Clinical Investigation Plan

Study medical device: Alveogyl

Short title: ALVE study

Full study title: Prospective, multicentre clinical trial measuring the impact of treatment with ALVEOGYL in patients with post-extraction dry socket

VERSION AND DATE OF THE CIP: Version 3 – 22/01/2025

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FRANCE:

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Regulatory situation: Observational study registered as "other investigation Case 1 Clinical Investigation PMCF"

INDIA:

Study number registration: CI/MD/2022/66273

Regulatory situation: Pivotal clinical study

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REVISION HISTORY

CIP version	Date	Summary of revisions
Version 1.0	08 March 2022	Initial version
Version 1.1	06 May 2022	Modifications brought upon comments from the French Ethics Committee (session of 19/04/2022): eligibility criteria, study duration, and risks were modified.
Version 2	04 December 2023	Modifications to extend recruitment period.
Version 3	22 January 2025	Modifications to extend recruitment period.

SIGNATURES PAGE

STUDY REGISTRATION ID: 2022-A00208-35 (ID RCB in France) – CI/MD/2022/66273 (India)

STUDY TITLE: Prospective, multicentre clinical trial measuring the impact of treatment with ALVEOGYL in patients with post-extraction dry socket

The Sponsor, the international study coordinating investigator and the Statistician have approved the CIP version (Version 3 – 22/01/2025), and confirm hereby to conduct the investigation according to the CIP (and are not allowed to deviate from it), the current version of the World Medical Association Declaration of Helsinki, ISO 14155:2020 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

	Date	Signature
Sponsor Representative: Farid BENABDALLAH		
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LIST OF ABBREVIATIONS

ABBREVIATION	SIGNIFICATION
ADE	Adverse Device Effect
AE	Adverse Event
ASR	Annual Safety Report
CA/RA	Competent Authority / Regulatory Authority
CDSCO	Central Drugs Standard Control Organisation
CIP	Clinical Investigation Plan
CRA	Clinical Research Associates
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Agreement
DD	Device Deficiency
EC / IRB	Independent Competent Ethic Committee / Independent Institutional Review Board
e-CRF	electronic-Case Report Form
GCP	Good Clinical Practice
IFU	Instructions for Use
ISF	Investigator Site File
MDR	Medical Device Regulation (alias of the "Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices")
PI	Principal Investigator
PMCF	Post-Market Clinical Follow-Up
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale

PROTOCOL SUMMARY

Short Title	ALVE study
Full Title	Prospective, multicentre clinical trial measuring the impact of treatment with ALVEOGYL in patients with post-extraction dry socket
Study medical device	Alveogyl
Study objectives	Primary objective: To measure the impact of Alveogyl treatment on pain at 7-day post-treatment. Secondary objective: To measure the impact of Alveogyl treatment on painkiller intake. To measure the impact of Alveogyl treatment on healing. To measure the impact of Alveogyl treatment on local inflammation. To measure the impact of Alveogyl treatment on antiseptic effect. To measure the impact of Alveogyl treatment on hemostasis. To measure the safety and complication rate of Alveogyl treatment.
Primary outcome	Pain Visual Analog Scale (VAS) at 7 days post-treatment
Secondary outcomes	- Painkiller intake: Analgesic use [Time Frame: at 3 days, 5 days and 7 days post-treatment] - Healing: Evaluation of healing of the alveolar mucosa. [Time Frame: at 7 days post-treatment]. - Local inflammation: Signs of inflammation around the gingival mucosa (oedema, redness, sensitivity) [Time Frame: at 7 days post-treatment]. - Antiseptic effect: Clinical signs (e.g., gum pain, swollen gum lining, fever, halitosis). [Time Frame: at 7 days post-treatment]. - Hemostasis: presence or absence of bleeding [Time Frame: after Alveogyl placement]. - Safety: Complication rate [Time Frame: From Alveogyl placement to 7 days post-treatment]
Study design and methods	ALVE study is a clinical investigation assessing Alveogyl performance and safety in patients with post-extraction dry socket. The study will take place in India and in France where the study device is already marketed. In India, the study is regulatorily considered as a pivotal clinical study in accordance with the Indian regulation. In France – European Union, the study is regulatorily considered as an observational, post-market clinical follow-up study with additional non-invasive and non-cumbersome procedures: the clinical investigation is under

	the category "Other Investigation (Case 1: Clinical Investigation Post-Market Clinical Follow-Up)" in accordance with the European Medical Device Regulation (EU MDR). Management of dry socket application protocol is at the discretion of the Investigator. Patients treated with the study device will be screened and eligible patients will be included in the study after obtaining their consent. The primary outcome will be pain assessed by Visual Analog Scale (VAS) for adults at 7 days post-treatment. VAS is a 10-point line from "no pain" (0 point) to "worst imaginable pain" (10 points). A corresponding scale will be used for children as appropriate. Additionally, patients will self-evaluate their pain level, their painkiller use and the feeling of Alveogyl (clove) taste at day 3 and day 5 at home. All data will be recorded in either paper or electronic Case Report Form (CRF) and monitored by the Sponsor's designee. Self-evaluation by the patients will be recorded in a paper datasheet.
Study population	All patients with permanent teeth are eligible to participate into the study: Male and female patients, adults and children. Note: Age of study population is defined by the permanent tooth requirement as first permanent teeth erupt on children.
Inclusion criteria	- Male or female patient, adult or child - Positive diagnosis of dry socket occurring after the extraction of a permanent tooth (mature or immature) - Signed informed consent - Patient affiliated to a Health Insurance Scheme ("sécurité sociale")
Exclusion criteria	- Spreading infection in the alveolar socket - Placement of Alveogyl done immediately after tooth extraction - Multiple post-extraction dry sockets - Patient treated with cervico-facial radiotherapy - Immunodeficiency related to any diseases or current treatments - Psychiatric patient or patient unable to assess his/her pain via the study Pain VAS - Patient with history of hypersensitivity to one of the components - Patient on post extraction of deciduous teeth - Participation in another clinical investigation
Number of patients	120 patients It is estimate that about 90 patients will be included in India in about 10 investigational sites, and about 30 patients will be included in France in 2 investigational sites.

Follow-up(s)	Patients will be evaluated at visit 1 – Day 0 and clinically followed at 7-day post-treatment (visit 2 – Day 7). Some data will be collected at home, at Day 3 and Day 5: Pain VAS, painkiller use, and feeling of Alveogyl (clove) taste.
Study duration	Patient enrolment will last 30 months (estimate). Each patient's participation will last 8 days. The entire study is expected to last 30.5 months.
Statistical and analytic plan	The assumption is that 92% of patients will have no pain or mild pain at Day 7 (primary outcome). This assumption is supported by the literature that reports a mean pain of 1.4 with standard deviation of 1.1 at Day 7, leading to a very large probability that patients have no pain / mild pain (VAS<4) at Day 7. The sample size n=120 is based on the half-width (precision) of the 95% confidence interval of p=0.92: with n=113, the half-width will be 0.05 and 7 patients are added in case of a few non-evaluable patients.

Table 1: Schedule of Study Procedures

Study Phase	Visit 1	Patients' self-evaluation at home		Visit 2
TIMELINE	Day 0	Day 3	Day 5	Day 7
Informed Consent	X			
Review Inclusion/Exclusion Criteria	X			
Demographics/Medical History of interest	X			
Prior/Concomitant Medications of interest	X			
Clinical examination**	X			X
Pain evaluation based on VAS	X	X	X	X
Treatment with Alveogyl paste	X			
Evaluation of the presence of Alveogyl paste (via its clove taste) in the socket		X	X	X
Evaluation of painkiller use		X	X	X
Serious and non-serious adverse events assessment	X			X*
Device deficiency	X			X*

* Investigator will report at Visit 2 - Day 7 all safety issues (serious and non-serious adverse events and device deficiencies) which occur since Visit 1 -Day 0

** Including evaluation of the alveolus healing status, evaluation of the mucosa inflammation status, evaluation of bleeding status, and of the presence/absence of superinfection.

1 BACKGROUND AND RATIONALE

1.1 BACKGROUND AND RATIONALE FOR THE CLINICAL INVESTIGATION

Dry socket (or alveolar osteitis), is the most common complication following a dental extraction [1] and one of the most studied complications in dentistry [2]. The incidence of dry socket varies between 1% and 5% of all dental extractions, with up to 38% of dry socket cases associated with mandibular third molars [3], [4]. Dry socket develops as a postoperative complication when a blood clot fails to develop, dissolves, or dislodges at the site of the extraction before the socket is healed [5]. Socket that has been left exposed might be accumulated with food debris and bacterial biofilms that further hinder the healing process of the socket. Moreover, bacteria collected inside the socket may even ferment the food particles inside it, which in turn exacerbates the already compromised situation of the socket. Most commonly, patients suspected of suffering from dry socket present with acute pain from the exposed socket that lingers for many days until the socket is completely covered by the epithelium.

The treatment of alveolitis depends on each professional's clinical experience mainly due to the fact of its complex etiology. Traditionally, the treatment of dry socket has been irrigation, surgical intervention, and placement of medicated dressings.

Alveogyl (Septodont, Saint-Maur-des-Fossés – France) is a paste used as dressing in case of dry socket. Alveogyl has been sold and used worldwide since 2010; Alveogyl is one of the treatments advised for clinical management of alveolar osteitis.

Regulatory context in India:

Alveogyl is a Class B medical device according to current Medical Device Regulations (Medical Devices Rules 2017) and CDSCO Notice File NO. 29/Misc/3/2018-DC(85) dated 06/06/2018 Annexure 1.

In the context of recommendations of the Subject Expert Committee to perform a pivotal clinical investigation in India to support the registration of Alveogyl under the Drugs & Cosmetics Act 1940 & Rules 1945 and Medical Device Rules 2017, this study is put in place with the aim to confirm the safety and efficacy (performance) of Alveogyl in the treatment of dry socket.

Regulatory context in France and Europe:

Alveogyl is CE-marked as a class IIa medical device according to article 9 and rule 7 of the annex IX of Directive 93/42/EEC intended to be used in dentistry.

The results of this clinical study will be part of the clinical evidence for supporting the device claims and for CE-marking under the European Medical Device Regulation (MDR) 2017/745.

1.2 CLINICAL EVIDENCE TO DATE

In 2009, a double-blind, randomized, controlled pilot study in 106 patients has been performed to evaluate the performance and the clinical safety of two new pastes developed by Septodont: RD113/06

(35 patients) and RD113/08 (36 patients) in the treatment of dry socket in comparison to Alvogyl (35 patients). RD113/08 was the project name for the current commercialized and study device Alveogyl.

Results of the study showed that Alveogyl provides a favourable environment for the healing of the alveolar mucosa and is considered as safe for patients with a dry socket.

No publication exists on this study, only a clinical report in French is available upon request.

1.3 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

The study device Alveogyl is a paste already marketed and used in India and France for several years (8 years in India, 12 in France).

ALVE study is a clinical study assessing Alveogyl performance and safety in patients with post-extraction dry socket.

Efficacy of a method used for dry socket management is usually measured through the relief of patient's pain and the promote of alveolar mucosa healing [6]. The study objectives and outcomes measured were notably based on this information.

Additionally, the following clinical performance and clinical safety parameters claimed by the manufacturer for the study device will be verified through the results obtained in the current study:

- Provides a favourable environment for physiological tissue healing,
- Reduces pain,
- Reduces local inflammation and reduces risks of contamination due to its barrier effects.
- Hemostasis support

1.4 JUSTIFICATION OF THE CHOICE OF THE INVESTIGATION POPULATION

The target population for this study is the same as the intended population specified in the study device's instructions for use: patients with permanent teeth (mature or immature).

As permanent teeth can erupt in children (permanent teeth typically begin erupting around age 5), minors are eligible to participate in the study. Other vulnerable patients can be included in the study as there is no additional risk for this population.

1.5 RISK EVALUATION (RISK-TO-BENEFITS RATIONALE)

1.5.1 Anticipated clinical benefits

It is expected that Alveogyl provides the following clinical benefits:

- Pain reduction
- Inflammation reduction
- Limit infection with its barrier effect

1.5.2 Anticipated adverse events related to device or procedure

The following possible adverse events related to the device or to the procedure of dry socket treatment have been identified during clinical evaluation and risk analysis:

- Mouth ulceration,

- Pain,
- Paresthesia,
- Infections (osteitis, abscess),
- Swelling,
- Hypersensitivity/irritation reactions
- Local inflammation,
- Temporary fever,
- Bleeding gum,
- Delayed healing,
- Possible increased bone resorption (the material should be removed in the area that receives future implants),
- Ulceration.

1.5.3 Risks associated with participation in the clinical investigation

Septodont's last Clinical Safety Review analysis reported that Alveogyl is safe under the recommendation of use: there is indeed, up to 31-Dec-2020, only 22 reported cases out of 40 489 595 patients exposed. All the reported safety concerns retrieved are identified as either being associated with the dental procedure (i.e., paresthesia, dysaesthesia, pain) or to the product itself (irritation, hypersensitivity).

As the study medical device is used in its indication according to the Instructions For Use (IFU) with only collection of clinical data, there is no additional risks associated with patients participation in this clinical study. The patient will be treated as per standard practice and following the IFU (see Annex 1).

1.5.4 Possible interaction with concomitant medical treatments as considered under the risk analysis

There is no interaction with a concomitant medical treatment that may present a risk.

1.5.5 Steps that will be taken to control or mitigate the risks

All identified risks have been estimated and evaluated according to the risk management plan and the results are logged in the risk analysis table of the study device (see Annex 2).

Each risk has been reduced as far as possible, using risk control measures when possible. All the risk control measures have been implemented.

After implementation of all risk control measures, there is no unacceptable residual risk.

All the information for safety that has emerged from the risk analysis has been included in the instructions for use, including risk control measures and residual risks.

1.5.6 Rationale for benefit-risk ratio

The clinical risks of the study device are consistent with the state-of-the-art (based on competitors' products results in the same indication). The overall residual risk is considered acceptable.

The clinical evaluation of the study device concluded on a favourable benefit-risk ratio of Alveogyl in patients with dry socket as the product provides a favourable environment for physiological tissue healing.

The results of this clinical study should confirm the favourable benefit-risk ratio.

2 DESCRIPTION OF THE STUDY DEVICE

2.1 STUDY DEVICE

2.1.1 Description

The name of the study medical device is Alveogyl.

In India, Alveogyl is a Class B medical device according to current Indian Medical Device Regulations (Medical Devices Rules 2017) and CDSCO Notice File NO. 29/Misc/3/2018-DC(85) dated 06/06/2018 Annexure 1.

In Europe, Alveogyl is a CE-marked Class IIa medical device according to article 9 and rule 7 of the annex IX of Directive 93/42/EEC intended to be used in dentistry.

The product is commercialized in Europe since 2010 and in India since 2014 and is currently on the market in nearly 90 countries worldwide.

Alveogyl is a paste used as dressing to treat dry socket and is intended to be applied on the patient's dental socket by a dental professional only.

Composition and role of the materials are detailed in the following table.

Table 2: Composition of Alveogyl

Raw material	CAS number	Quantity (g/100g)	Role
[redacted]	[redacted]	[redacted]	[redacted]
Eugenol	[redacted]	[redacted]	[redacted]
Calcium carbonate	[redacted]	[redacted]	[redacted]
Mint natural flavor [redacted]	[redacted]	[redacted]	[redacted]
[redacted] Penghawar djambi fiber	[redacted]	[redacted]	[redacted]
Sodium dodecyl sulfate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The product is packaged in a jar containing 10g of Alveogyl as presented in the following picture.

Packaging level	Component	Raw material
Primary packaging	Glass bucket / jar	[redacted]
	Obturator	[redacted]
	Cap	[redacted]
Secondary/sales packaging	Card Box	[redacted]

Figure 1: Primary and secondary packaging of Alveogyl

2.1.2 Intended purpose

Dry-Socket Surgical dressing.

NOTE: Please refer to the IFU for more information.

2.1.3 Indications

Alveogyl is a paste used as dressing in case of dry socket.

NOTE: Please refer to the IFU for more information.

2.1.4 Patient population

Patient with permanent teeth (mature or immature).

NOTE: Please refer to the IFU for more information.

2.1.5 Users

For professional dental use only.

NOTE: Please refer to the IFU for more information.

2.1.6 Experience / Training needed

There is no special training needed to use the study device as it is a CE-marked device used for several years and already in the Indian and French market and has similar use as other pastes in the market.

2.2 MANUFACTURER

Septodont

58 Rue du Pont de Créteil, 94100 Saint-Maur-des-Fossés - FRANCE

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

3.1.1 Primary objective

To measure the impact of Alveogyl treatment on pain at 7-day post-treatment.

3.1.2 Secondary objectives

To measure the impact of Alveogyl treatment on painkiller intake.

To measure the impact of Alveogyl treatment on healing.

To measure the impact of Alveogyl treatment on local inflammation.

To measure the impact of Alveogyl treatment on antiseptic effect.

To measure the impact of Alveogyl treatment on hemostasis.

To measure the safety and complication rate of Alveogyl treatment.

3.2 STUDY ENDPOINTS

3.2.1 Primary endpoint

Pain Visual Analog Scale (VAS) at 7 days post-treatment

3.2.2 Secondary endpoints

Painkiller intake: Analgesic use [Time Frame: at 3 days, 5 days and 7 days post-treatment]

Healing: Evaluation of healing of the alveolar mucosa. [Time Frame: at 7 days post-treatment].

Local inflammation: Signs of inflammation around the gingival mucosa (oedema, redness, sensitivity) [Time Frame: at 7 days post-treatment].

Antiseptic effect: Clinical signs (e.g., gum pain, swollen gum lining, fever, halitosis). [Time Frame: at 7 days post-treatment].

Hemostasis: presence or absence of bleeding [Time Frame: after Alveogyl placement].

Safety: Complication rate [Time Frame: From Alveogyl placement to 7 days post-treatment]

4 INVESTIGATIONAL PLAN

4.1 STUDY DESIGN

ALVE study is a clinical investigation assessing Alveogyl performance and safety in patients with post-extraction dry socket. The study will take place in India and in France where the study device is already marketed.

In India, the study is regulatorily considered as a pivotal clinical study in accordance with the Indian regulation.

In France – European Union, the study is regulatorily considered as an observational, post-market clinical follow-up study with additional non-invasive and non-cumbersome procedures: the clinical

investigation is under the category "Other Investigation (Case 1: Clinical Investigation Post-Market Clinical Follow-Up)" in accordance with the European Medical Device Regulation (EU MDR).

Management of dry socket application protocol is at the discretion of the Investigator. Patients treated with the study device will be screened and eligible patients will be included in the study after obtaining their consent.

The primary outcome will be pain assessed by Visual Analog Scale (VAS) for adults at 7 days post-treatment. VAS is a 10-point line from "no pain" (0 point) to "worst imaginable pain" (10 points). A corresponding scale will be used for children as appropriate.

Additionally, patients will self-evaluate their pain level, their painkiller use and the feeling of Alveogyl (clove) taste at day 3 and day 5 at home.

All data will be recorded in either paper or electronic Case Report Form (CRF) and monitored by the Sponsor's designee.

4.2 STUDY DURATION, ENROLMENT AND SITES

4.2.1 Duration of enrolment

Patients' enrolment will last 30 months (estimate).

4.2.2 Duration of study participation

Each patient will be clinically examined at visit 1 – Day 0 (at the time of positive diagnosis of dry socket and use of Alveogyl) and at 7 days post-treatment (visit 2 – Day 7).

Each patient's participation will last 8 days.

4.2.3 Number of investigational sites and patients estimated

120 patients will be enrolled in the clinical study.

The clinical study will be conducted at approximately 10 investigational sites in India which should recruit about 90 patients, and at 2 sites in France which should recruit about 30 patients.

4.3 STUDY POPULATION

4.3.1 Inclusion criteria

Patient fulfilling all the following criteria is eligible for the clinical investigation:

- Male or female patient, adult or child
- Positive diagnosis of dry socket occurring after the extraction of a permanent tooth (mature or immature)
- Signed informed consent
- Patients affiliated to a Health Insurance Scheme ("sécurité sociale")

4.3.2 Exclusion criteria

The presence of any of the following exclusion criteria will lead to the exclusion of the patient:

- Spreading infection in the alveolar socket
- Placement of Alveogyl done immediately after tooth extraction
- Multiple post-extraction dry sockets

- Patient treated with cervico-facial radiotherapy
- Immunodeficiency related to any diseases or current treatments
- Psychiatric patient or patient unable to assess his/her pain via the study Pain VAS
- Patient with history of hypersensitivity to one of the components
- Patient on post extraction of deciduous teeth
- Participation in another clinical investigation

4.4 PATIENT INFORMATION AND INFORMED CONSENT

The Principal Investigator (PI) or designee explains to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each patient is informed that the participation in the study is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The patients are informed that he/she can ask any question. Time is given to the patients to read and understand the consent form.

The patients are informed that authorised individuals other than their treating physician may examine his/her medical records.

All patients are given a patient information document and a consent form describing the study and providing sufficient information for the patients to make an informed decision about their participation in the study.

The formal consent of a patient, using the approved consent form, is obtained before the patient is enrolled into the study and submitted to any study procedure.

The patient should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the patient and the PI (or her/his designee). The signed consent form is then retained as part of the investigation records.

4.4.1 Minors/underage patients

For minor/underage patients the study's investigator or designee will discuss with the patient's parent or legal representative, who may give his/her informed consent on the patient's behalf. The minor patient will also be informed about the study within his/her ability to understand: a dedicated information sheet will be provided to the minor patient.

4.4.2 Other vulnerable subjects

Other vulnerable patients can be included in the study (i.e. individuals with lack or loss of autonomy due to immaturity or disability, persons in nursing homes, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and persons kept in detention). There is no additional risk nor contraindication for this type of population.

If the patient is unable to make the decision to participate in this study, the study's investigator or designee will discuss with the patient's legal representative.

4.5 STUDY PROCEDURES

4.5.1 Visit 1 – Day 0

During this visit (same day as dry socket diagnostic and procedure of Alveogyl treatment), the following elements will be performed:

☒ Eligibility criteria: Prior to patients' enrolment into the study, patients' inclusion and exclusion criteria will be reviewed by the investigator.

☒ Patient informed consent: see §4.4

☒ Medical record review: which will be extracted from the patients' medical chart (i.e., Date of birth (MM-YYYY), gender, risk factors); medical information related to tooth extraction and dry socket before the procedure (such as date of tooth extraction, numbered of the extracted tooth, etiology of the tooth extracted, …); Concomitant therapy.

☒ Clinical signs or symptoms: such as presence of gum infection/periodontitis, time after which the pain started, blood clot within the alveolar socket, halitosis, confirmation of the diagnosis of dry socket, local inflammation evaluation, bleeding evaluation,…

☒ Visual Analog Scale: pain assessment through the VAS before the procedure

Placement of Alveogyl use is done according to the instruction for use (IFU, Annex 1)

Before inserting the paste, the socket shall be re-examined.

The inside of the socket should be thoroughly cleaned (i.e., irrigated and/or curetted) to remove all debris.

Take a small pellet (about 0.20 g) of paste and place it gently into the prepared dental socket. Do not suture.

Note 1: The management of dry socket paste application protocol is at the discretion of the Investigator, knowing that there are available guidelines (e.g., Canadian Dental Association, 2013).

Note 2: For more details on the procedure of use, precautions and warnings see IFU.

The following information will be collected:

☒ Clinical signs or symptoms: medical information related to dry socket

☒ Procedure information: type of pre-Alveogyl treatment (curettage, cleaning, local anaesthesia etc.); feedbacks on the study device (manipulation, consistency, placement); Post-Alveogyl treatment information (local inflammation evaluation, bleeding evaluation,…)

☒ Visual Analog Scale: pain assessment through the VAS after the procedure

4.5.2 Follow-up visit (Visit 2 – Day 7)

During patients' follow-up visit at 7-day post-treatment, the following elements will be evaluated:

☒ Clinical signs or symptoms: medical information related to dry socket (local inflammation evaluation, infection of the studied socket, healing evaluation, presence or not of Alveogyl paste in the socket,…)

☒ Serious and non-serious adverse events and Alveogyl deficiency since Visit 1 (See §6.3)

☒ Visual Analog Scale: pain assessment through the VAS

☒ Painkiller use

Additionally to the clinical follow-up visit at 7-day post-treatment, patients have to complete at home a form at Day 3 and Day 5 post-treatment with the following information to collect:

☒ Visual Analog Scale: pain assessment through the VAS

☒ Presence or not of Alveogyl clove taste feeling

☒ Painkiller use

4.5.3 Unscheduled visits

Patients may come back before the scheduled visit at 7 days post-treatment for various reasons (e.g., pain, other adverse events). In this case, the following information will be recorded in the study CRF:

- Date of the visit
- Reason of the visit
- Clinical signs or symptoms: medical information related to dry socket (local inflammation evaluation, infection of the studied socket, healing evaluation, presence or not of Alveogyl paste in the socket,…)
- Type of treatment if applicable and information on whether if Alveogyl was re-used during the visit.

4.5.4 Patient completion/Withdrawal

Patients may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules or AEs.

The Investigator may also withdraw patients who violate the study plan, or to protect the patients for reasons of safety or for administrative reasons. It will be documented whether each patient completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the patient completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.6 STUDY EARLY TERMINATION

The Sponsor may terminate the study prematurely according to certain circumstances, for example:

a) ethical concerns,
b) insufficient patient recruitment,
c) when the safety of the patient is doubtful or at risk, respectively,
d) alterations in accepted clinical practice that make the continuation of the investigation unwise,
e) early evidence of benefit or harm of the experimental intervention.

The Sponsor may terminate the inclusion of patients at a study site at any time after the study initiation visit. Specific instances that may precipitate such termination are:

a) multiple or severe CIP violations, or non-compliance without justification and/or repeated failure to follow remedial actions
b) unauthorized use of the study device in another clinical study
c) no patients have been enrolled
d) inaccurate and/or incomplete data recording on a recurrent basis

In the event of termination of Investigator participation, all study materials, as applicable, must be returned to the Sponsor, unless this action would jeopardize the rights, safety or well-being of the patients. The Ethic Committee (EC/IRB) and Competent/Regulatory Authority (CA/RA), if applicable, should be notified.

5 STATISTICAL METHODS

5.1 HYPOTHESIS

The assumption is that the use of Alveogyl will allow to get a minimal residual pain at Day 7 post-treatment.

5.2 DETERMINATION OF SAMPLE SIZE

The determination of the sample size is based on the assumption that 92% of patients will have no pain or mild pain at Day 7 after the use of Alveogyl. The pain is assessed through a 10-point visual analogic scale (VAS) and a score strictly less than 4 is considered as mild pain or no pain [7].

The assumption of 92% is supported by the literature that reports a mean pain of 1.4 with standard deviation of 1.1 at Day 7, leading to a very large probability that patients have no pain / mild pain (VAS<4) at Day 7 [8].

The selected sample size is n=120, which will allow to estimate the proportion of no pain or mild pain with a satisfactory precision: the half-width of the 95% confidence interval of p=0.92 is 0.05 with n=113 patients and 7 patients are added in case of a few non-evaluable patients at Day 7 post-treatment.

5.3 STATISTICAL CRITERIA OF TERMINATION OF THE STUDY

N/A. As this is a study with a device already in the market, it is not expected that the study device will do any harm to the patient that would justify an early termination of the study. Any unexpected serious adverse events will be reported and analysed by Septodont vigilance department.

5.4 STATISTICAL METHODS FOR PLANNED ANALYSES

A statistical analysis plan will be developed separately.

Quantitative data will be reported with n, n missing, mean, standard deviation (SD), median, minimum, maximum and 1st and 3rd quartiles.

Qualitative data will be reported as n, n missing and percentage (calculated over the non-missing data).

5.4.1 Analysis populations

Included population (intention-to-treat population - ITT): all included patients.

Evaluable population (per-protocol population - PPP): all patients from the included population with no exclusion criteria and with VAS available at Day 7.

5.4.2 Baseline Data

Baseline data will be described in the included population: demography, characteristics of the tooth extraction, clinical characteristics of the dry socket will be reported. The pain measured with VAS just before the treatment with Alveogyl and just after will be described as well as the clinical signs just after the placement of Alveogyl (local inflammation, bleeding).

The ease of use for the dentist will be described too.

In case the size of the evaluable population is much smaller than the included population (10% less), the description of baseline data of the patients will be performed also in the evaluable population.

5.4.3 Analysis of Primary endpoint

The primary endpoint is the binary variable (yes / no) defined as the VAS at Day 7 < 4 (i.e., “Yes" when VAS is <4, “No” when VAS is ≥4).

It will be reported with a percentage and a 95% confidence interval (with the exact method) in the evaluable population.

5.4.4 Analysis of Secondary endpoints

The secondary analyses will consist of:

- Evolution of VAS from the day (D0) of use of Alveogyl to 7 days post treatment. Summary statistics of VAS will be provided at Day D0, D3, D5 and D7 in available observations (no imputation for missing values will be made). For each timepoint, difference with measure at D0 will also be calculated.
- The complication rate will be calculated: number and proportions of the events (quoted in §1.5.2) occurring post treatment
- Description of the clinical signs at D7 and at intermediary visits (if any) to measure the impact of Alveogyl treatment on healing, on antiseptic effect, on local inflammation, and on hemostasis: number and proportions.
- The use of painkillers at D3 and at D7 will be described.
- A listing of the adverse events (AE) will be provided organized by type of AE (Adverse Event ; Adverse Effect related to Alveogyl ; Deficiency of Alveogyl ; Other type or Unknown)

5.4.5 Interim analyses

N/A. No interim analysis is planned.

5.4.6 Deviation(s) from the original statistical plan

If any, additional analyses or changes from the initial plan will be described in the study report.

5.5 HANDLING OF MISSING DATA AND DROP-OUTS

No data will not be imputed, only available data will be used in the analyses.

6 SAFETY MANAGEMENT

6.1 DEFINITIONS

For sake of clarity, the source of each definition wording is given between brackets.

Adverse Event (AE) (Art. 2 §57 MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the Medical Device.

Adverse Device Effect (ADE) (ISO14155)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

Use error (ISO14155)

User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user

Incident (Art. 2 §64 MDR)

Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency (Art. 2 §59 MDR)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

Serious Adverse Event (SAE) (Art. 2 §58 MDR)

Any adverse event that led to any of the following:

(a) death,

(b) serious deterioration in the health of the subject that resulted in any of the following:

(i) life-threatening illness or injury,

(ii) permanent impairment of a body structure or a body function,

(iii) hospitalisation or prolongation of patient hospitalisation,

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

(v) chronic disease,

(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Device deficiency with Serious Adverse Device Effect (SADE) potential ((Art. 80 §1 c) MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Serious incident: (Art. 2 § 65MDR)

Means any incident that directly or indirectly led, might have led or might lead to any of the following:
(a) the death of a patient, user or other person,

(b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,

(c) a serious public health threat;

Serious public health threat: (Art. 2 § 66MDR)

Event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

Causal Relationship of SAE (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

e) Not related: The relationship to the device or procedures can be excluded.

f) Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
g) Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
h) Causal relationship: The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

6.2 SAFETY DATA RECORDING

From the "Visite 1 - Day 0" date until patient end of study (i.e., withdrawal/end of follow-up/lost to follow-up), all adverse events (serious and non-serious), exposure during pregnancy and device deficiencies that occur will be fully investigated, recorded and classified by the Investigator in line with the definitions provided in the norm ISO14155:2020 and guideline MEDDEV 2.7/3.

Investigators will check patients file during clinical follow-up visit and ask patients if they experienced any complications since the index procedure / last visit.

Safety data will be reported in the Case Report Form.

Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to Medical Device and/or investigation procedure (ISO14155).

Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor shall review all DDs and determine and document in writing whether they could.

The Sponsor provides the Competent/Regulatory Authority (CA/RA) (if applicable) and the Ethic Committee (EC/IRB) with the documentation at their request.

6.3 SAFETY DATA REPORTING

6.3.1 Reporting to the Sponsor

The following events are to be reported to the Sponsor by the PI (or authorized designee) without delay and not later than 3 calendar days after becoming aware of the event:

- All SAEs related and unrelated to the studied device
- Health hazards that require measures
- Unanticipated Serious Adverse Device Effect
- Device deficiencies including use error, malfunction, and incident irrespectively of occurrence of AE.

Non serious AE and exposure to the device during pregnancy are transmitted weekly to the sponsor.

Safety data as described above in section 6.1 Definition in addition to exposure during pregnancy are reported in the dedicated form: CRF and vigilance report form provided by the sponsor available in the Investigator Site File and send to the sponsor according to the timelines described above by email to [redacted] copy [redacted]

In case of serious public health threat or in case of death or unanticipated serious deterioration in a person's state of health, the sponsor must be informed immediately by phone (tel: [redacted] and the dedicated form sent in parallel by email.

A detailed follow-up report containing all additional exams and/or pseudonymized surgical report should be sent to the sponsor as soon as they are available according to the same process and timelines.

The Sponsor will evaluate SAEs with regard to causality and seriousness. Device deficiencies are also assessed regarding their potential to lead to an SAE (DD with SADE potential).

The Sponsor will manage the information on safety according to its procedure.

Reconciliation with the CRO and Septodont medical affairs department are performed in monthly basis with Septodont vigilance department.

Appropriate vigilance training is provided to the CRO.

6.3.2 Reporting to Ethic Committee and Competent/Regulatory Authority

The sponsor will submit the case reports to the Ethic Committee and to Competent/Regulatory Authority as required in the country regulation.

In France:

It is done according to the timelines described in the Article 87 and 90 of the MDR:

- a serious public health threat must be reported immediately and not later than 2 days after the manufacturer becomes aware of that threat
- in the event of death or unanticipated serious deterioration in a person's state of health, the reporting to the CEC must be performed immediately and not later than 10 days after the manufacturer becomes aware of that threat
- in case of any serious incident and after having established the causal relationship between the incident and the device (or such causal relationship is reasonably possible), the reporting to the CEC must be performed immediately and not later than 15 days after the manufacturer become aware.

In India:

All SAE/SADE/USADEs must be reported to the sponsor/legal representative and manufacture within 24 hrs of the investigator team becoming aware of them.

All the SAE/SADE/USADEs will be reported to Institutional Review Board/ Ethics Committee as per local regulatory requirements through an email or telephonically, and Reports of related and unexpected SAEs should be submitted to Ethics Committee within 14 days of the Chief Investigator becoming aware of the event, using the SAE report form.

Full details of the event, treatment, and an assessment of the relationship to study procedures must be provided in the report with detailed information as mentioned in table 7 of Medical Device Rule 2017, DCGI or latest local regulatory requirement.

The Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice but should notify the monitor of such actions and record them in the subject's Case Report Form.

6.4 ADVERSE EVENTS CATEGORIZATION

The adverse events are categorized by the PI and the Sponsor using the following algorithm:

Does the AE meet the seriousness criteria?

1. No, it is not serious
   Is the relationship to the device or the procedure possible, probable or causal?
   - No: non-related AE
   - Yes: ADE
2. Yes, it is serious: SAE
   Is the relationship to the device or the procedure possible, probable or causal?
   - No: non-related SAE
   - Yes: SADE

Is it anticipated (within expected type, severity and frequency of the complications)?

1. No: unanticipated SADE (USADE)
2. Yes: anticipated SADE (ASADE)

6.5 EMERGENCY CONTACT

In case of serious public health threat or in case of death or unanticipated serious deterioration in a person's state of health, or any major safety issue the sponsor must be informed immediately by phone tel: [redacted] and an email is sent with the CRF and vigilance report form sent in parallel by email to [redacted] copy [redacted]

In India, investigator must also contact his/her contact CRO monitor as defined in investigator's site binder.

6.6 DATA MONITORING COMMITTEE

N/A

7 ETHICAL AND REGULATORY ASPECTS

The final positive decision of the EC/IRB and of the CA/RA (if applicable) on the conduct of the investigation will be made and given in writing to the Sponsor before the study can start. Additional requirements set by the authorities must be implemented.

7.1 REGISTRATION OF THE STUDY

The study is registered in France under the following RCB number: 2022-A00208-35 and in India under the following number CI/MD/2022/66273.

7.2 STUDY APPROVAL

7.2.1 Ethics Committee (EC/IRB)

The sponsor will submit the study to the Ethics Committee (EC/IRB) and obtain EC/IRB approval before the start of the study. Each PI at each participating site ensures that approval from the EC/IRB is obtained and filed in the Investigator Site File (ISF) before the study starts.

Substantial amendments are submitted for approval. The regular or premature end of the study as well as the interruption of the study is reported to the EC/IRB. The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the study and within 3 months after a premature end of the investigation.

7.2.2 Competent/regulatory authorities (CA/RA)

The Sponsor will submit the investigation to the CA/RA and obtain regulatory approval (if applicable) before the start of the study. Each PI at each participating investigational site ensures that approval from the CA/RA is obtained and filed in the Investigator site file before the study starts.

Any additional requirements imposed by the EC/IRB or CA/RA shall be followed.

7.3 COMPLIANCE STATEMENT

This clinical study will be conducted in full accordance with local Regulation Authority, the Norms ISO14155:2020 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, this CIP, the European Regulation on Medical Devices 2017/745 (MDR) and with the ethical principles laid down in the Declaration of Helsinki.

The investigators will perform the study in accordance with this CIP, will obtain patients' consent and will report any adverse events. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of participating patients during and after the study.

The EC/IRB and the CA/RA (if applicable) will receive the Annual Safety Report (ASR) and be notified about investigation stop/end in agreement with local requirements.

8 STUDY DEVICE ACCOUNTABILITY

8.1 LABELLING

There is no specific labelling for this study: investigators will use the Alveogyl jars they have bought for their current needs (commercial use, with commercial labelling). Indeed, Alveogyl is commercialized in India and in France, and is used in its indication in this study.

8.2 STORAGE CONDITIONS

The study device is used as intended in the IFU.

Device storage is according to the IFU (Annex 1)

8.3 SUPPLY (AND RE-SUPPLY)

The investigators have Alveogyl in their stock. No dedicated Alveogyl will be delivered for the clinical study. if there is a need for re-supply, the shipment is as per standard commercial procedures.

The batch numbers used for each patient will be recorded in the CRF.

8.4 RETURN, ANALYSIS OR DESTRUCTION OF THE STUDY DEVICE

After the study end, the remaining products are kept by the investigators and will be used by the investigators for the patients that need to be treated by Alveogyl in the commercial use.

In case of device deficiencies, including malfunction, usability issues, or inadequacy in the information supplied by the manufacturer including labelling, the devices will be returned to the Sponsor for analysis.

9 QUALITY ASSURANCE AND CONTROL

9.1 DATA HANDLING AND RECORD KEEPING

9.1.1 Case report forms

The Investigator or designee will be responsible for completing, in a timely manner, a (paper or electronic) Case Report Form (CRF) for each patient enrolled in this study.

Note: The person(s) authorized by the PI to enter the data in the CRF must be listed on the delegation log.

Specific instructions and training for its use and completion will be provided by the CRO or by Septodont to the study staff. CRFs are to be completed as information becomes available.

The Investigator will sign and date the indicated places on the CRF. This will confirm that a thorough inspection of the audited data therein has been made and will thereby certify the content of the forms.

9.1.2 Specification of source data and source documents

Source data must include the original documents relating to the investigation, as well as the medical treatment and medical history of the patient.

Source data for this study will include the original patient records maintained by the study sites, as per their ongoing standard of care. This could include details on the patient's medical history, any imaging data (i.e., radiography), and procedural records for any prior surgeries or interventions.

Source data also include index procedure report, visit dates, informed consent forms, SAEs, SADEs, USADEs, concomitant medication and results of relevant examinations.

Original source data will be kept at the site and made available during site monitoring or audit visits.

9.1.3 Record keeping of essential clinical investigation documents

All CRF information, study records, reports and source documents that support the CRF must be retained in the files of the investigator according to national requirements following notification by the Sponsor or designee that all investigations have been completed, and will further be retained in accordance with local and international guidelines as identified in the Clinical Trial Agreement (CTA). This documentation must be accessible upon request by international regulatory authorities or the Sponsor (or designee). The Sponsor or designee must approve archiving or transfer of the documentation for relocation purpose of premises, in writing, prior to the actual file transfer. The investigator must notify the Sponsor, in writing, of transfer location, duration, and the procedure for accessing study documentation. The investigator must contact the Sponsor, or designee, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice must be submitted to the Sponsor, or designee, indicating the name and address of the person accepting primary responsibility. The EC/IRB must be notified in writing of the name and address of the new custodian.

In France, patients' data must be kept up to two years after the last study results publication or, if there is no publication intended, up to the final study report signature. Investigators personal data will not be kept beyond 15 years after the end of the study. All these information will then be archived in paper or electronically (for more information, see §9.2.4 - Archiving).

9.2 DATA MANAGEMENT

9.2.1 Data management system

Clinical data management will be performed in accordance with data cleaning procedures.

If data are recorded in an e-CRF, appropriate computer edit programs will be run to verify the accuracy of the database. The investigator will be queried on incomplete, inconsistent or missing data.

If paper CRF are used, Septodont's designee will directly collect the completed and signed CRF from the investigational sites. Septodont's designee will enter the data collected in a datasheet and send the data to the statistician for analysis.

9.2.2 Data security, access and back-up

If data are recorded in an e-CRF, access to the e-CRF is granted by the CRO to Investigators and designees after completion of a user access form. The access is limited by a login and only authorized users can access the e-CRF. Upon the study start-up visit to the investigational site, access to the e-CRF is provided.

If paper CRF are used, paper CRF will be provided to the investigational sites upon the study start-up visit to the investigational site. Septodont's designee will verify that access to completed CRF is secured (storage in a secured place with limited access).

9.2.3 Electronic and central data validation

Study data are entered in a paper CRF or an e-CRF by the investigational site team. The investigators validate the data entered by signing all required pages (e.g., patient inclusion, adverse events). All data entered in the CRF are monitored by a trained and qualified Clinical Research Associates (CRAs).

9.2.4 Archiving

As specified in the norm ISO14155, the sponsor and principal investigator shall maintain the clinical investigation documents. They shall take measures to prevent accidental or premature destruction of these documents.

Clinical investigation documents include but are not limited to CIP, patients informed consent form and clinical investigation report.

All the documents of the investigation must be archived for a minimum of 15 years after regular or premature termination of the investigation by the Sponsor and each investigation sites.

9.3 MONITORING

Monitoring the clinical study at the investigational site through trained and qualified CRAs is the responsibility of the CRO in India and of the Sponsor in France.

Monitoring visits will be performed according to the monitoring plan. During on-site monitoring, the Informed Consent Forms will be checked and a sample of clinical data will be verified compared to CRF data. Patient confidentiality will be maintained at all time. Emphasis will be on the complete reporting by the study staff of AEs and SAEs.

Each clinical site will be visited during the study to ensure a high degree of data quality. These site monitoring visits will be conducted to verify that the data are authentic, accurate and complete, that patients' safety and rights are protected, that the study is conducted according to this current CIP, and that any other study agreements, GCP and all applicable regulatory requirements are met. The investigator and the head of the medical institution (where applicable) agree to allow the CRA direct access to all relevant documents. It is important that the investigator and the study staff are available during the monitoring visit and possible audits and that sufficient time is devoted to the process. Findings from the review and source documents will be discussed with the investigator.

Remote site monitoring may also be performed to ensure complete quality study data and patient adherence to the protocol. On a regular basis, the monitoring organization will contact each site to discuss the progress of the study with respect to patient enrolment, timely attendance of patients to their follow-up visits and other relevant study aspects such as data query resolution.

Each participating centre will receive a close-out visit to resolve any outstanding issues and to perform the final source data verification.

9.4 AUDITS AND INSPECTIONS

To ensure compliance with GCP and regulatory requirements, a member of the Sponsor's (or a designated CRO's) quality assurance unit, may arrange to conduct an audit to assess the performance of the study at the investigational site and of the study documents originating there. The investigator

agrees to cooperate with the Sponsor and/or its designee in the conduct of these audits and provide access to medical records and other relevant documentation (source data/documents), as required. The investigator/institution will be informed of the audit outcome.

Regulatory authorities worldwide (EC/IRB and CA/RA) may inspect the investigational site during and after the study. The investigator should contact the sponsor immediately as soon as notified of this inspection, and must cooperate with the regulatory authority inspections as required.

9.5 SUBJECT PRIVACY, CONFIDENTIALITY, DATA PROTECTION

The Sponsor and the PI affirm and uphold the principle of the Patients' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the patients shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Patient confidentiality will be maintained throughout the study in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code will be used for this study.

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

For data verification purposes, authorised representatives of the Sponsor, the CA/RA or the EC/IRB may require direct access to parts of the medical records relevant to the study, including patient's medical history.

9.6 STORAGE OF BIOLOGICAL MATERIAL AND RELATED HEALTH DATA

N/A. No biological material is used for this clinical study.

10 PUBLICATION AND DISSEMINATION POLICY

Results of this study will not be submitted for presentation or publication without the prior written permission of the Sponsor.

The publication and communication rights can be found in the Clinical Trial Agreement negotiated with each study centre: neither the complete nor any part of the study results carried out under this CIP, nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study Sponsor.

Any written or oral communication of the study results has to receive the preliminary agreement of the Coordinating Investigator and of the Sponsor.

At the study termination, a manuscript may be prepared for publication in a peer-reviewed scientific journal. Publication of the main results from any single centre will require the prior written approval of the Sponsor.

The study investigators may publish or communicate results, with the prior written approval of the Sponsor and the Coordinating Investigator. They must provide the Sponsor and Coordinating Investigator a copy of any oral presentation or written publication at least 30 days in advance of the

submission for publication. The Sponsor and Coordinating Investigator have the right to comment on the appropriateness of the data analysis and presentation.

11 FUNDING AND SUPPORT

11.1 FUNDING

The study is sponsored by Septodont, without external funding.

11.2 OTHER SUPPORT

N/A.

12 INSURANCE

Patients who participate in this clinical study will be insured against any injury related to the study, according to local regulation requirements.

Insurance will be provided by the Sponsor. A copy of the certificate is filed in each investigation site file and the sponsor file.

Note: In France, this clinical study is considered as a Post-Market Clinical Follow-up study with non-invasive and non-cumbersome additional procedures. Therefore, no specific insurance is required.

13 MEDICAL TREATMENT / COMPENSATION OF THE PATIENT

At the visit 1 – Day 0, the patient is consulting his/her dentist in a context of post-extraction dry socket: this medical consultation and the treatment by Alveogyl, are not supported by the sponsor; Septodont is only supporting the data collection. The patient transportation for this visit is supported only in India (a lump sum of 1000 Indian rupees).

At visit 2 – Day 7, the visit cost is supported by Septodont if no medical consultation is specifically scheduled for the dental/medical healthcare of the patient. However, if the patient needs to come for a dental/medical healthcare reason at this visit, the medical consultation and any treatment done to the patient won't be supported by Septodont. Septodont is only supporting the data collection. Septodont is also supporting transportation fee reimbursement for this visit 2 (a lump sum of 50 euros in France, and a lump sum of 1000 Indian rupees in India).

14 REFERENCES

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APPENDICES

Annex 1. Alveogyl – Instructions for use

This Instruction for use is in commercial batches released up to May 2022.

This Instruction for use is in commercial batches released from May 2022.

Annex 2. Alveogyl – Risk analysis

Other essential study documents (e.g., investigators list, Informed consent forms, CRF…) are available elsewhere.