Nantes University Hospital, France.
- Dr Zahi Badran, PUPH, PhD, DDS, Dental Faculty Nantes University Hospital, France.

Centers involved in the clinical investigation

Two centers will be involved in the clinical study. They already use Biomatlante RCM for GBR and GTR in oral/maxillofacial bone defects:

	Center n°1: Dental Care Center - Nantes University Hospital	Center n°2 Private Dental Practice – Saïd Kimakhe
Principal Investigator	Dr. Saïd Kimakhe	Dr. Saïd Kimakhe
Investigators	Dr. Xavier Struillou	
	Dr. Philippe Lesclois	
	Dr Zahi Badran	

Each center will perform treatment in oral maxillofacial defects and will participate to patient recruitment during the whole study. The patients will be recruited during the consultations.

V.4.ACTIONS UPON PATIENT WITHDRAWAL

If a patient withdraws prematurely from the study, study personnel should make every effort to complete the full panel of assessments scheduled until the 12-week visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant adverse event, which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

VI. STUDY INTERVENTION

VI.1. DEVICE DESCRIPTION

This medical device is a Resorbable Collagen Membrane intended for use in Guided Tissue Regeneration or Guided Bone Regeneration procedures.

The Resorbable Collagen Membrane is crosslinked according to a controlled manufacturing process in accordance with current standards. Type I and III collagen fibres are extracted from the porcine epidermis and purified.

The Resorbable Collagen Membrane is hydrophilic and provides a barrier function for 12 weeks to prevent colonization of the surgical site by cells of connective and epithelial tissues.

The Resorbable Collagen Membrane allows the diffusion of biological fluids for a total resorption in 24 weeks.

The Resorbable Collagen membrane is easy to handle. Flexible, it adapts perfectly to all bone geometries.

The Resorbable Collagen Membrane is available in several dimensions: 15x25mm, 20x30mm and 30x40mm.

VI.2. INTENDED USE

The Resorbable Collagen Membrane is intended for use in Guided Tissue Regeneration or Guided Bone Regeneration procedures.

The claimed performance of the Resorbable Collagen Membrane is as follows: a barrier function that prevents the colonization of bone defect by connective and epithelial tissues.

VI.3. SURGICAL INTERVENTION

The Resorbable Collagen Membrane is indicated for the treatment of oral and maxillofacial bone defects and in periodontal diseases. This membrane is exclusively reserved for adults. It has not been tested on pregnant or breastfeeding women.

During this study, the investigators' practices will not be modified. For each type of surgery, the surgeon will perform all his acts in accordance with his current practice, without adding any additional procedure.

The Resorbable Collagen Membrane should be handled in accordance with the manufacturer's recommendation using gloves and/or sterile instruments. This membrane can be cut to the appropriate shape and can be used directly or previously hydrated to facilitate its handling, especially when the surgeon intends to shape or fold the membrane at the implantation site.

The Resorbable Collagen Membrane can be sutured for better immobilization. The manufacturer recommends that the implant site be completely closed to avoid exposure of the Resorbable Collagen Membrane.

VI.4. CONTRAINDICATIONS

- Acute infections
- Known collagen allergies (if any type of allergy is suspected, adequate tests should be performed in advance)
- Fever and/or local inflammation

VI.5. AUTHORIZED OR FORBIDDEN TREATMENTS AND PROCEDURES

No prior or concomitant medication will be prohibited.

VII. STUDY ASSESSMENTS AND PROCEDURES

VII.1. MAIN EVALUATION CRITERION

This principal objective is to observe the performance of the RCM at 1, 2 and 12 weeks post surgery in terms of tissue regeneration. It will be assessed by the evaluation of mucose health on the implantation site at the different times of follow-up. The mucosa aspects that will be reported are the following: swelling, wound closure and colour.

- Swelling is defined by the presence of one or more swellings in the wound. The total absence of swelling at 12 weeks will be considered as the efficacy endpoint. This swelling is assessed subjectively by the investigator with the naked eye or by photography.
- Mucosal healing is characterized by wound closure. Complete wound closure will be considered as the efficacy criterion. This wound closure is assessed subjectively by the investigator with the naked eye or by photography.
- The colour at the implantation site can take on 3 aspects: pink - identical to the surrounding mucosa - Red. Pink colours and identical to the surrounding mucosa will be considered as the efficacy criteria. This colour is assessed subjectively by the investigator with the naked eye or by photography.

VII.2. SECONDARY EVALUATION CRITERIA

The secondary objectives are to evaluate the safety of the RCM during the 12 weeks follow-up and evaluate the radiographic analysis of periodontal tissues.

The evaluation of the safety will be conducted by recording all the adverse events from screening through the 12-week visit (12 weeks \pm 1 week).

The evaluation of the radiographic analysis of periodontal tissues will be performed before the surgery and at the 12 weeks post-surgery visit.

The details of this evaluation are the following :

- The radiographic examination is a decisive act in the establishment of the periodontal diagnosis.
- Retroalveolar plates should be used with the long cone technique.
- The necessary equipment is a 70 to 90 kv (Kilovolts) generator equipped with a long cone, Rinn angulators to parallel the film to the major axis of the tooth and standard size films for the premolar, molar and pedodontic areas for the anterior areas.
- A complete periodontal check-up includes 1 to 2 standard pictures for the premolar and molar areas of each hemiarcade, 3 to 5 pedodontic pictures for the upper and lower anterior areas and 1 to 2 “bite wing” pictures on each side.
- The interpretation of this radiographic assessment allows to make a precise examination of dental and periodontal structures.
- To examine and reassess a specific defect, the radiographic examination with a resin bite can be standardized on the Rinn angulator to reproduce the incidence.

In this study, the radiographic examination is performed in order to:

- Assess the Probing Pocket Depth (PPD): it corresponds to the distance between the top of the marginal gingiva and the bottom of the pocket
- Assess the Clinical Attachment Level (CAL): it corresponds to the distance between the enamel-cementum junction and the bottom of the pocket.

For a better reproducibility of the results, the radiographies will be recorded in the eCRF and the analysis of the radiographies will be carried out by the coordinating investigator, Dr. Saïd Kimakhe in association with the scientific expert Guy Daculsi.

The description of the radiographic analyses and the presentation of these results will be in a separate document from the statistical report produced by the CRO.

VII.3. MANAGEMENT OF ADVERSE EVENTS AND NEW FACT

The investigator records the adverse events or abnormal analysis results defined in the protocol as determinants for the safety assessment, keeps a documentary record and notifies the sponsor.

The investigator informs the sponsor of all adverse events that occurred in the participants.

VII.3.1. DEFINITION OF ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a medical device, which does not necessarily have a causal relationship with this device. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the eCRF.

Adverse events will be monitored and documented from the time of informed consent to the end of study participation. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with the signing of informed consent, investigators should make an assessment for adverse events at each visit and record the event on the adverse event on the eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, transfusion) should be recorded as an adverse event.

Any medical condition already present at the time of screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

VII.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death: AE causes or contributes to the death;
- A life-threatening adverse event: AE places the subject at immediate risk of death; it does not refer to AE which hypothetically might have caused death if it were more severe;
- Requires hospitalization or prolongation of existing hospitalizations: AE requires at least an overnight admission or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (i.e. plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion;
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect;
- An important medical event: AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

VII.3.3. CLASSIFICATION OF AN ADVERSE EVENT

VII.3.3.1. SEVERITY OF EVENT

The severity of AEs must be assessed by the Investigator according to the following definitions. The term “severity” is used to describe the intensity of a specific event. This has to be distinguished from the term “serious”.

- Mild: Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

VII.3.3.2. RELATIONSHIP TO STUDY PRODUCT

The clinician must always determine the relationship between all adverse events and the investigated medical device by examining and evaluating the participant on the basis of temporal relationship between the AE and application of the device and his/her clinical judgment. In a clinical trial, the investigated medical device must always be suspected. The degree of certainty about causality will be graded using the categories below:

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related:** The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician

VII.3.3.3. EXPECTED ADVERSE EVENTS

The most frequent adverse events expected from RCM observed in patients are:

- Post-operative infection
- Discomfort
- Irritation
- Fever
- Inflammatory reaction
- Allergy

Some side effects may be treated with medication or require reoperation.

VII.3.4. ADVERSE EVENTS REPORTING

Complete and accurate data on all AEs experienced for the duration of the reporting period, will be reported in the eCRF.

It is important that each AE report includes a description of the event, whether it is considered serious, its duration (onset and resolution dates), its severity, its relationship to the investigational product, any other potential causality factors, any treatment given or other action taken and its outcome.

As defined in Article R5212-17 of the French Public Health Code, all incident or risk of incident resulting from the use of a medical device brought to the investigator's attention will be the subject of a spontaneous report from the investigator to the local vigilance correspondent on whom he depends or, failing that, to the French National Agency for the Safety of Health Products (Agence Nationale de Sécurité et du Médicament = ANSM) in accordance with the usual procedures in force.

These declarations should be addressed at :

Direction de la surveillance – Plateforme de réception et d'orientation des signalements

E-mail: materiovigilance@ansm.sante.fr

Fax: 01.55.87.37.01

All AEs occurring from the time of informed consent until end of study participation must also be reported to the Sponsor.

All AEs that the Investigator considers related to the medical device occurring after the end of study participation must be reported to the Sponsor.

To report the AE, the AE form can be filled. When the form is completed, signed and dated, it must be sent to the Sponsor, specifically to the vigilance contact:

Vigilance contact :

Nancy TRICHEREAU

Quality Assurance Manager

E-mail: materiovigilance@biomatlante.com

Phone: 06.21.90.58.43

Immediately after receiving the follow-up information, the Investigator must update the AE form and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to the Sponsor.

For any research involving the human, where an unexpected serious adverse reaction or a new fact relevant to the research or product under investigation is likely to prejudice to the safety of the appropriate persons, the proponent and the Investigator shall take appropriate urgent safety measures.

VII.3.5. NEW FACTS REPORTING

A new fact is defined as any new safety data which may lead to a reassessment of the relationship between the benefits and risks balance of the research or the product being investigated, changes in the use of the product, the conduct of the research or documents relating to the search, or to suspend or interrupt or modify the protocol of the search or similar searches. (R.1123-46 of the French Public Health Code).

In the case of a new medical fact, the Sponsor, will be responsible for reporting new facts to the authorities in accordance with national regulations, as follows:

- Inform without delay the ANSM about the new medical fact, at the following email address: aec-essaiscliniques@ansm.sante.fr with the following subject: Fait nouveau / trial number/ international non-proprietary name (INN) or substance code and including:
 - - ID-RCB N°,
 - - Title of the study protocol,
 - - Protocol code number,
 - - Summary of the new fact and urgent safety measures implemented if necessary,
 - All relevant information for the evaluation of the new fact.
- Inform without delay the director of the Agence Régionale de Santé (ARS; regional health agency) and the Ethical Committee (CPP).

Any follow-up information with regards to the new safety medical fact will be reported to the regulatory authorities within 8 calendar days, and details regarding the urgent safety measures set up will be sent within 15 days to the regulatory authorities.

VIII. STATISTICAL ASPECTS

VIII.1. SAMPLE SIZE DETERMINATION

As the study is descriptive, the calculation of study size is not calculated based on considerations relating to formal hypothesis tests. The required number of patients is calculated to guarantee that the endpoints associated with the main objective of the study could be estimated with sufficient precision.

The choice of a target of 90% of patients with tissue and bone regeneration at 12 weeks post-surgery is based on an estimation of the kinetics of reconstruction according to the literature (similar products resorbable membrane but with or without filling with different bone substitute) [3, 5, 10, 11, 17, 18, 20]. The score will be from 88.8% to 100% with follow-up from 4 to 12 months (due to evaluation of the bone void filler and not only the collagene membrane).

For the primary endpoint of effectiveness as measured by the performance of the RCM (binary endpoint) with a 90% target frequency (as hypothesized) and a confidence level of 95%, the following precisions can be achieved. The calculation was made using SAS®.

Precision	Target frequency of performance	Number of patients to evaluate	Number of patients to recruit
8.3%	90%	50	56
6.8%	90%	75	83
5.9%	90%	100	111
5.3%	90%	125	139
5.0%	90%	150	165

Table 2 Sample size determination

With 50 patients, a precision around 8.3% can be achieved.

Accounting for a maximum of 10% dropouts or missing data, 56 patients should be recruited in the cohort.

VIII.2. ANALYSIS SETS

Four populations will be defined:

- Screened population will include all patients entering the study,
- Safety Set (SS) population will include all patients who received the RCM product,
- Full Analysis Set (FAS) efficacy population will include all patients who received the RCM product and in whom at least one efficacy information has been collected after the application of the RCM,
- Per-Protocol (PP) efficacy population will include all patients in FAS population without any major protocol deviation.

Remark: according to the ICH E9 recommendations, this subset of patients corresponds to a subset of the full “intention-to-treat” analysis set (including all randomized patients), being the full analysis set (FAS).

VIII.3. MISSING VALUES AND DROP-OUT

For the primary analysis (FAS analysis), a patient with missing data on the one of primary efficacy endpoint (swelling, wound closure or colour of the implantation site) will be considered as non efficacy of the product for this patient. Sensitivity analyses will be performed according to the following scenarios:

- No missing data will be imputed
- The missing data for the one of primary efficacy endpoint (swelling, wound closure or colour of the implantation site) will be considered as efficacy of the product.

VIII.4. STATISTICAL ANALYSIS

VIII.4.1. GENERAL CONSIDERATION

A Statistical Analysis Plan will be written by the biostatistician detailing the statistical analysis. The document will constitute the reference document as far as statistical analyses and methodologies are concerned. This document will be approved and signed by the Sponsor and the Principal Investigator before the first database lock.

The statistical analysis will be performed on SAS® version 9.4 or later (or equivalent statistical software).

Quantitative variables will be described by the number of values entered, the number of missing data, the mean, the standard deviation, the 95% CIs for the means, the median, the 1st and 3rd quartiles, the minimum and maximum.

Qualitative variables will be described by the number of data filled in, the number of missing data, the frequency and the percentage of each modality. The 95% CIs of the percentages will be performed using exact confidence limits method.

All variable in the database will be described using descriptive statistics and all individual data will be presented in listings.

An interim analysis is planned in this study protocol in order to obtain the first results for December 2019.

No sub-group analysis is planned.

VIII.4.2. ANALYSIS OF THE PRIMARY ENDPOINT

The primary endpoint analysis will be performed on FAS population. The primary endpoint will be analyzed on the PP population if the difference in the number of subjects between FAS and PP is more than 10%.

The primary efficacy endpoint is the mucosa aspects reported by swelling, wound closure and colour.

The composite primary endpoint will be summarized using descriptive statistics with binary outcome.

For patients who do not have swelling on the surgical site, with a complete wound closure on the surgical site and pink colour or identical colour to the surrounding mucosa on the surgical site, the investigational product will be considered as efficacious. If at least one of the primary endpoint performance is not satisfied, the investigational product will be considered ineffective for the patient.

Sensitivity analyses using different analyses sets and missing data handling as described above will be performed (see section “Missing values / dropouts”). The PP analysis will be considered as confirmatory analysis.

VIII.4.3. SAFETY ANALYSES

The safety analysis will be performed on SS population.

Safety endpoints will be AEs and SAEs all through the study.

AEs will be coded using MedDRA dictionary (latest version available). AEs will be classified according to period of occurrence: pre-treatment AEs and Treatment-Emergent AEs.

- Pre-treatment AEs are defined as adverse events occurring before the introduction of the investigational product.
- Treatment-Emergent AEs are defined as an adverse event that emerges after introduction of the investigational product having been absent pre-treatment, or worsens relative to the pre-treatment state.

AE reporting will focus on TEAEs. TEAE will be summarised and detailed using descriptive statistics by:

- seriousness,
- intensity,
- action taken with investigational product,
- other action taken,
- relationship to study treatment,
- severity according to the relationship with patient identifications

The number/frequency of patients with each TEAE will be displayed by System Organ Class and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) classification.

All SAEs will be listed separately with the same information that the TEAE.

VIII.4.4. RADIOGRAPHIC ANALYSIS

The radiographic analysis of periodontal tissues will be reviewed and analysed by the clinical expert and the coordinating investigator.

The radiographic data will be recorded in the eCRF. The description of the radiographic analyses and the presentation of these results will be in a separate document from the statistical report produced by the CRO.

VIII.4.5. BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics of demographics and other baseline characteristics will be presented on the FAS population.

VIII.4.6. RELEVANT MEDICAL AND SURGICAL HISTORIES

Relevant medical and surgical histories will be determined by the Investigator and will be describe on the FAS population.

Relevant medical and surgical histories will be coded using MedDRA dictionary (latest version available) and will be describe using descriptive statistics by:

- Number (percentages) of subjects with relevant medical histories
- Number (percentages) of relevant medical histories by subject
- Number (percentages) of relevant medical histories and number (percentages) of subjects with relevant medical histories by SOC
- Number (percentages) of relevant medical histories and number (percentages) of subjects with relevant medical histories by SOC and by PT

VIII.4.7. EXPLORATORY ANALYSES

For exploratory purposes, factors associated with improved performance such as age, relevant medical and surgical histories and life habits will be investigated using logistic regression.

VIII.5. PLANNED INTERIM ANALYSES

One interim analysis is planned in this study protocol in order to obtain the first results for December 2019.

This study is descriptive, no randomized, open-label and single arm, so no alpha inflation or adjusted p-value are to be considered.

VIII.6. SUB-GROUP ANALYSES

No sub-group analysis is planned

IX. DATA ACCESS RIGHTS AND SOURCE DOCUMENTS

BIOMATLANTE, sponsor of the research, is identified as the data processing controller. As a result, it must be in compliance and ensure that the data will be processed by the various research actors, in accordance with Law 78-17 of 6th January 1978 amended by Law 2014-344 of 17th March 2017, known as “Informatique et Libertés”, and the European Regulation 2016/679 of 27th April 2016 (known as “GDPR”).

IX.1. ACCESS TO DATA

Agreement to participate in the protocol means that the individuals carrying out the research will make documents and individual data that are strictly necessary to follow-up, quality control and audit available to the individuals who have a right to access these documents in accordance with applicable legal and regulatory provisions.

IX.2. SOURCE DATA

This includes all information contained in the original documents, or in authenticated copies of these documents, relating to clinical examinations, findings or other activities carried out as part of the research and necessary to the reconstitution and evaluation of the research. The documents in which source data are recorded are called source documents.

The source documents to be used will be:

- Medical patient file
- Clinical picture
- X-rays

IX.3. DATA CONFIDENTIALITY

In accordance with applicable legal provisions, individuals who have direct access to source data take all the necessary precautions to ensure the confidentiality of information relating to research, participants and particularly their identity, as well as the results obtained. These individuals, like the investigators and the person who performs data monitoring, are subject to the conditions of professional secrecy.

During the research project or at the end of it, the collected data on participants and data transmitted to the sponsor by the investigators (or any other involved specialists) will be codified. The data must not, under any circumstances, clearly indicate the names of the participants or their address.

Only the first letter of the name and surname of the subject will be recorded, together with a research-specific coded number indicating the order of inclusion of the subjects for each center.

The sponsor will ensure that each participant of the research project will be informed about access to data relating to him or her and strictly necessary for quality control.

IX.4. PSEUDONYMIZATION PROCEDURE

In the context of this study, the personal data of patients will be processed in order to meet the research objectives.

For this purpose, patient's medical data will be transmitted to the sponsor. For each patient, these data will be identified by the number attributed to the research center and the identification number of the patient.

The number attributed to the research center is attributed as follows:

- **Clinical center N°01** : Dental Care Center – Nantes University Hospital
- **Clinical center N°02** : Private dental practice – Dr S.Kimakhe

The patient identification number is attributed as follows:

- Number corresponding to the order of inclusion in the research center
- First letter of the patient's first name
- First letter of the patient's name

Center N°: _0 1_ Patient N°: _0_ _1_ _X_ _X_ <div style="text-align: center; margin-top: 5px;">Inclusion N°</div>
Investigator : _____

Only the investigators, their collaborators and the person responsible for the quality control of the data will have access to directly identifying data (name, date of birth, etc) via the correspondence table.

X. QUALITY CONTROL AND ASSURANCE

X.1.DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All information required by the protocol must be recorded in the electronic case report forms.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form derived from source documents should be consistent with the data recorded on the source documents. Clinical data will be entered directly from the source documents.

X.2. RESEARCH FOLLOW-UP

A Clinical Research Associate (CRA) will ensure research follow-up. The CRA will be responsible, under the Coordinating Investigator, for:

- Logistics and monitoring of the research;
- Providing reports on its progress and sharing them with the research stakeholders (sponsor, Methodology and Management Centre, etc.);
- Verifying the completeness of the case report forms (request for additional information, corrections, etc.);

The CRA will work in accordance with standard operating procedures, in collaboration with the research associate delegated by the sponsor.

X.3. QUALITY ASSURANCE AND QUALITY CONTROL

A CRA will visit each centre, during the implementation of the research, once or several times during the course of the research project, according to the monitoring plan defined for the research and the frequency of inclusions. The elements to be reviewed during these visits are defined by the monitoring plan. All visits will be subject to a written monitoring report. The sponsor will be in charge of the quality survey of the study.

Following written monitoring plan, the clinical research associate will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Manufacturing Practices).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

X.4. DATA MANAGEMENT

X.4.1. DATA HANDLING

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

X.4.2. COMPUTER SYSTEMS

Data will be processed using a validated computer system conforming to regulatory requirements.

X.4.3. DATA ENTRY

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

X.4.4. MEDICAL INFORMATION CODING

For medical information, the latest version at the time of study start of the Medical Dictionary for Regulatory Activities (MedDRA) for medical history and adverse events will be used.

X.4.5. DATA VALIDATION

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs panel for each patient will be electronically signed by the Investigator.

X.5. PROTOCOL DEVIATION

A protocol deviation is any non-compliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or manufacturer recommendation requirements. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site investigator to use continuous vigilance to identify deviations. All deviations must be reported in study source documents.

Examples of protocol deviations are presented below (non-exhaustive list):

- The membrane has not been installed,
- Violation of inclusion/non-inclusion criteria,
- Post-inclusion protocol violation,
- Non compliance with visit scheduled.

All protocol deviation will be listed before the data review meeting and reviewed during this meeting and classified as “minor” or “major”.

Number and frequency of patients with protocol deviations will be tabulated.

X.6. AUDIT AND INSPECTION

Individuals appointed by the sponsor and independent of those conducting the study may carry out audits at any moment. The audit is designed to check the safety of the participants and the respect of their rights, compliance with applicable regulations and data reliability.

An inspection may also be undertaken by a competent authority (ANSM in France or EMA within the framework of a European study, for example).

The audit, as well as the inspection, may be applied to any stage of the research, from protocol development to the publication of results and the classification of data used or produced as part of the research project.

The investigators shall comply with the sponsor’s requirements regarding the audit and the competent authority’s inspection of the research.

XI. ETHICAL AND REGULATORY CONSIDERATIONS

XI.1. COMPLIANCE WITH REFERENCE TEXTS

The sponsor and the investigators undertake to ensure that the research is conducted in compliance with Law no. 2012-300 on research involving human participants of 5 March 2012 and the Declaration of Helsinki (which can be found in its entirety on the website <http://www.wma.net>).

Data recorded during the course of the study will be subject to data processing at ATLANSTAT under Law no. 78-17 on information technology, files and freedoms of 6th January 1978, amended by Law no. 2004-801 of 6th August 2004.

This research project will be conducted according to the ISO 14155 : 2011 standard “Clinical Investigation of medical devices for human subjects – Good Clinical Practice”.

This research project will receive the positive endorsement of the CPP (Committee for the Protection of Persons – French equivalent of an Ethical Committee) and will be reported to the ANSM (the French National Agency for the Safety of Health Products).

This research project falls within the framework of the “Reference methodology” (MR-003). The Sponsor signed a commitment of compliance with this “Reference methodology”.

The research project will be registered on the website <http://clinicaltrials.gov/>

The research project will be registered in the European database EudraCT under ID-RCB number.

XI.2. AMENDMENTS TO THE PROTOCOL

Any substantial amendment, i.e. any amendment that may have a significant impact on the protection of persons, on the validity conditions and on the results of the research, on the quality and safety of tested products, on the interpretation of scientific documents that support the conduct of the research or on its conduct methods, is subject to a written amendment submitted to the sponsor; the latter must obtain, prior to implementing the amendment, a positive endorsement by the CPP.

Non-substantial amendments, i.e. those that do not have a significant impact on any aspect of the research project, shall be reported to the CPP for information purposes only.

All amendments are validated by the sponsor and all of the participants affected by the amendment, prior to submission to the CPP. This validation may require calling a meeting of all the committees set up for the research project.

All amendments to the protocol must be reported to the individuals carrying out the research, who shall commit to respecting their content.

XII. STORAGE OF DOCUMENTS AND DATA RELATING TO THE STUDY

The duration of the archiving period is defined by the sponsor according to the applicable procedures and regulations.

The patient data will be kept up to 2 years after the last publication of the research results, or, in absence of publication, until the final report of the research is written.

In accordance with the decree of 11th August 2008 fixing the period of storage by the sponsor and the investigator of documents and data relating to biomedical research other than that relating to medicinal products for human use, they will then be archived for a minimum period of 15 years.

Data processing operations of investigators and other professionals involved in the conduct of the research may not be stored for more than 5 years after the end of the last research in which the person participated. They will be then archived for a minimum period of 15 years.

XIII. RULES CONCERNING PUBLICATION

XIII.1. SCIENTIFIC COMMUNICATION

The analysis of data provided by the centres will be carried out by ATLANSTAT (except radiographic analyses, which will be performed by coordinating investigator and clinical expert). The analysis will result in a written report, submitted to the sponsor. This report will allow for the preparation of one or more publication(s).

Any written or oral communication of the results of the research project must receive prior approval of the investigator and, if applicable, of any committee set up for the research project.

The publication of the main results will mention the name of the Sponsor, of all the people who included or followed-up research participants, of methodologists, biostatisticians and data managers who participated in the research, of members of the committee(s) set up for the research project. The international rules for writing and publishing shall be taken into account (IMCJE's *Uniform Requirements for Manuscripts*, April 2010).

XIII.2. COMMUNICATION OF THE RESULTS TO PARTICIPANTS

Upon their request, participants will be informed of the overall results of the research projects explained in the patient information.

XIII.3. DATA TRANSFER

ATLANSTAT will ensure data management. The conditions for transferring all or part of the research database will be decided by the sponsor and be subject to a written agreement. The data will be transferred in a pseudonymized form, the study participant number will be used to identify the patient. Data transfer will be encrypted and no data transfer is planned outside the European Union.

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