Note: This document is a translation in English of the protocol, which was written in French.

OPTIFILL Trial

Evaluation of the Efficacy Rate of Endodontic Treatment at 2 Years After Root Canal Filling With a Ready-to-use Root Canal Sealer PA1704 Versus BioRoot™ RCS:

a Randomized Controlled Trial.

Category 1 research involving humans — IDRCB No.: **2020-A01790-39-PP**

CLINICAL TRIAL PROTOCOL

Version No. 2.0 of 02/01/2023

Sponsor:
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Version history:

Version	Date	Author	Changes/comments
1.0	09/07/2020	SLB Pharma	Creation — version for regulatory submission
1.1	25/09/2020	SLB Pharma	Initial notice: amendments required by the CPP (interim notice dated 17/09/2020)
2.0	02/01/2023	SLB Pharma	MS01: Study extension with 5-year clinical follow-up of PA1704 arm

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List of abbreviations

AADE	Expected Adverse Device Effect
ADE	Adverse Device Effect
AE	Adverse Event
ANSM	French National Agency for the Safety of Medicines and Health Products
CIP	Clinical Investigation Plan
CNIL	Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority)
CPITN	Community Periodontal Index of Treatment Needs
CPITN	Community Periodontal Index of Treatment Needs (ICBTP in French)
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DMFT	Decayed, Missing due to caries and Filled Permanent Teeth
EC	Ethics Committee
eCRF	Electronic Case Report Form
ER	Endodontic re-treatment
ET	Endodontic treatment
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	Gutta-percha
HAS	Haute Autorité de Santé (French Health Authority)
LPPR	List of reimbursable products and services
MD	Medical Device
MDCG	Medical Devices Coordination Group
mITT	Modified Intention to Treat
mm	Millimetres
NaOCl	Sodium hypochlorite
NI	Non-Inferiority
NSAIDs	Non-steroidal anti-inflammatory drug

NSR	Number of Subjects Required
PEC	Principal Outcome Measure
PP	Per Protocol
PROBE	Prospective, Randomized, Open, Blinded Endpoint (clinical trial design)
RIHS1	Category 1 research involving human subjects
RM	Reference Methodology
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
TRA	Toxicological Risk Analysis
UADE	Unexpected Adverse Device Effect
VAS	Visual Analogue Scale

Approval form — Clinical Trial Protocol

Version No. 2.0 dated 02/01/2023
OPTIFILL Trial

Evaluation of the Efficacy Rate of Endodontic Treatment at 2 Years After Root Canal Filling With a Ready-to-use Root Canal Sealer PA1704 Versus BioRoot™ RCS: a Randomized Controlled Trial..

Sponsor – SEPTODONT

Name and title	*Job title*	*Date (dd/mm/yyyy)*	*Signature*
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Jean-Christophe Perles	Clinical Trial Lead Manager		

Coordinating Investigator

Name and title	*Job title*	*Date (dd/mm/yyyy)*	*Signature*
Prof. Stéphane Simon (DDS, MS)	Investigator — coordinator		

Service provider — SLB PHARMA

Name and title	*Job title*	*Date (dd/mm/yyyy)*	*Signature*
[redacted]	CEO		
[redacted]	Clinical project manager — biostatistician		

1. General information

2.1. Identity of sponsor, coordinating investigator and trial sites

Study title	**Evaluation of the Efficacy Rate of Endodontic Treatment at 2 Years After Root Canal Filling With a Ready-to-use Root Canal Sealer PA1704 Versus BioRoot™ RCS: a Randomized Controlled Trial.**
Sponsor project code	20/001
Product code / study code	PA1704/OPTIFILL
ID-RCB number:	**2020-A01790-39-PP**
Version and date of clinical trial plan	V2.0 of 02/01/2023
Sponsor	SEPTODONT 58, rue du Pont de Créteil 94107 Saint-Maur-des-Fossés Cedex Tel.: +33 (0)1 49 76 70 00 [redacted] www.septodont.fr Contacts: Farid Benabdallah, Director of Medical Affairs Jean-Christophe Perles, Clinical Trial Lead Manager Raphael Haddad, Clinical Trial Project Manager
Coordinator	Prof. Stéphane Simon [redacted] 76000 ROUEN Contact: Tel: [redacted] Email: [redacted]
Trial sites	Multicenter trial taking place in France and Belgium. The trial sites will be both public and private. The investigators will be generalist dental surgeons and exclusive endodontists. The trial sites are listed in the document “List of investigators”.

2.1. General synopsis of the clinical trial

Study title	**Evaluation of the Efficacy Rate of Endodontic Treatment at 2 Years After Root Canal Filling With a Ready-to-use Root Canal Sealer PA1704 Versus BioRoot™ RCS: a Randomized Controlled Trial.**
Keywords	Endodontic treatment; endodontic retreatment; permanent root canal sealer (cement)
Methodology / Study design	Multicenter, prospective, randomized, open-label and blind study to assess the primary criterion (PROBE design). PA1704 versus BioRoot™ RCS non-inferiority study.
Study schedule	Duration of recruitment period: 9 months, Expected duration of participation for each subject: 24 months (BioRoot™ RCS arm) or 5 years (PA1704 arm), Total planned duration of the clinical trial: 5 years and 9 months.
Medical devices being studied	This study relates to 2 implantable dental medical devices. PA1704 and BioRoot™ RCS are 2 permanent root canal filling materials for initial or repeated endodontic care, manufactured by Septodont. These are tricalcium silicate-based cements; they come in 2 different formats and are used in combination with gutta-percha: • **PA1704 is the medical device under investigation**: Class IIa MD available in ready-to-use format; the cement is prepared in a syringe. • **BioRoot™ RCS is the medical device comparator**: Class III MD, CE marked and used in accordance with the instructions. It comes in a mixing box comprising of a vial of powder composed of tricalcium silicate, zirconium oxide and povidone and an aqueous solution of calcium chloride and polycarboxylate. The powder and liquid must be mixed extemporaneously by the dental surgeon to form the cement.
Aims of the study	The aim of the clinical trial is to evaluate the performance and safety of the PA1704 ready-to-use filling material compared to BioRoot™ RCS cement. Main objective: Evaluation of the 24-month efficacy rate of endodontic treatment determined on the basis of radiological and clinical criteria. Secondary objectives: - Evaluation of the 6-month efficacy rate determined on the basis of radiological and clinical criteria, - Evaluation of the 12-month efficacy rate determined on the basis of radiological and clinical criteria, - Assessment of the efficacy of the PA1704 ready-to-use filling material at 3.5 and 5 years, determined on the basis of radiological and clinical criteria. - Radiological assessment of the quality of the apical filling:

	○ Adequate obturation length versus over-obturation and under-obturation (evaluated at T0 using an immediate post-op X-ray scan), ○ Density (assessed at T0, 6 months, 12 months, 24 months for the 2 filling materials, and additionally assessed at 3.5 years and 5 years for the PA1704 ready-to-use filling material) ○ Resorption of extruded material in the periapical space in the event of over-filling (assessed at 6 months, 12 months, 24 months for the 2 filling materials, and re-assessed at 3.5 years and 5 years for the PA1704 ready-to-use filling material), - Description of the pain experienced by the patient in the 7 days post-operation. - Description of the use painkillers taken orally during the 7 days post-operation (frequency, cumulative dose, class of painkiller), - Evaluation of tooth functionality and pain on percussion at each clinical follow-up visit (coronal restoration treatment (within 45 days), 6 months, 12 months, 24 months for the 2 filling materials, and additionally assessed at 3.5 years and 5 years for the PA1704 ready-to-use filling material). - Evaluation of adverse events occurring after endodontic treatment (continuous evaluation up to 24 months for the BioRoot™ RCS filling material, and up to 5 years for the PA1704 ready-to-use filling material), - Description of the surgical technique for first-line endodontic treatment (ET) or repeat endodontic treatment (RET) and any perioperative complications, - Evaluation of operator comfort and satisfaction with the use of the filling material.
Outcome measures	<u>Primary outcome measure</u>: Efficacy rate at 24 months of treatment based on radiological criteria assessed blind by independent reviewers (complete healing, reduction of lesions, failure) AND clinical criteria assessed by the investigator (functionality of tooth and pain levels). <u>Secondary outcome measure</u>: - Efficacy rate at 6 months based on radiological and clinical criteria, - Efficacy rate at 12 months based on radiological and clinical criteria, - 3.5-year efficacy rate based on radiological and clinical criteria (PA1704 arm only), - 5-year efficacy rate based on radiological and clinical criteria (PA1704 arm only), - Post-operative pain experienced by the patient (VAS 0-100 mm) at T0 (start of session), end of surgery, 12h, 24h, 48h, 72h and 7 days,

	Pain assessment at each visit (coronal restoration at 45 days, 6 months, 12 months, 24 months, 3.5 years and 5 years in the PA1704 arm only): Patient interview + evaluation by practitioner after percussion, - Use of pain relief taken orally between T0 and D7, - Additional dental consultation for complications or significant postoperative pain, - Quality of apical obturation at T0 (complete obturation, under-obturation or over-obturation), - Evolution of material resorption over time, in the event of over-filling at T0 (6 months, 12 months and 24 months, then at 3.5 years and 5 years in the PA1704 arm only), - Root canal filling density at T0, 6 months, 12 months, 24 months, 3.5 years and 5 years, in the PA1704 arm only. - Adverse events: Number of patients with at least 1 AE, and number of AEs (description of symptoms, attributability to the filling material or surgical technique). - Description of surgical technique: description of the type of instruments used, type of irrigation solutions and irrigation technique used, method of applying the filling material and condensing the gutta-percha. - Operator comfort and satisfaction: comfort, ease of handling the device, ease of applying the material, difficulties encountered, time, reproducibility of root canal preparation and filling, advantage of the ready-to-use form, overall practitioner satisfaction.
Eligibility criteria for patient volunteers	<u>Inclusion criteria</u>: - Men or women aged over 18 years, - Patients requiring endodontic treatment on *a* single tooth, in accordance with the latest HAS recommendations; treatment may be first-line (ET) or repeat (ER), on a monoradiculated or pluriradiculated tooth. - Patients who are geographically stable and/or regularly monitored by the practice, and who can be monitored over 24 months, - Patients who have signed their consent form, - Patients affiliated to a social security / insurance scheme (Art L1121-11 of CSP). <u>Dental exclusion criteria</u>: - Patients with a formal contraindication to endodontic treatment, - Patient with a known contraindication to the use of BioRoot™ RCS or PA1704 filling material: endodontic treatment on immature or provisional teeth, known hypersensitivity to any of the compounds in the formula. <u>Exclusion criteria related to participation in the clinical trial</u>: Patients meeting at least one of the following criteria cannot be included in the study.

	These criteria are not contraindications to the use of a permanent root canal filling material, but the first 4 on the list are confounding factors known to negatively influence healing rates and prognosis: - Endodontic treatment of a tooth with a calcified root canal, - Endodontic treatment of teeth with suspected perforation, - Patients with a non-stabilized systemic disease such as diabetes or thyroid disorders, or who are immunocompromized or have undergone radiotherapy of the jaw. - Patients suffering from active non-stabilized and untreated periodontitis. - Simultaneous participation in another interventional trial, - Vulnerable subjects referred to in Articles L.1121-5 to 8 and L.1122-1-2 of the Public Health Code and Article 66 of Regulation (EU) 2017/745 on medical devices are excluded from the trial: Pregnant women, breast-feeding mothers, persons deprived of their liberty, hospitalized without consent or admitted to a health or social establishment for purposes other than research, minors, adults under legal protection (guardianship or trusteeship) or unable to express their consent, persons in emergency situations unable to express their prior consent.
Forecast number of cases	Based on the assumption that there is no difference in efficacy at 24 months between the 2 filling materials (PA1704 and BioRoot™ RCS) and that the expected efficacy rate of BioRoot™ RCS after initial and repeated endodontic treatment is 90% (Zavattini et al., 2020; Chybowski et al., 2018, Bardini et al., 2019), we calculate that a minimum of 66 subjects per group must be included **to show non-inferiority of PA1704 over BioRoot™ RCS** with a confidence interval of 80%, a unilateral alpha risk of 5% and a 13% difference in efficacy tolerance between the 2 products (Ng YL. et al 2007; Ng YL. et al., 2008; Eyuboglu et al., 2016). By including an additional 20% of patients in order to take into account those lost to or withdrawn from the study, **the number of patients that must be included is 80 in each group, or 160 patients in total**. Patients will be included either due to indication for initial endodontic treatment or due to indication for repeat treatment; the proportion of repeat treatments will be 30%.
Study procedure	Patients will be selected and included during consultations with the investigating dental surgeons. Once a diagnosis requiring first-level endodontic treatment or re-treatment is given, the investigator will offer the patient the opportunity to participate in the study and will seek to obtain their consent after introducing them to the study, in accordance with Good Clinical Practice. Once the endodontic treatment has been completed and the permanent coronal restoration has been carried out, patients will be monitored regularly for 2 years, with 3 follow-up visits scheduled: at 6 months, 12 months and 24 months. At each visit, a clinical examination and a retro-alveolar X-ray will be carried out to assess the results of the treatment. At the end of the 24-month follow-up period, only patients treated with the PA1704 ready-to-use filling material will be offered the option of continuing

	the clinical follow-up for up to 5 years; in which, at their annual dental check-up in the 4th and 5th years following the endodontic treatment, a clinical examination and a retro-alveolar X-ray will be performed to assess the results of the treatment. Study procedure: **V0 — Selection visit**: - diagnosis (preoperative 2D retro-alveolar X-ray) and verification of eligibility, - oral information about the trial and delivery of patient information and consent form, **V1 — Enrolment visit** - Collection of written **consent** - Recording in the eCRF of **patient characteristics at enrolment** (sex, age, oral-dental status, history and treatments) AND characteristics of the **tooth to be treated** [tooth number, number of canals to be filled, initial or repeat endodontic treatment, pulpal and periapical diagnosis, preoperative pain *(if root canal preparation and filling are carried out over several sessions, preoperative pain is recorded at the start of each session*)]. - **Randomization** (PA1704 vs BioRoot™ RCS filling material). - **Endodontic treatment** in 1 or 2 sessions depending on each practitioner's usual practice and the clinical situation (initial or repeat endodontic treatment): **1)** removal of the old filling material in case of retreatment, **2)** root canal preparation, **3)** standardized root canal obturation (obturation cements will be used with Gutta-Percha cones in accordance with the manufacturer's recommendations using the single cone technique or cold lateral condensation), - Immediate post-operative **X-ray check** (=T0) to verify the level of the apical filling. - **Temporary (or permanent, if applicable) sealed coronal reconstruction** (glass ionomer cement or bonded composite). *Permanent coronal reconstruction must be carried out within 45 days (see V2 visit)* ; *this can be carried out on the same day as the endodontic treatment if the conditions are met. The use of a temporary cement such as Cavit® is strongly discouraged in this trial. If this is used between sessions, it must be for a short period; a sealed restoration operation must be scheduled within a maximum of 3 weeks. The use of IRM® cement is not permitted in this trial.* - Explanations and delivery of the **patient record** for recording post-operative pain over 7 days (starting from the root canal filling session), taking of analgesics and adverse events. - Schedule the next consultation: either the V2 visit to perform the usual permanent coronal restoration (if the restoration was provisional at V1 i.e. within 45 days), or the V3 follow-up visit at 6 months if the permanent coronal restoration was performed at V1. **Telephone consultation at D7** Check that the follow-up booklet has been completed correctly and remind the investigator how to return it.

	Questionnaire about the occurrence of AEs since treatment (T0). **V2 — Visit for permanent coronal restoration (to be carried out within 45 days of the temporary restoration operation)** If the investigator performs the usual permanent coronal reconstruction: - Collection of the completed patient record, - Clinical examination: verification of the functional status of the treated tooth and percussion test (lateral and axial), - Reporting of AEs. - Permanent coronal or coronal-radicular reconstruction. If the usual permanent coronal restoration was not carried out by the investigator BUT by the patient's usual dentist: - Record data in the follow-up letter from the usual dentist relating to 1) the functional state of the treated tooth and the result of the percussion test, 2) the technique and materials used for the permanent coronal restoration, 3) any AEs. - Collection of the completed patient record. **V3 — Clinical follow-up visit at 6 months (± 1 month) — Standard practice** - **Clinical examination**: Verification of the functional status of the treated tooth and percussion test (lateral and axial), - Reporting of AEs. - Retro-alveolar **X-ray check** to assess endodontic treatment at 6 months: 1) density of root canal filling, 2) progress of resorption of extruded material where applicable, 3) apical lesion (absence/ appearance/always present compared against T0) and progress in the size of an existing lesion. - Procedures in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion are detailed in the Clinical Investigation Protocol. **V4 — Clinical follow-up visit at 12 months (± 1 month) – Standard practice** - **Clinical examination**: verification of the functional status of the treated tooth and percussion test (lateral and axial), - Reporting of AEs. - Retro-alveolar **X-ray check** to assess endodontic treatment at 12 months: 1) density of root canal filling, 2) progress of resorption of extruded material where applicable, 3) apical lesion (absence/ appearance/always present compared against T0) and progress in the size of an existing lesion. - Procedures in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion are detailed in the Clinical Investigation Protocol. **V5 — Clinical follow-up at 24 months (± 1 month) — Standard practice** - **Clinical examination**: verification of the functional status of the treated tooth and percussion test (lateral and axial), - Reporting of AEs.

	- Retro-alveolar **X-ray check** to evaluate endodontic treatment at 24 months: 1) density of root canal filling, 2) progress of resorption of extruded material where applicable, 3) apical lesion (absence/ appearance/always present compared against T0) and progress in the size of an existing lesion. - Procedures in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion are detailed in the Clinical Investigation Protocol. **PA1704 arm: V6 — Clinical follow-up visit at 3.5 years (± 6 months) — Standard practice** - **Clinical examination**: Verification of the functional status of the treated tooth and percussion test (lateral and axial), - Reporting of AEs. - **Retro-alveolar X-ray check** to evaluate the results of the endodontic treatment at 3.5 years: 1) density of root canal filling, 2) progress of resorption of extruded material where applicable, 3) apical lesion (absence/appearance/always present compared against T0) and progress in the size of an existing lesion. - Procedures in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion are detailed in the Clinical Investigation Protocol. **PA1704 arm — optional: V7 — Clinical follow-up visit at 5 years (± 6 months) — Standard practice** - **Clinical examination**: Verification of the functional status of the treated tooth and percussion test (lateral and axial), - Reporting of AEs. - **Retro-alveolar X-ray check** to evaluate the results of endodontic treatment at 5 years: 1) density of root canal filling, 2) progress of resorption of extruded material where applicable, 3) apical lesion (absence/appearance/always present compared against T0) and progress in the size of an existing lesion. - Procedures in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion are detailed in the Clinical Investigation Protocol. **Centralized and independent X-ray check-up campaigns** 5 centralized blind radiography review campaigns have been planned. Two (2) qualified and independent reviewers will assess the X-rays at the end of the 6-month clinical follow-up (V3) of all patients, then at the end of the 12-month clinical follow-up (V4), at the end of the 24-month clinical follow-up (V5), then at the end of the 3.5-year follow-up (V6) and the 5-year follow-up (V7) for patients treated with the PA1704 material only (for X-ray reviews at the V6 and V7 visits, the reviewers will be blind to the centre but not to the treatment, as only the PA1704 arm is addressed in these visits). For each X-ray review campaign, the following X-ray criteria is evaluated: - Evaluation of the apical lesion (evolution in relation to T0): complete healing / incomplete healing / failure. - Root canal filling density, - Resorption of extruded material, where applicable.

Statistical Methods	Non-inferiority study: we aim to show that the 2-year efficacy rates of the 2 filling materials PA1704 and BioRoot™ RCS are comparable. Performance evaluation will be based on the "Per Protocol" (PP) population. A supportive analysis will be carried out on the "Intention to Treat" (ITT) population. A safety assessment will be carried out on the "Tolerance" population. Descriptive analyses: The clinical data collected at enrolment and at each visit, as well as variations between each occasion, if applicable, will be described in each group and in the total population. Descriptive statistics will be presented according to the nature of the criterion analyzed: - Quantitative variable: cohort, number of missing data, mean, standard deviation, median, minimum, maximum; - Qualitative variable: absolute frequencies (N) and relative frequencies (%) per class in each group, number of missing data. Comparative analyses (for an NI study): *Analysis of the primary performance criterion:* this will be carried out using 2 approaches, in accordance with the literature: - **Primary soft criteria analysis**: treatment rates with complete or incomplete cure are compared against failure rates, - **Secondary analysis of strict criteria**: treatment rates with complete healing are compared against rates of failure or incomplete healing (complete healing can take up to 4 or 5 years). The comparison of efficacy rates between the 2 groups will be carried out using the Dunnett and Gent χ^2 test (Dunnett CW and Gent M. 1977; Elie C. et al., 2008). We will reject the null hypothesis H0 and **conclude that the new PA1704 material is not inferior to the BioRoot™ RCS reference material if the difference in 2-year efficacy rate between the 2 products is greater than the non-inferiority limit, set at 13%**. In addition, the difference in the 2-year efficacy rate between the 2 materials are to be calculated; its unilateral confidence interval of 95% will be provided and the lower limit is will be compared against the non-inferiority limit. *Additional analyses*: The primary performance criterion will also be analyzed depending on covariates (prognostic factors at enrolment, factors related to the surgical procedure), including: - Indication for endodontic treatment: initial versus retreatment, - Diagnosis at T0: presence versus absence of apical lesion, - Operating technique used, type of irrigation solution used to clean the root canal, technical platform (whether or not a microscope is used). *Analysis of secondary performance and safety criteria*: As a general rule, 2 independent means are compared using the Student's t-test; if the variances are unequal (verified by the Fisher's test), Welch's test will be used instead of the Student's test. If the conditions for applying the Student test are not met ($n < 30$), the non-parametric Wilcoxon test is used.

	2 independent percentages are compared using Pearson's Chi-2 test. If the conditions for application are not met (at least one theoretical number < 5), Fisher's exact test is used. The tolerance analysis will focus on the Tolerance population. Tolerance data is to be expressed as the number of adverse events (AEs) and the number of patients reporting at least one AE. Severity, cause (filling material or surgical technique) and the time of occurrence shall be described. The proportions of AEs and patients with AEs will be compared between the 2 groups. Defects in the devices will be described in the form of a list and proportions will be compared between the 2 groups. Number of statistical analyses planned: No interim analysis of the primary criterion is planned. The main analysis will only be carried out after the 2-year follow-up of all patients enrolled. Two interim analyses of secondary performance and safety criteria have been planned. These will be carried out after 6 and 12 months' follow-up for all included patients. For patients treated with the PA1704 ready-to-use filling material and who agree to be followed-up with for up to 5 years, a descriptive analysis of secondary performance and safety criteria at 3.5 years and 5 years will be carried out at the end of their participation.

2. Description of the ready-to-use root canal filling material (PA1704 medical device under investigation)

2.1. Description of the ready-to-use filling material PA1704 and its intended use.

Description of the material:

PA1704 is a new root canal filling material for dental use. Its composition, based on tricalcium silicate, zirconium oxide, calcium carbonate and povidone is very similar to that of BioRoot™ RCS material (see Composition below). Both are cements based on Active Biosilicate Technology (ABS) and manufactured by Septodont.

Unlike BioRoot™ RCS, which comes as two “powder + solution” products to be mixed extemporaneously, PA1704 is a ready-to-use paste packaged in a clear syringe. PA1704 is a homogeneous paste with a creamy consistency, white to slightly grey in color, easily extractable from the syringe. Once injected, the paste hardens *in situ* on contact with the residual water in the root canal.

Clinical indications:

PA1704 is indicated for the permanent filling of permanent teeth canals, in cases of inflamed or necrotic pulp. It is also indicated after a repeat treatment procedure.

It is used in combination with gutta-percha using the single cone technique or cold lateral condensation.

Medical device class:

PA1704 is an implantable medical device with permanent contact (> 30 days) with dental tissue (dentine); it is a class IIa medical device.

Packaging — Presentation:

PA1704 is available in 2 multi-use packs [redacted]:

- [redacted]
- Box containing 1 syringe of 0.5 g of cement ([redacted] single-use flexible intra-canal tips, 1 protective cap, 1 gripping wing.

For this trial, only 0.5 g syringes will be used. One syringe is to be used for 1 patient.

Packaging:

- Primary packaging: syringe and cap
- Secondary packaging [redacted]
- Tertiary packaging: box.

Unlabelled syringe with protective cap:

Unlabelled syringe with intra-canal tip and gripping wing ready for injection of PA1704 cement into the canal:

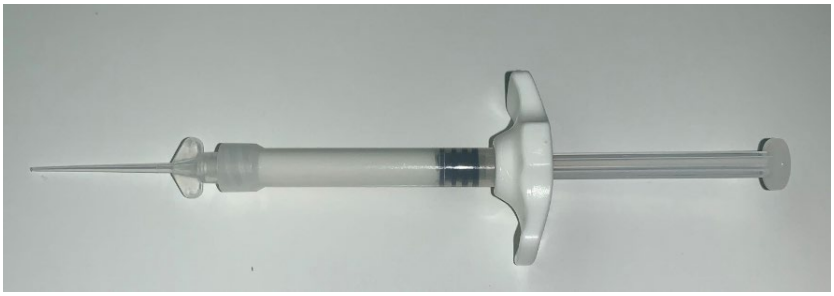

Figure 1: Presentation of the unlabelled medical device PA1704

Composition:

Components	**Role**
[redacted] tricalcium silicate	[redacted]
Zirconium oxide	[redacted]
Propylene glycol	[redacted]
Calcium carbonate	[redacted]
[redacted]	[redacted]
Povidone [redacted]	[redacted]
Aerosil [redacted]	[redacted]

Table 1: Composition of PA1704

Technical specifications:

The specifications of PA1704 cement, determined in accordance with EN ISO 6876:2012, are detailed below and are compared with BioRoot™ RCS (the comparator chosen for this trial).

[redacted]

Table 2: Technical specifications of PA1704 cement.

2.2. Manufacturer

Name and address of manufacturer:

SEPTODONT

58 rue du Pont de Créteil

94107 SAINT MAUR DES FOSSES CEDEX — FRANCE

Tel.: 33 (0)1 49 76 70 00.

2.3. Model or type name or number.

Name: PA1704

2.4. Traceability during and after the clinical trial (batch number).

In accordance with Regulation (EU) 2017/745 on medical devices, Annex I, Chapter III, Article 23.2(q), the following information is to appear on the label:

- Name of the device,
- The words "**Single-use Medical Device reserved exclusively for OPTIFILL clinical trials (ID-RCB number: 2020-A01790-39-PP)**",
- The contents of the packaging and destination of the device;
- The name, company name or registered trademark of the manufacturer, together with the address of its registered office;
- The batch number of the device (preceded by the words "BATCH NUMBER" or an equivalent symbol),
- The date of manufacture (yyyy/mm/dd)
- The date by which the device must be used or implanted safely (yyyy/mm/dd)
- An indication of any special storage and/or handling conditions that may apply,
- Where necessary, any required warnings or precautions must be brought immediately to the attention of the user of the device or any other person.

In addition, the patient's trial identifier is also to be transferred by the investigator to each syringe used, to be recovered at the end of the surgical procedure. The indication "PATIENT __ __ __—__ __" is to be marked on each device.

2.5. Planned objective of the PA1704 device in the proposed clinical trial.

PA1704 is a permanent root canal cement. The aim is to achieve permanent obturation of the root canal(s) using gutta-percha cones, while preserving the functionality of the filled tooth.

2.6. Target population and indications for use

Target population: permanent and mature monoradiculated or pluriradiculated teeth.

Clinical *indications*:

- Permanent root canal filling in the case of inflamed or necrotic pulp.
- Permanent root canal filling after a re-treatment procedure.

Contraindications:

- Immature or temporary teeth.
- Known hypersensitivity to one of the ingredients.

2.7. Summary of the training and experience required to use PA1704 filling material.

PA1704 is a professional dental product. It should be used by dentists carrying out endodontic treatment, whether they are general practitioners or exclusive endodontists, following the instructions for use given in the following chapter.

2.8. Instructions for using PA1704 filling cement and precautions.

Injection of PA1704 into the root canal:

1/ Clean the root canal and shape it using standard endodontic procedures.

2/ Select a master gutta-percha cone and check that it fits the length of the working area

3/ Rinse with sterile saline solution to remove any residual irrigation solution, then dry without completely dehydrating the root canal.

4/ Open the protective sachet and take out the syringe.

Note the patient identifier on the label (PATIENT _ _ _—_ _).

5/ Take out the endodontic tip supplied with the PA1704

CAUTION: It is recommended to use conventional means (techniques) to hold the filling material in the canal with the endodontic tip.

6/ Remove the syringe cap and screw on an endodontic tip as far as it will go.

CAUTION: Make sure that the tip is correctly screwed on to prevent it coming off the syringe during treatment.

7/ The gripping wing can be placed on the syringe to make it easier to push the plunger.

CAUTION: Make sure that the gripping wing is correctly clipped in to prevent it coming off when the material is injected.

8/ Before injecting cement into the canal, check that the cement comes out of the syringe by ejecting a small quantity of material; if the syringe is blocked, do not use it, dispose of it in the syringe recovery box, complete the eCRF defect form and enter the information in the patient's medical record.

9/ Insert the tip into the canal, up to a maximum of the first third of its length; check that the tip is not stuck in the canal, nor being forced in, then gently inject the material, without forcing it and gradually and slowly withdraw the tip from the canal while continuing to inject the product.

10/ Complete the obturation by inserting the master gutta-percha cone (single cone technique) or several gutta-percha cones (lateral condensation technique) to the length required.

11/ Assess the quality of the root canal filling by performing an intraoperative X-ray scan (2D retro-alveolar image; details in Chapter 6.1),

12/ Use a heat source to cut the cone at the entrance to the filled canal.

13/ Complete the procedure by lightly condensing the upper part of the gutta cone with a large-diameter vertical endodontic compactor

14/ Assess the quality of the root canal filling by taking an X-ray (postoperative check) at T0. The images obtained are to be transferred into the eCRF.

After filling with the PA1704 product:

15/ Perform a sealed coronal restoration.

16/ If it is necessary to fit an anchor pin, this should be done after the PA1704 material has fully hardened in the canal, i.e. 7 days.

These instructions for use of the PA1704 device are set out in an instruction sheet which will be supplied to each investigator (see Appendix 1).

2.9. Storing the syringe after use

1/ Unscrew the endodontic tip and discard it (see "Disposal" section),

2/ Remove any excess paste from the end of the syringe with a clean, dry cloth and replace the cap.

CAUTION: Make sure the cap is screwed on tightly.

3/ Clean the syringe with ethanol then store it in the recovery box provided by the CRO (Reminder: the PA1704 syringes used are to be recovered at the end of the clinical trial).

CAUTION: Check that the patient identifier is noted on the syringe label.

2.10. Re-treatment procedure

Remove the existing cement sealant using conventional removal techniques. Then follow the instructions given in the previous sections on "Injecting into the root canal".

2.11. Warnings

- In the root canal, the length of the working area should not exceed 2 mm from the X-ray apex to avoid apical extrusion.

- Do not bend the end cap too much to prevent breaking it.

- In the event of skin or eye contact, the product may cause irritation. Do not handle the device without appropriate personal protective equipment.

- Use a dam to ensure that the cement does not touch the mucosa and is not swallowed.

- Do not use a hot filling technique. If this technique is used, the technical specifications are not guaranteed.

- Using PA1704 without gutta-percha cones will compromise endodontic and retreatment procedures.

2.12. Storing PA1704:

Store PA1704 below 30°C, away from moisture.

Do not exceed the expiry date shown on the outer packaging. The product is currently valid for: 24 months from date of manufacture.

Note: Batch validity tests are currently carried out by SEPTODONT in line with Directive 2003/94/EC, which defines Good Manufacturing Practice. To date, the results obtained indicate a validity period of 24 months. The validity date will be updated as and when required.

2.13. Disposal of products:

Disposal of waste (excess cement, tips, packaging): no specific recommendations; dispose of these in accordance with your usual procedures.

Disposal of PA1704 syringes: store syringes used for treatment and defective syringes in the collection box provided by the CRO; these are to be collected at the end of the clinical trial.

3. Rationale for the design of the clinical trial

3.1. General information on endodontic treatment and cements:

3.1.1. Definition of endodontic treatment

The aim of root canal treatment, or endodontic treatment, is to treat pulpal and periapical diseases, thereby transforming an infected tooth into a healthy, asymptomatic and functional part of the dental arch. Diagnosis of pulpal disease is based on the symptoms described by the patient, data from clinical examination and any tests carried out and X-ray examination (HAS 2008).

Treatment consists of removing all organic substances from the canal (tissue residues, bacteria, products of inflammation) by first mechanically cleaning and disinfecting the canal and then completely filling it with appropriate biocompatible sealing materials (cement and gutta-percha). The aim of endodontic treatment is to prevent re-infection of the root canal and to eliminate the apical lesion by **sealing it tightly all the way to the apex, including the canal branches**. Successful endodontic treatment means closely following each of the operative stages:

- **Preparing the root canal:** enlargement of the canal space using endodontic files, then cleaning the site with disinfectant solutions.
- **Root canal obturation:** the canal space is sealed using a non-resorbable, biocompatible thermoplastic substance called “gutta-percha”, bound to the canal walls with a film of cement (MD under investigation or comparator MD), which is then condensed in the canal; complete three-dimensional sealing of the entire canal system, as close as possible to the cement-dentine junction without excessively over— or under-filling at the apex, is the expected result (AAE 1994).
- **The crown is** temporarily restored and sealed and then, several days later, a standard permanent crown is fitted.

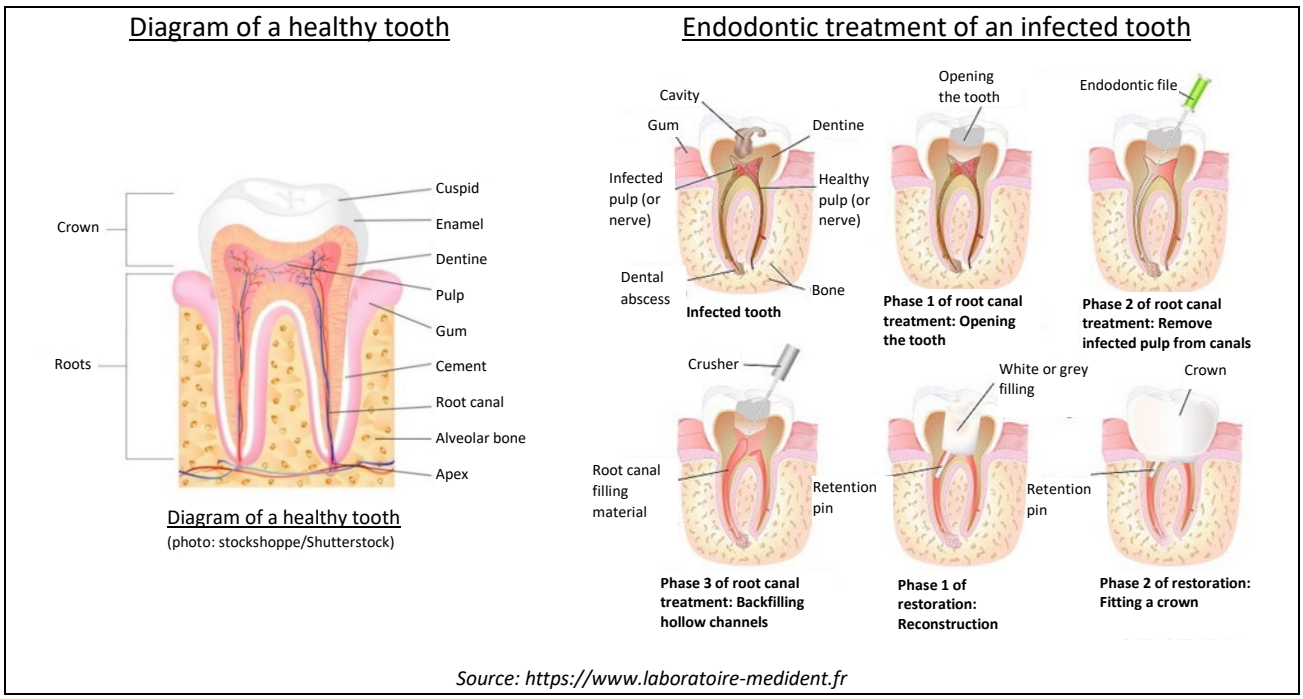

Figure 2: Stages of endodontic treatment

3.1.2. Efficacy of endodontic treatment

It can take several years for a periapical lesion to heal completely, so that the success of the treatment can be assessed. According to Ørstavik (1996) and the recommendations of the European Society of Endodontology (2006), **a minimum period of 12 months is essential to assess the efficacy of a treatment** on the basis of clinical and radiological criteria. Ørstavik (1996) reported that the peak incidence of healing occurs at 1 year; he also showed that 88% of roots in which the extent of the radiolucency had decreased after 4 years had already begun to regress during the first year. Extending the follow-up to 3 or 4 years may be necessary to record a stable treatment result (Friedman 2002). However, the longer the follow-up period after endodontic treatment, the lower the percentage of patients who present for their follow-up visit (recall rate), which may invalidate the trial results (Friedman 2002). Ørstavik et al. (2004) found that patients who were absent at the follow-up visit demonstrated more clinical symptoms and felt that their treatment had failed.

Therefore, all root canal treatments should be **evaluated clinically and immediately by X-ray at 1 year and then periodically,** depending on the situation (ANDEM 1996 ; European society of endodontology, 2006).

To assess the success of a treatment, Wu et al. (2011) suggest measuring **effective or ineffective treatment rates,** rather than using the terminology "success and failure rates":

- An **effective endodontic treatment** is defined by the absence of symptoms and partial or complete healing of the apical lesion,
- An **ineffective treatment** is defined as the development of a lesion or the increase in size of a pre-existing lesion, whether or not associated with the emergence of clinical signs or symptoms in the patient; this unfavorable development leads to the endodontic treatment having to be repeated.
- If the tooth is asymptomatic and the size of the apical lesion has not changed significantly, the efficacy of the treatment is considered **uncertain** and monitoring must continue.

The efficacy of **initial or repeated endodontic treatment** is affected by a number of preoperative clinical and technical factors. Clinically, pulp diagnosis, state of the canal (calcified canal, presence of a perforation) or the presence of a pre-operative peri-radical lesion can have a negative impact on the result. From a technical point of view, several root canal preparation and obturation techniques exist and studies have not led to the conclusion that one technique is superior to another (HAS 2008). Nevertheless, the level to which the root canal is filled at the apex is a deciding factor in the prognosis; full obturation of the root canal up to the X-ray apex is expected; in the case of under-filling (i.e. the canal is not completely filled and the X-ray image shows that the apical limit of the filler is less than 2 mm in relation to the X-ray apex), the result is a medium-term resumption of infection and necrosis of the remaining nervous and vascular tissues, leading to inflammation and pain and the need to undertake repeated endodontic treatment.

Based on two systematic reviews of the literature, Ng et al found that the efficacy rate (i.e. complete or partial cure) was **85.2% (IC95%: 82.2–88.3%) after initial root canal treatment and 77.2% (IC95%: 61.1–88.1%) after repeated** endodontic treatment (Ng 2007; Ng 2008). These meta-analyses are based on dozens of clinical studies conducted over the last few decades, the methodologies for which vary widely, particularly in terms of the root canal filling cements used and the length of patient clinical follow-up after treatment (6 months to 20 years follow-up interval depending on the study; few studies had a follow-up of more than 4 years).

3.1.3. Root canal obturation cements

There are different types of root canal cements. These include zinc oxide-Eugenol-based cements, resin-based materials and **calcium silicate-based cements**. Cement sealants are used in conjunction with gutta-percha cones. On the one hand, they bind the material to the canal walls and, on the other, they fill the spaces inaccessible to the gutta-percha material despite it being compacted (lateral canals and other branches). Together they are very stable and provide a good seal.

Calcium silicate-based cements are of interest in endodontics due to their physical-chemical and biological properties: these materials are **biocompatible, have antimicrobial activity and can promote healing of periapical tissues** (Zhang 2009; Zhang 2010). In addition to their radiopaque and adhesive properties, these cements have a hydrophilic profile, creating a moist environment close to the dentine (Koch and Brave 2010). Secondly, thanks to their malleability, they have a lower viscosity and a better sealing quality than other products. These cements produce hydroxyapatite, which creates a favorable environment for interacting with the dentine.

Bioroot™ RCS is a tricalcium silicate-based cement, developed by Septodont (Saint-Maur des Fossés, [redacted] It is available as two products (powder and liquid) to be mixed; [redacted] the cement does not shrink during the setting phase, making the canal seal very airtight (Simon and Flouriot 2016). This sealing cement is indicated for the permanent filling of root canals in the case of inflamed or necrotic pulp, and also after a retreatment procedure. It is used in combination with gutta-percha using the single cone technique or cold lateral condensation. In a recently published clinical study comparing BioRoot™ RCS to resin-based cement (AH Plus), Zavattini et al (2020) reported **a one-year complete or partial cure rate of 90%** (95% CI: 80–96%; n=53 teeth treated with BioRoot™ RCS). Another clinical study comparing BioRoot™ RCS with zinc oxide-Eugenol cement (Pulp Canal Sealer) showed, in 39 patients who received **BioRoot™ RCS for initial treatment (n=13) or retreatment (n=26), an overall one-year efficacy of 76.9%** (95% CI: 61.6–87.3%) based on strict radiological criteria (i.e. complete cure; Bardini 2019). Finally, data collected [redacted]

Other tricalcium silicate-based cements are available in ready-to-use form (e.g.: Endosequence Bioceramic Sealer, BUSA, USA); the ready-to-use form packaged in syringes facilitates use and presents a lower risk of

heterogeneity during preparation (Yang and Lu 2008). The results of a retrospective study, in which 307 patients were treated with Endosequence Bioceramic Sealer ready-to-use cement and monitored for an average of 30 months, showed an overall efficacy rate of initial and repeat endodontic treatment of 90.9% (83.1% complete cure, 7.8% incomplete cure, 9.1% ineffective treatment; Chybowsky 2018).

The Septodont laboratory has developed **a new calcium silicate-based cement in the form of a ready-to-use material packaged in syringes: PA1704.** It is a class IIa implantable medical device, not CE marked. The PA1704 material has a very similar composition to BioRoot™ RCS and is used for the same endodontic indications. The performance and safety of the PA1704 device need to be assessed before it can be marketed in Europe and the USA.

3.2. Preclinical performance data for the PA1704 device:

[redacted]

3.3. Clinical data on the safety and performance of the PA1704 device:

No clinical experiments have been completed on the use of PA1704. This OPTIFILL clinical trial will be the first use of PA1704 in humans.

However, given the similarities between the 2 filling materials, PA1704 and BioRoot™ RCS, the clinical performance and clinical safety data that will be collected on the new ready-to-use material should be the same as those obtained since 2015 on the BioRoot™ RCS device.

3.4. Rationale for the OPTIFILL clinical trial

Regulatory context:

This OPTIFILL trial is a **pre-CE marking** clinical trial, the aim of which is to evaluate the performance and safety of the PA1704 device in patients for the first time, with a view to its future marketing in Europe and the USA.

Clinical data collected from patients treated with PA1704 will be compared with data collected from the comparator group treated with Bioroot™ RCS. These will also be used by Septodont to feed into the **post-marketing monitoring** plan for the Bioroot™ RCS device.

In order to generate long-term clinical data on the PA1704 MD, as part of the EC marking application filed with the notified body, the sponsor wishes to evaluate the performance and safety of the PA1704 MD for up to 5 years, which is the life span claimed for the BioRoot™ RCS comparator MD.

Objectives:

The aim of this study is to show that the performance and safety of the new filling material are not affected by the change in presentation. To this end, the chosen methodology is a **non-inferiority study of the PA1704 device compared to the BioRoot™ RCS**. The main objective was to assess the **24-month efficacy rate** of endodontic treatment (initial or repeat), determined on the basis of radiological and clinical criteria. Performance and safety at 6 and 12 months are also assessed. The evaluation of the performance and safety PA1704 for up to 5 years has been incorporated into the OPTIFILL study in order to obtain the data needed to monitor the benefit-risk ratio of this new medical device. The OPTIFILL trial is a prospective, randomized, open-label trial with the primary criterion blind. This trial is multicenter and is being conducted in France and in Belgium; the investigators are general dental surgeons and exclusive endodontists.

4. Risks and benefits of the PA1704 investigational device and clinical trial

4.1. Expected clinical benefits of the PA1704 material.

For patients, the expected benefits are linked to treatment:

- Permanent obturation of the root canal(s),
- Preserving the functionality of the filled tooth.

There is no individual benefit linked to patient participation in this trial.

For dental surgeons, the expected benefits of PA1704 are of a practical nature, as the cement is in a ready-to-use format.

4.2. Adverse effects expected from the PA1704 device.

The expected adverse effects from this device on the patient are not known and will be investigated during this trial.

4.3. Residual risks associated with PA1704

At this stage in the verification and validation of the design of the PA1704 device, all the identified risks associated with the manufacture and use of the medical device in the intended indication have been taken into account. In order to minimize or eliminate these risks, contraindications, warnings and precautions for use have been reported in chapter 2 and the Investigator's Brochure.

There is no unacceptable residual risk associated with PA1704.

4.4. Risks associated with taking part in clinical trials.

In this clinical trial, with the exception of the MD under investigation PA1704, all examinations, surgical procedures and products used (including the comparator MD) are the same as those used in current practice.

The risks are the same as in current practice, i.e. those associated with anesthesia and mechanical treatment procedures, disinfection and obturation of the canal:

- Risks associated with the anesthetic protocol: reactions associated with high plasma uptake of the anesthetic (e.g. in the event of inflammation at the injection site or accidental intravascular administration: tremors, dizziness, malaise), local reactions at the injection site.
- Risks associated with mechanical root canal treatment: over— or under-filling, fracture of an instrument in the canal, ingestion of an instrument, post-operative pain, fracture or cracking of a root.
- Risks associated with root canal disinfection: ingestion of disinfectant (usually hypochlorite), allergy, irritation.
- As far as the root canal filling stage is concerned, the possible risks are under— and over-filling. These clinical situations can lead to post-operative pain that is not related to the cement itself, but to re-infection and tissue necrosis, on the one hand, and ligament and nerve tissue compress on the other. Compression of the periapical tissues can lead to paresthesia or hypoesthesia. In most cases, repeat endodontic treatment is necessary in the event of under-filling.

4.5. Possible interactions with concomitant medical treatments.

None.

4.6. Steps taken to control or mitigate risks.

See Chapter 2.11 entitled "Warnings".

4.7. Rationale for the benefit-risk ratio.

The clinical trial does not entail any benefit for the people who take part in the trial, but does not present any significant risk or constraint.

5. Objectives and hypotheses of the clinical trial

5.1. Primary and secondary objectives.

The aim of the clinical trial is to evaluate the performance and safety of the ready-to-use filling material PA1704 compared to BioRoot™ RCS.

Main objective:

Evaluation of the 2-year efficacy rate of endodontic treatment determined on the basis of radiological and clinical criteria.

The radiological criteria will be assessed by independent blind reviewers; the clinical criteria will be assessed by the investigator.

Secondary objectives:

- Evaluation of the 6-month efficacy rate determined on the basis of radiological and clinical criteria,
- Evaluation of the 12-month efficacy rate determined on the basis of radiological and clinical criteria,
- Evaluation of the efficacy of the PA1704 ready-to-use filling material at 3.5 years and 5 years, determined on the basis of radiological and clinical criteria,
- Radiological assessment of the quality of the apical filling:
    - Adequate obturation length versus over-obturation and under-obturation (evaluated at T0 using an immediate post-op X-ray scan),
    - Density (radiopacity + vacuity) assessed at T0, 6 months, 12 months, and 24 months for the 2 filling materials, and additionally assessed at 3.5 years and 5 years for the PA1704 ready-to-use filling material,
    - Resorption of extruded material in the periapical space in the event of over-filling; assessed at 6 months, 12 months and 24 months for the 2 filling materials, and further assessed at 3.5 years and 5 years for the PA1704 ready-to-use filling material,
- Description of the pain experienced by the patient in the 7 days post-operation.
- Description of the use painkillers taken orally during the 7 days post-operation (frequency, cumulative dose, class of painkiller),
- Assessment of tooth functionality and pain on percussion at each follow-up visit (coronal restoration at 45 days, 6 months, 12 months and 24 months for the 2 filling materials, and additionally assessed at 3.5 years and 5 years for the PA1704 ready-to-use filling material).
- Evaluation of adverse events occurring after endodontic treatment (continuous evaluation up to 24 months for the BioRoot™ RCS filling material, and up to 5 years for the PA1704 ready-to-use filling material),
- Description of the surgical technique for first-line endodontic treatment (ET) or repeat endodontic treatment (RET) and any perioperative complications,
- Evaluation of operator comfort and satisfaction with the use of the filling material.

5.2. Hypothesis to be accepted or rejected on the basis of statistical data from the clinical trial.

The OPTIFILL clinical trial is a non-inferiority trial; the aim is to show that the 2-year efficacy rates for the 2 filling materials PA1704 and BioRoot™ RCS are comparable.

i.e.:

π_N = 2-year efficacy rate of PA1704 based on soft radiological and clinical criteria,

π_R = 2-year efficacy rate of BioRoot™ RCS based on soft radiological and clinical criteria,

$\Delta = \pi_N - \pi_R$, the difference in efficacy at 2 years between the 2 treatments,

Δ_L = limit corresponding to a clinically insignificant difference (i.e. the greatest difference in tolerated efficacy between the 2 products) (see Chapter 7.2 for details).

The hypotheses are:

H0: $\Delta \leq -\Delta_L$, PA1704 is inferior to BioRoot™ RCS

H1: $\Delta > -\Delta_L$, non-inferiority of PA1704 compared to BioRoot™ RCS

Using Dunnett and Gent's χ^2 test (Dunnett CW and Gent M. 1977; Elie C. et al., 2008), we will reject H0 and **conclude that the new PA1704 material is not inferior to the BioRoot™ RCS reference material if the difference in efficacy between the 2 products is greater than the non-inferiority limit** (see Figure 3).

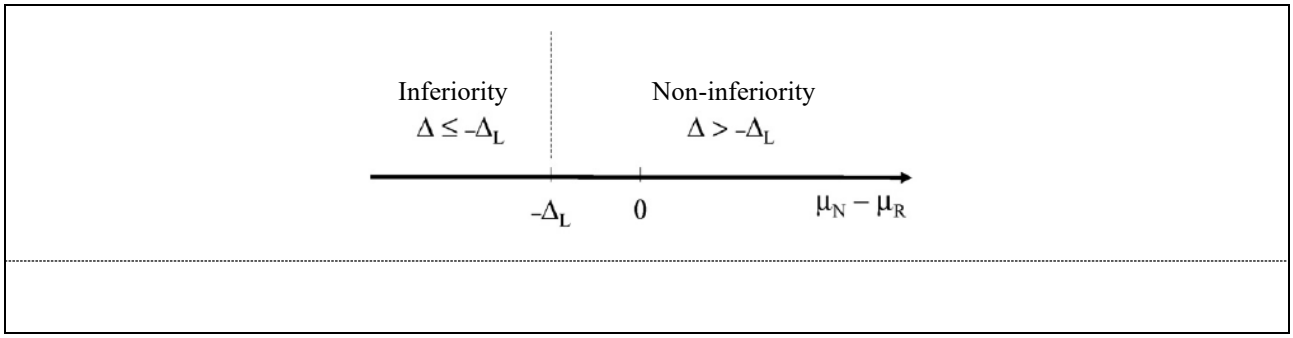

Figure 3: Non-inferiority trial and associated hypotheses (according to Elie et al., 2008).

5.3. Claims and expected performance of the device under investigation that need to be verified.

- Permanent filling of the root canals of permanent and mature teeth.
- Preservation of tooth function.

5.4. Risks and undesirable effects expected from the device, which must be assessed.

The adverse effects of the device are not known in the patient and will be investigated, in particular the occurrence of any allergic reaction, as soon as the material is applied to the root canals.

6. Clinical trial design

6.1. General points and methodology

✓ *Methodology — trial design*

Prospective, multicenter, randomized, controlled, open-label study, with blind evaluation of the primary criterion and several secondary criteria (PROBE design).

Parallel group design (1:1):

- The arm receiving the device under investigation: PA1704
- The arm receiving the comparator medical device: BioRoot™ RCS.

✓ *Measures to reduce or avoid bias.*

Randomization and stratification:

Before the trial is set up, the CRO's biostatistician will computer-generate a block randomization list stratified by clinical indication (initial endodontic treatment (ET) versus re-treatment (ER)). The randomization system will be integrated directly into the electronic CRF.

Randomization will be carried out by the electronic CRF once the eligibility criteria have been checked, the clinical indication (ET or ER) has been determined and all this information has been recorded in the specific module by the investigator.

It should be noted that the proportion of ERs will be 30% of the overall sample, which is close to the rate reported in a French Health Insurance survey (Masson 2002). The rate of ER may vary between sites: some investigators, because of their specialty in endodontics, will include a majority of patients with an indication for re-treatment, whereas GP investigators will probably have more indications for first-line treatment.

Blind:

Investigators and patients will not be blind to the medical device allocated due to the different ways in which the 2 products are presented and used. On the other hand, two independent qualified assessors (previously calibrated under the supervision of the study coordinator) will conduct the blind, centralized review of the retro-alveolar X-rays taken at T0 (reference radiograph obtained immediately post-operatively), 6 months, 12 months, 24 months, 3.5 years and 5 years (Refer to Section "*Equipment to be used to evaluate clinical trial variables and arrangements for monitoring maintenance and calibration.*" section of this chapter); they will be blinded to centre, patient, indication (initial or repeat endodontic treatment), and treatment arm; the files will first be anonymized by the CRO.

✓ *Outcome measures*

Primary criterion (composite criterion):

The primary criterion is the **2-year efficacy rate of endodontic treatment** based on radiological criteria assessed blind by independent reviewers (complete healing, reduction of lesions, failure) AND clinical criteria assessed by the investigator (tooth functionality and pain).

Secondary criteria:

Reminder of secondary objectives	Secondary outcome measure	Time of evaluation (*assessor*)
Evaluation of the 6-month efficacy rate determined on the basis of radiological and clinical criteria	Radiological criteria (complete healing, reduction of lesions, failure) AND clinical criteria (tooth functionality and pain)	6 months (radiological criteria assessed by blind *reviewers*; clinical criteria assessed by *investigator*)
Evaluation of the 12-month efficacy rate based on radiological and clinical criteria	Radiological criteria (complete healing, reduction of lesions, failure) AND clinical criteria (tooth functionality and pain)	12 months (radiological criteria assessed by blind *reviewers*; clinical criteria assessed by *investigator*)
Assessment of the 3.5-year efficacy rate of the endodontic treatment determined on the basis of radiological and clinical criteria (PA1704 arm only)	Radiological criteria (complete healing, reduction of lesions, failure) AND clinical criteria (tooth functionality and pain)	3.5 years ± 6 months (radiological criteria assessed by *reviewers blind to the centre*; clinical criteria assessed *by the investigator*)
Evaluation of the 5-year efficacy rate on the basis of radiological and clinical criteria (PA1704 arm only)	Radiological criteria (complete healing, reduction of lesions, failure) AND clinical criteria (tooth functionality and pain)	5 years ± 6 months (radiological criteria assessed by*reviewers blind to the centre*; clinical criteria assessed by *the investigator*)
Radiological evaluation of the quality of the apical filling (in terms of the level of apical filling, density and resorption of the extruded material)	Level of obturation at the X-ray apex (complete obturation, under-filling or over-filling)	T0 immediate post-op (*investigator*)
	Density: radiopacity and presence of vacuity	T0, 6 months, 12 months, 24 months for the 2 arms, And 3.5 years, 5 years for the PA1704 arm. *(investigator + blind reviewer*)
	Resorption of extruded material in the periapical space in the event of over-filling	6 months, 12 months, 24 months for the 2 arms, And 3.5 years, 5 years for the PA1704 arm. *(investigator + blind reviewer*)
Description of the pain experienced by the patient in the 7 days post-operation.	Preoperative pain (VAS 0-100 mm), Post-operative pain at different times after root canal obturation, Maximum post-operative pain felt between T0 and 7 days, Time to onset of maximum pain	Preoperative (at the start of each endodontic treatment session, i.e. 1 or 2 sessions for root canal preparation and obturation), T0 (end of endodontic treatment), T12h (or before going to bed or getting up the next day depending on the time at T0), T24h, T48h, T72h and 7 days (*patient, investigator*)

Description of the use of *oral* painkillers in the 7 days following surgery	Classes of painkillers, Reason for use, Frequency of painkiller intake, Cumulative dose over 7 days Proportion of patients who used an *oral* painkiller between T0 and D7	T0 to D7 (*patient, investigator*)
Evaluation of adverse events following endodontic treatment	Proportion of patients with at least 1 AE Number of AEs; Type of AE, intensity, level of attribution to the filling material or surgical technique. Number of additional dental consultations for complications or significant postoperative pain. Number of faults and description.	Continuously from T0 to 24 months for the BioRoot™ RCS arm, and 5 years for the PA1704 arm*(investigator)*
Description of the surgical technique for first-line endodontic treatment (ET) or repeat endodontic treatment (RET) and any perioperative complications,	Type of anesthesia, Technique for removing the old filling material (ER only), Type of endodontic instruments used to shape the canal, Type of disinfectant and rinsing solutions used and solution activation technique used, Gutta-percha condensation technique, Coronal restoration technique, Description of any intra-operative complications.	T0 (*investigator*)
Evaluation of operator comfort and satisfaction with the use of the material	Comfort, practicality of handling the device, ease of applying the material, difficulties encountered, time, reproducibility of root canal preparation and obturation, Advantages and disadvantages of the ready-to-use form compared with the powder-liquid form. Overall practitioner satisfaction.	T0 (CRF— *investigator*) then at the end of the trial (overall satisfaction questionnaire — *investigator*)

Table 3: List of secondary outcome measures.

✓ *Methods and times for evaluating, recording and analyzing variables.*

Measurement time and people in charge of evaluation:

For each criterion, this information is given in the table above.
Generally speaking, the assessment of performance and safety criteria begins with the root canal obturation.

Method of evaluating the efficacy rate of initial or repeat endodontic treatment (at 6 months, 12 months and 24 months for the 2 arms; and 3.5 years and 5 years for the PA1704 arm):
Therapeutic efficacy is a composite criterion based on the radiological data assessed **in blind conditions** by reviewers AND on the clinical data assessed **in an open-label manner** by the investigator at the follow-up visits at 6 months, 12 months, 24 months, 3.5 years and 5 years (only the PA1704 arm for the last 2 visits).
With regard to the blind evaluation of the radiological criteria by two independent reviewers, the following clarifications are provided:

- The reviewers shall examine the anonymized retro-alveolar images (JPEG files as described in the imaging procedure in section "*Equipment to be used to evaluate clinical trial variables and arrangements for monitoring maintenance and calibration.*" of this chapter) and answer the following questions:
    - Apical lesion: **1)** Presence, absence or appearance of a lesion compared with the T0 reference image? **2)** In the case of a pre-existing lesion at T0, what is the evolution of the size of the lesion (reduction, stabilization or increase)?
    - Root canal filling density: **1)** Is the radiopacity sufficient? **2)** Presence of at least one bubble in the filling material?
    - Resorption of extruded material where applicable: Is the extruded material still present in the apical space?
- Timetable: 5 centralized image review campaigns are planned, one before each statistical analysis:
    - 1st review campaign: At the end of the 6-month follow-up of all enrolled patients, a blind review of the T0 reference image and the 6-month follow-up image,
    - 2nd campaign: after 12 months' clinical follow-up of all patients, blind review of the 12-month check-up image,
    - 3rd campaign: After 24 months of clinical follow-up for all patients, a blind review of the 24-month check-up image,
    - 4th campaign: After approximately 3.5 years of clinical follow-up of the patients treated with the PA1704 MD, a centre-blind review of the 3.5-year follow-up image,
    - 5th campaign: After approximately 5 years of clinical follow-up of the patients treated with the PA1704 MD, a centre-blind review of the 5-year follow-up image.

By combining the responses relating to the radiological and clinical criteria, 3 levels of treatment efficacy are obtained: Effective treatment, Ineffective treatment, Efficacy uncertain (see table below).
Treatment efficacy will be evaluated using 2 complementary approaches:

- Main analysis on soft criteria: the rates of effective or uncertain treatment are compared with the rates of ineffective treatment,
- Secondary analysis based on strict criteria: rates of effective treatment are compared with rates of uncertain or ineffective treatment.

T0	Check-ups at 6, 12 and 24 months		
Radiological criteria	**Radiological criteria (blind reviewer)**	**Clinical criteria (investigator)**	**Conclusion Treatment efficacy rate**
No lesions	No lesions (complete healing)	asymptomatic, functional tooth	Effective treatment
No lesions	Appearance of lesion (failure)	asymptomatic, functional tooth	Ineffective treatment
No lesions	Appearance of lesion (failure)	symptomatic, non-functional tooth	Ineffective treatment
Presence of lesion	No lesions (complete healing)	asymptomatic, functional tooth	Effective treatment
Presence of lesion	Reduction in lesion size (incomplete healing)	asymptomatic, functional tooth	Effective treatment
Presence of lesion	Reduction in lesion size (incomplete healing)	symptomatic, non-functional tooth	Efficacy uncertain
Presence of lesion	Stabilization of lesion size	symptomatic or non-functional tooth	Ineffective treatment
Presence of lesion	Stabilization of lesion size	asymptomatic tooth, functional tooth	efficacy uncertain
Presence of lesion	Increase in lesion size (failure)	symptomatic or non-functional tooth	Ineffective treatment
Presence of lesion	Increase in lesion size (failure)	asymptomatic tooth, functional tooth	Ineffective treatment

Table 4: Evaluation of the efficacy of endodontic treatment based on clinical and radiological criteria.

- ✓ *Equipment to be used to evaluate clinical trial variables and arrangements for monitoring maintenance and calibration.*

Apart from the radiology equipment connected to a computer, no specific equipment is needed to collect the outcome measures.

Retro-alveolar X-rays are taken with an angulator using the parallel planes technique; the **entire tooth should be visible in the image** (crown to apex, passing through the root). There are no other specific settings imposed for the devices.

The images will be converted to .jpg format, without filters, and anonymized before being uploaded to the eCRF.

- ✓ *Procedures for replacing subjects, if necessary.*

See Chapter 7.4

6.2. Medical devices under investigation (ready-to-use material PA1704) and comparator (BioRoot™ RCS powder-liquid material)

✓ *Comparator Medical Device Description — BioRoot™ RCS:*

The selected comparator MD was the BioRoot™ RCS permanent root canal filling material. [redacted] BioRoot™ RCS is a Class III implantable medical device for dental use manufactured by Septodont. BioRoot™ RCS is based on Active Biosilicate Technology (ABS). It is a mineral root canal cement composed mainly of tricalcium silicate, zirconium oxide and calcium chloride. It comes in the form of **two products (powder-liquid) that are to be mixed**. Clinical indications, contraindications, characteristics, instructions for use, warnings, storage and disposal procedures are detailed in the instructions for use (see Annexe 3).

Thus, the medical device under investigation (PA1704) and comparator device (BioRoot™ RCS) are 2 calcium silicate-based cements, which are used for the same endodontic indications but come in 2 different forms, as a powder-liquid mixture or as a ready-to-inject paste. The 2 medical devices are similar and the aim of this study is to show that the performance and safety of the new material are not affected by the change in presentation.

✓ *Exposure to medical devices under investigation and comparator*

Patients included in the study will randomly receive one of 2 filling materials, PA1704 or BioRoot™ RCS, to treat one tooth (one or more root canals depending on the type of tooth affected by pulpal disease). The medical device is administered (implanted) only once, on the day of the endodontic treatment. The material is implanted for the long term, as it is intended to seal the root canals permanently. It is not intended to be removed during the trial, nor after the end of the trial, except where the treatment has failed with an indication to restart treatment.

✓ *List of any other medical devices or medicines to be used during the clinical investigation.*

Initial or repeated endodontic treatment is a surgical procedure that involves several stages and requires the use of several surgical instruments, solutions and filling materials. Several endodontic techniques exist for the preparation and filling of a root canal; these are authorized for trial purposes and practitioners shall maintain their usual practice.

The medical devices and medicines used are:

- Instruments available for shaping the canal: all types of file or broach, manual or mechanical (continuous or alternating rotation system, with or without apex locator).
- Irrigation solutions used to clean the canal:
    - Disinfectant solutions: sodium hypochlorite (NaOCl, mandatory), Chlorhexidine (not systematic),
    - Chelating rinse solutions: EDTA, HEDP, citric acid or other solutions. Solution activation techniques may vary (sonic system, ultrasound, Erbium Yag laser, other laser, other).
- A neutral, semi-solid, compactable filling material to be combined with the luting cement: a master cone of gutta-percha (single cone technique) or several cones of gutta-percha (cold lateral condensation technique).
- Watertight coronal reconstruction material: glass ionomer cement or bonded composite (the use of a temporary cement such as Cavit® is strongly discouraged and the use of IRM® cement is not authorized within the framework of this trial).

✓ *Number of devices under investigation to be used and their justification.*

A total of 80 patients will receive PA1704 (single dose, amount required for a monoradiculated or multiradiculated tooth) and 80 patients will receive BioRoot™ RCS (single dose, amount required for a monoradiculated or multiradiculated tooth).

Number of PA1704 MD to be used: 1 syringe of 0.5 g of cement can seal up to 5 canals. One syringe will be used for a single patient. **80 syringes will have to be used**.

Number of Bioroot™ RCS MD to be used: bearing in mind that one kit can seal 35 canals (i.e. 1 kit used for several patients) and that a vial of powder can be kept for 6 months after opening, 2 BioRoot™ RCS kits will be needed in each investigating center to cover the 9-month recruitment period.

Delivery of MDs to centers: 2 BioRoot™ RCS kits and 15 PA1704 syringes will be delivered to each investigating center at the set-up visit; sachets containing additional caps, grip wings and endodontic tips will also be provided. Depending on the number of patients included, the number of canals to be filled, any device defects and the products' validity date, additional medical devices will be delivered to the investigating practices if necessary.

6.3. Selection of subjects for the study

✓ *Study population*

Patients requiring first-line or repeat endodontic treatment and meeting the eligibility criteria described in the following paragraph will be able to take part in the trial.

Patients taking part in this clinical trial will not be able to take part in any other trial. However, there is no exclusion period at the end of this trial for participation in any other study.

✓ *Inclusion criteria for patient selection.*

The characteristics required for a patient to be included in the trial are:

- Men or women aged over 18 years,
- Patients requiring endodontic treatment on a single tooth, in accordance with the latest HAS recommendations; treatment may be first-line (ET) or repeat (ER), on a monoradiculated or pluriradiculated tooth.
- A patient who is geographically stable and/or regularly monitored by the practice, and who can be monitored for 2 years,
- Patients who have signed their consent form,
- Patients affiliated to a social security / insurance scheme (Art L1121-11 of CSP).

✓ *Non-inclusion criteria for subject selection.*

The following characteristics exclude certain subjects from inclusion in the trial:

Dental exclusion criteria:

- Patients with a formal contraindication to endodontic treatment,
- Patient with a known contraindication to the use of BioRoot™ RCS or PA1704 filling material: endodontic treatment on immature or provisional teeth, known hypersensitivity to any of the compounds in the formula.

Exclusion criteria related to participation in the clinical trial:

Patients meeting at least one of the following criteria cannot be included in the study.
These criteria are not contraindications to the use of a permanent root canal filling material, but the first 4 on the list are confounding factors known to negatively influence healing rates and prognosis:

- Endodontic treatment of a tooth with a calcified root canal,
- Endodontic treatment of teeth with suspected perforation,
- Patients with a non-stabilized systemic disease such as diabetes or thyroid disorders, or who are immunocompromized or have undergone radiotherapy of the jaw.
- Patients suffering from active non-stabilized and untreated periodontitis.
- Simultaneous participation in another interventional trial,
- Vulnerable subjects referred to in Articles L.1121-5 to 8 and L.1122-1-2 of the Public Health Code and Article 66 of Regulation (EU) 2017/745 on medical devices are excluded from the trial: Pregnant women, breast-feeding mothers, persons deprived of their liberty, hospitalized without consent or admitted to a health or social establishment for purposes other than research, minors, adults under legal protection (guardianship or trusteeship) or unable to express their consent, persons in emergency situations unable to express their prior consent.

✓ *Time of enrolment.*

Patients will be included after diagnosis of the need for endodontic treatment.

✓ *Criteria and procedures for withdrawing a subject or interrupting his or her participation.*

The criteria for premature termination of a person's participation in the trial are as follows:

- Withdrawal of patient consent,
- Investigator's decision (reason to be specified),
- Serious adverse event,
- Treatment failure with need for repeat treatment notified before the 24-month follow-up for patients treated with the BioRoot™ RCS filling material, or before the 5-year follow-up for patients treated with the PA1704 ready-to-use filling material,
- Subject lost to follow-up (see definition below*),
- Subject wrongly included (non-compliance with at least one major inclusion and/or exclusion criterion).

Subjects will be able to withdraw their consent and ask to leave the trial at any time for any reason.

The investigator may permanently discontinue a subject's participation for any reason that is in the best interests of the subject, particularly in the case of serious adverse events.

*Definition ofLost to follow-up: the patient is considered lost to follow-up and prematurely withdrawn from the study if he/she fails to attend the follow-up visits scheduled in the protocol (scheduled appointment or, in the event of impediment or cancellation, any other new appointment scheduled), and the investigating center has not heard from the patient, despite repeated attempts to organize and conduct the visit by the investigating center. A patient who is absent from a follow-up visit (at 6 or 12 months, for example) but who attends the end-of-study visit at 24 months is not considered lost to follow-up (this is an interruption of clinical follow-up; the primary criterion collected at 24 months is available).
If a patient is lost to follow-up, the investigator will contact the patient or a family member by telephone to obtain the information needed to close the patient's file (clinical trial completion form).

✓ *Stopping all or part of the clinical trial*

The reasons for temporary or permanent early termination of the trial are as follows:

1) decision of the Sponsor,
2) decision of the person directing and supervising the trial,
3) decision of the institution responsible for the trial.

✓ *Procedures for the premature termination of a person's participation in the trial*

If a patient withdraws prematurely from the OPTIFILL trial, the investigator must document the reasons as fully as possible.

Withdrawal from the trial can only take effect after confirmation by the investigator and the SLB Pharma CRO. Patient withdrawals from the trial are always permanent and patients cannot be included in the trial a second time (for treatment on another tooth, for example). Patients will not be replaced.

The early termination of the OPTIFILL trial will have no impact on the patient's care by his or her dental surgeon. The patient will continue to be monitored as usual by his/her dental surgeon.

In the event of premature termination of the clinical trial, information will be transmitted by the CRO to the competent authorities of each European Member State and to the Ethics Committees within 15 days.

6.4. Timetable for the clinical trial

The trial schedule is defined as follows:

- Duration of recruitment period: 9 months are to be set aside to enrol 160 subjects,
- Expected duration of participation for each subject: 24 months (± 1 month) for patients treated with the BioRoot™ RCS material, or 5 years (± 6 months) for patients treated with the PA1704 material,
- Total planned duration of the clinical trial: 5 years and 9 months.

From the first subject enrolled and on behalf of the sponsor, the CRO shall immediately inform the competent authorities in France (ANSM) and Belgium (AFMPS), as well as the relevant ethics committees, of the effective start date of the trial (Effective start date = date of signature of the consent form by the first person to take part in the trial).

The end of the trial corresponds to the moment at which participation by the last person to take part in the trial comes to an end. The end date of the trial will be sent by the CRO, on behalf of the sponsor, to the competent authorities and ethics committees within 90 days.

6.5. Trial procedure

6.5.1. Description of any procedure related to the clinical trial to which people are subjected during the trial.

All examinations, the frequency of dental consultations and the products used, with the exception of the medical device under investigation, are to be standard practice and comply with the latest HAS recommendations (HAS 2008).

This chapter is divided into successive sections:

- Instructions for use of PA1704 and BioRoot™ RCS filling materials (reminder of Chapters 2.8 and 6.2),
- A description of the materials and techniques recommended to achieve a coronal restoration of a temporary and then permanent nature,
- The procedure for patient visits.

✓ *Instructions for use of PA1704 and BioRoot™ RCS filling materials*

Steps	PA1704 *(Reminder of chapter 2.8)*	BioRoot™ RCS *(Reminder of chapter 6.2 and instructions for use)*
Mixing instructions	Not applicable (ready-to-use cement in syringe)	1. Retrieve some powder using the spoon supplied with the kit. Place a level spoonful of powder on the mixing block. 2. Release a single dose of mixing solution. Open it by turning the sealed cap. Pour 5 drops of the single dose onto the mixing block. 3. Prepare the root canal cement by gradually adding the powder to the liquid. Mix until a smooth paste is obtained (about 60 seconds). The mixture must be prepared extemporaneously. 4. Rinse and clean used instruments immediately to remove any residual material.
Injecting the cement into the root canal:	1. Clean the root canal and shape it using standard endodontic procedures. 2. Select a master gutta-percha cone and check that it fits the length of the working area. 3. Rinse with sterile saline solution to remove any residual irrigation solution, then dry without completely dehydrating the root canal. 4. Open the protective bag and take out the syringe. Make a note of the patient identifier on the label. 5. Use the endodontic tip supplied with the PA1704. 6. Remove the syringe cap and screw on an endodontic tip as far as it will go. 7. The gripping wing can be placed on the syringe to make it easier to squeeze the plunger. 8. Before injecting the cement into the canal, check that the cement comes out of the syringe by ejecting a small quantity of	1. Clean the root canal and shape it using standard endodontic procedures. 2. Select a master gutta-percha cone and check that it fits the length of the working area. 3. Rinse with sterile saline solution to remove any residual irrigation solution, then dry without completely dehydrating the root canal. 4. Prepare BioRoot™ RCS according to the mixing instructions above. 5. Slowly enter the canal, applying a layer of BioRoot™ RCS to the canal walls using the gutta-percha cone or lentulo spiral (do not exceed 600-800 rpm). 6. Complete the filling procedure by inserting the master gutta-percha cone (single cone technique) or several gutta-percha cones (lateral condensation technique) previously coated in BioRoot™ RCS to the length of the working area. 7. Assess the quality of the root canal filling by taking an X-ray (intraoperative check),

	material; if the syringe is blocked, do not use it, dispose of it in the syringe collection box and complete the defect form in the eCRF. 9. Insert the tip into the canal, up to a maximum of the first third of its length; check that the tip is not stuck in the canal or being forced in, then gently inject the material, without forcing it, and gradually and slowly withdraw the tip from the canal while continuing to inject the material. 10. Complete the filling procedure by inserting the master gutta-percha cone (single cone technique) or several gutta-percha cones (lateral condensation technique) to the length of the working area. 11. Assess the quality of the root canal filling by taking an X-ray (intraoperative check), 12. Cut the cone with a heat source at the entrance to the filled canal. 13. Complete the procedure by lightly condensing the upper part of the gutta cone with a large-diameter vertical endodontic compactor 14. Assess the quality of the root canal filling by taking an X-ray (intraoperative check) at T0. 15. Create a watertight coronal restoration (see below). 16. If it is necessary to fit an anchor pin, this should be done after the PA1704 material has fully cured in the canal, i.e. 7 days.	8. Cut the cone with a heat source at the entrance to the filled canal. 9. Complete the procedure by lightly condensing the upper part of the gutta cone with a large-diameter vertical endodontic compactor 10. Assess the quality of the root canal filling by taking an X-ray (intraoperative check) at T0. 11. Create a watertight coronal restoration (see below). 12. If it is necessary to fit an anchor pin, this should be done after the BioRoot™ RCS material has fully cured in the canal, i.e. between 1 week and 1 month.

Table 5: Instructions for use of PA1704 and BioRoot™ RCS filling materials

✓ *Description of the materials and techniques recommended to achieve a quality coronal restoration*

Description of the materials and techniques recommended to achieve a quality temporary coronal restoration	Description of the materials and techniques recommended to achieve a standard permanent coronal restoration
After the root canal treatment, the coronal part should be protected with a watertight coronal reconstruction material, i.e. a **glass ionomer cement or a bonded composite**. The use of a temporary cement such as **Cavit® is strongly discouraged** in this trial. If this is used between sessions, it must be for a short period; a sealed restoration operation must be scheduled within a maximum of 3 weeks. The use of **IRM® cement is not permitted** in this trial. Check that there is no overbite (*to avoid post-operative pain caused by physical pressure that is unrelated to the root canal filling*).	Permanent crown reconstruction must be carried out within 45 days, in accordance with good dental practice. Any restoration technique can be considered in this context, whether direct or indirect. A bonded or cemented coronal or coronal-radicular reconstruction covered by a transitional prosthesis is an acceptable technique, if such a step is necessary as part of the overall treatment plan. If a root anchor is required for the final restoration, its seat should not be prepared in the same session as the filling.

Table 6: Materials and techniques for temporary and permanent coronal restoration.

6.5.2. Visit procedure

Each patient enrolled in the study will be followed-up with for 2 years or 5 years, depending on the randomized group:

- Arm of the comparator medical device — BioRoot™ RCS: Once the endodontic treatment has been completed and the permanent coronal restoration has been carried out,3 follow-up visits are scheduled: A visit at 6 months,12 months, and 24 months.
- Arm of the investigational medical device — PA1704: Once the endodontic treatment has been completed and permanent coronal restoration has been carried out, there will be 5 follow-up visits: A visit at 6 months, 12 months and 24 months; at the end of the 24-month follow-up period, patients will be offered 2 further visits: One in the 4th year after the endodontic treatment (approx. 3.5 years ± 6 months) and one visit in the 5th year after the endodontic treatment (approx. 5 years ± 6 months).

For each patient and at each visit, a clinical examination and a retro-alveolar X-ray will be performed to assess the results of the treatment. The procedure for taking the images is described in Section "*Equipment to be used to evaluate clinical trial variables and arrangements for monitoring maintenance and calibration.*" of Chapter 6.1.

The procedure for the visits is as follows (see the diagram in section Table 7):

V0 — Selection visit:

— diagnosis (including a preoperative 2D retroalveolar X-ray; the entire tooth — from the *crown to the root to the apex* — must be visible in the image; the image must be uploaded to the eCRF after the patient has been included; no blind review of this image),

— verification of eligibility,

— information about the trial and handover of consent form,

Patients will be included after diagnosis of the need for endodontic treatment.

V1 — Enrolment visit (T0)

— Collection of written **consent**

— Recording of patient characteristics at enrolment:

- Sex, age, history and treatment at enrolment, smoking status,
- Oral-dental health: DMFT index and CPITN index (record each value and then the CPITN index will be calculated automatically in the eCRF),
- Characteristics of the tooth to be treated: tooth number, number of canals to be filled, indication for initial or repeat endodontic treatment, pulp diagnosis (irreversible pulpitis, necrotic pulp, living pulp with indication for ET) and periapical diagnosis (presence of an apical lesion, symptomatic tooth), preoperative pain (see pain record in the patient record detailed in the paragraph below).

— **Randomization** of the medical device (PA1704 or BioRoot™ RCS) stratified according to endodontic treatment indication (randomization system integrated in the eCRF).

— **Endodontic treatment** over 1 or 2 sessions, depending on the usual practice of each practitioner and the clinical situation (initial or repeat endodontic treatment) and following the instructions for use of the PA1704 or BioRoot™ RCS filling materials (see instructions above).

Record of data describing operating procedures in the eCRF: 1) preparation of the canal (technique for removing the old material in the event of re-treatment), 2) shaping and cleaning of the canal (instruments used, irrigation solutions and techniques, rinsing solution, drying), 3) number of gutta-percha cones used and condensation technique.

— **Immediate post-operative X-ray check (=T0; reference image for patient follow-up;** reminder: the entire tooth — from the *crown to the apex, including the root* — must be visible in the image):

- Evaluation of the level of obturation at the X-ray apex for each canal,
- Evaluation of obturation density (radiopacity and presence of voids),
- Upload the T0 image to the eCRF.

— **Quality coronal restoration**: the reconstruction can be either temporary or permanent if the conditions are right and according to the practitioner's habits. In all cases, the restoration must be watertight and made using glass ionomer cement or a composite (see recommendations above). Exclusive endodontic investigators must ensure watertight reconstitution.

— Explanations and handing over of the **patient record** for recording pre-operative and post-operative pain over 7 days, painkillers and AEs. The preoperative and T0 VAS is completed in the office in the presence of the dental surgeon or dental assistant in order to check that the evaluation tool has been properly understood; it should be noted that if the root canal preparation and filling are carried out over 2 sessions, preoperative pain levels will be recorded at the beginning of each session).

— Scheduling the **next consultation**: either the V2 visit to perform the standard permanent coronal restoration (if the restoration was temporary at V1 i.e. within 45 days), or the V3 follow-up visit at 6 months if the permanent coronal restoration was performed at V1.

— **Special features for exclusive endodontist investigators** (in particular, if they do not perform the usual permanent coronal reconstruction themselves; *care is generally provided by the patient's regular dental surgeon*): A letter is sent to the patient's usual dental surgeon reporting on the endodontic treatment, specifying the patient's enrolment in the trial and the need to collect data relating to the permanent coronal restoration and any AEs via the follow-up letter; a standard letter listing the data to be collected (functional status of the treated tooth, result of the percussion test, technique used for the permanent coronal restoration, occurrence ofAEs (symptoms, start and end dates, action)) are to be included in the endodontist's report letter. The patient's regular dentist will reply in his/her follow-up letter to the investigator.

Telephone consultation at D7

Verification that the follow-up booklet has been completed correctly and reminder of the procedure for returning it to the investigator [by post within 7-15 days (pre-stamped envelope pre-addressed to the investigating center provided) or handed in to the center during the V2 visit].

Questionnaire about the occurrence of AEs since treatment (T0).

V2 — Visit for permanent coronal restoration (to be carried out within 45 days of the temporary restoration operation)

If the investigator performs the usual permanent coronal reconstruction:

— Retrieval of the completed patient record,

— Clinical examination (standard practice): verification of the functional status of the treated tooth and percussion test (lateral and axial),

— Recording of AEs (interview + *via* the completed follow-up booklet).

— Standard permanent coronal or coronal-radicular reconstruction, bonded or cemented, covered by a prosthesis.

If the usual permanent coronal reconstruction is not carried out by the investigator BUT by the patient's usual dentist:

— Record data in the follow-up letter from the usual dentist relating to 1) the functional state of the treated tooth and the result of the percussion test, 2) the technique used for the permanent coronal reconstruction, 3) any AEs. If necessary, the investigator shall contact the patient's usual dentist to clarify the data before it is recorded in the eCRF.

— Retrieval of the completed patient record (sent by post).

Optional intermediate visits (routine care)

If the patient is seen for treatment outside the protocol (routine care) or for any emergency, the investigator shall collect all the information relevant to the trial (date of consultation, reason for consultation, occurrence of AEs, etc.).

V3 — Clinical follow-up visit at 6 months (± 1 month) — Standard practice

— **Clinical examination**: Verification of the functional status of the treated tooth and percussion test (lateral and axial),

— Recording of **AEs**.

— **Retro-alveolar X-ray check** to evaluate the results of endodontic treatment at 6 months: **1)** density of the root canal filling (radiopacity + presence of voids), **2)** progress of resorption of the extruded material

where appropriate, **3)** apical lesion (absence/appearance/still present compared with T0) and progress of the size of an existing lesion (reduction, stabilization or increase).

Upload the 6-month follow-up retro-alveolar image to the eCRF (reminder: the entire tooth – from the *crown to the apex, including the root* – must be visible in the image; see chapter 6.1).

— The investigator shall evaluate the efficacy of the endodontic treatment on the basis of the clinical and radiological criteria identified (*Note: Only the evaluation of the radiological criteria by the independent reviewers will be taken into account for the primary evaluation criterion (PEC); the investigator's evaluation is to be used to determine further clinical follow-up*).

Procedure in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion:

- If the investigator considers it to be an emergency (e.g. if the tooth is symptomatic and/or non-functional): the investigator will notify the patient of the failure of the endodontic treatment and schedule retreatment. In this case, the patient leaves the trial early due to the failure of the treatment and continues endodontic treatment outside the trial (end-of-trial form to be completed in the eCRF). Performance and safety evaluations now end. Failure notified at 6 months is carried forward as the PEC value (response at 24 months = failure). The patient will not be replaced.
- If the investigator considers that it is NOT an emergency (e.g. if the tooth is asymptomatic): medical advice should be sought from the trial coordinator (who will review the X-rays) before considering retreatment and early discharge from the trial for treatment failure.

V4 — Clinical follow-up visit at 12 months (± 1 month) — Standard practice

— **Clinical examination**: verification of the functional status of the treated tooth and percussion test (lateral and axial),

— Recording of **AEs**.

— **Retro-alveolar X-ray check** to evaluate the results of endodontic treatment at 12 months: 1) density of the root canal filling (radiopacity + presence of voids), 2) progress of resorption of the extruded material where appropriate, 3) apical lesion (absence/appearance/still present compared with T0) and progress of the size of an existing lesion (reduction, stabilization or increase).

Upload the 12-month follow-up retro-alveolar image to the eCRF (reminder: the entire tooth – from the *crown to the apex, including the root* – must be visible in the image; see Chapter 6.1).

— The investigator will evaluate the efficacy of the endodontic treatment on the basis of the clinical and radiological criteria identified (*Note: Only the evaluation of the radiological criteria by the independent reviewers will be taken into account for the primary evaluation criterion (PEC); the investigator's evaluation will be used to determine further clinical follow-up*).

Procedure in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion:

- If the investigator considers it to be an emergency (e.g. if the tooth is symptomatic and/or non-functional): the investigator will notify the patient of the failure of the endodontic treatment and schedule retreatment. In this case, the patient leaves the trial early due to the failure of the treatment and continues endodontic treatment outside the trial (end-of-trial form to be completed in the eCRF). Performance and safety evaluations now end. Failure notified at 12 months is carried forward as the PEC value (response at 24 months = failure). The patient will not be replaced.
- If the investigator considers that it is NOT an emergency (e.g. if the tooth is asymptomatic): medical advice should be sought from the trial coordinator (who will review the X-rays) before considering retreatment and early discharge from the trial for treatment failure.

V5 — Clinical follow-up visit at 24 months (± 1 month) — Standard practice

— **Clinical examination**: verification of the functional status of the treated tooth and percussion test (lateral and axial),

— Recording of **AEs**.

— **Retro-alveolar X-ray check** to evaluate the results of endodontic treatment at 24 months: 1) density of the root canal filling (radiopacity + presence of voids), 2) progress of resorption of the extruded material where appropriate, 3) apical lesion (absence/appearance/still present compared with T0) and progress of the size of an existing lesion (reduction, stabilization or increase).

Upload the 24-month follow-up retro-alveolar image to the eCRF (reminder: the entire tooth – from the *crown to the apex, including the root* – must be visible in the image; see Chapter 6.1).

— Where appropriate (in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion), notification of ET failure by the investigator: schedule retreatment.

For patients in the PA1704 group whose endodontic treatment is effective at 24 months: Offer to continue clinical follow-up for up to 5 years: Inform patients about the study (dedicated information note) and provide them with a consent form.

— Complete the end-of-study form at the end of the eCRF for patients whose clinical follow-up has been completed (all patients in the BioRoot™ RCS group are followed-up with for up to 24 months, and patients in the PA1704 group who decline to continue the clinical follow-up for up to 5 years or for whom treatment failure is notified at 24 months).

PA1704 arm: V6 — Clinical follow-up visit at 3.5 years (± 6 months) — Standard practice

— **Clinical examination**: Verification of the functional status of the treated tooth and percussion test (lateral and axial),

— Recording of **AEs**.

— **Retro-alveolar X-ray check** to evaluate the results of endodontic treatment at 3.5 years: 1) density of the root canal filling (radiopacity + presence of voids), 2) progress of resorption of the extruded material where appropriate, 3) apical lesion (absence/appearance/still present compared with T0) and progress of the size of an existing lesion (reduction, stabilization or increase).

Upload the 3.5-year follow-up retro-alveolar image to the eCRF (Reminder: The entire tooth – from the *crown to the apex, including the root* – must be visible in the image; refer to Chapter 6.1).

— The investigator will evaluate the efficacy of the endodontic treatment on the basis of the clinical and radiological criteria identified (*Note: Only the evaluation of the radiological criteria by the independent reviewers will be taken into account for the primary evaluation criterion (PEC); the investigator's evaluation will be used to determine further clinical follow-up*).

Procedure in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion:

- If the investigator considers it to be an emergency (e.g. if the tooth is symptomatic and/or non-functional): the investigator will notify the patient of the failure of the endodontic treatment and schedule retreatment. In this case, the patient leaves the trial early due to the failure of the treatment and continues endodontic treatment outside the trial (end-of-trial form to be completed in the eCRF). Performance and safety evaluations now end.
- If the investigator considers that it is NOT an emergency (e.g. if the tooth is asymptomatic): medical advice should be sought from the trial coordinator (who will review the X-rays) before considering retreatment and early discharge from the trial for treatment failure.

PA1704 arm: V7 — Clinical follow-up visit at 5 years (± 6 months) — Standard practice

— **Clinical examination**: Verification of the functional status of the treated tooth and percussion test (lateral and axial),

— Recording of **AEs**.

— **Retro-alveolar X-ray check** to evaluate the results of endodontic treatment at 5 years: 1) density of the root canal filling (radiopacity + presence of voids), 2) progress of resorption of the extruded material where appropriate, 3) apical lesion (absence/appearance/still present compared with T0) and progress of the size of an existing lesion (reduction, stabilization or increase).

Upload the 3.5-year follow-up retro-alveolar image to the eCRF (Reminder: The entire tooth – from the *crown to the apex, including the root* – must be visible in the image; refer to Chapter 6.1).

— The investigator will evaluate the efficacy of the endodontic treatment on the basis of the clinical and radiological criteria identified (*Note: Only the evaluation of the radiological criteria by the independent reviewers will be taken into account for the primary evaluation criterion (PEC); the investigator's evaluation will be used to determine further clinical follow-up*).

— Where appropriate (in the event of the appearance of a lesion or an increase in the size of a pre-existing lesion), notification of ET failure by the investigator: schedule retreatment.

— Complete the end-of-trial form at the end of the eCRF.

Table 7: Outline of the trial procedure

Actions	Participant	Visit V0 Selection	Visit V1 Enrolment (T0)	V1 + 7d	Visit V2 (within 45 days)	Visit V3 (M6 ± 1 month)	Visit V4 (M12 ± 1 month)	Visit V5 (M24 ± 1 month)	Visit V6 (3.5 years ± 6 months)	Visit V7 (5 years ± 6 months)
			Endo. treatment	**Call tel.**	**Care follow-up**	**Clinical follow-up**	**Clinical follow-up**	**Clinical follow-up**	**Clinical follow-up PA1704 arm**	**Clinical follow-up PA1704 arm**
Verification of the eligibility criteria	Investigator	x								
Trial information + Informed consent form	Investigator	x								
Collection of signed written consent form	Investigator		x							
Enrolment data: demographics, relevant history and treatments, COAD, CPITN, diagnosis of tooth to be treated	Investigator		x							
Randomization (1:1) with stratification	Investigator		x							
Surgical procedure for endodontic treatment + temporary coronal reconstruction	Investigator		x							
Retrieval of patient record (pain and AE over 7 days)	Investigator		x							
Post-op pain and AE assessment	Patient + Inv.		→	x						
Standard permanent coronal reconstruction	Investigator				X[(a)]					
Retro-alveolar image to be uploaded to eCRF	Investigator	x	x (immediate post-op)			x	x	x	x	x
Clinical examination (according to current practice): functional status of teeth + percussion test	Investigator				x	x	x	x	x	x
Evaluation of treatment quality and efficacy (X-ray criteria : apical lesion, filling density, material resorption)	Investigator		x			x	x	x	x	x
	independent reviewers		x			x	x	x	x	x
Vigilance (AE, defects)	Investigator		→	→	→	→	→	→	→	→
Evaluation of comfort, cement use	Investigator		x							

Legend: x: one-off action; → continuous action, [(a)] care carried out by the investigator or by the patient's usual dental surgeon if the investigator is an exclusive endodontist.

6.5.3. Description of the activities carried out by the Sponsor's representatives (excluding monitoring).

None.

6.5.4. Any known or foreseeable factor likely to compromise the results of the clinical investigation or the interpretation of the results.

None.

6.6. Monitoring plan and data management

6.6.1. Data Collection

For each patient, the data collected during the trial will be spread over 3 media:

- an electronic case report form (eCRF) for the investigator,
- a follow-up booklet to be completed by the patient,
- a database dedicated to blind X-ray review campaigns.

All the information required by the protocol must be provided on these media. They must include the data needed to confirm compliance with the protocol and all the data required for statistical analysis, and enable major deviations from the protocol to be identified.

The people responsible for filling in the CRFs must be defined and identified in the center's task delegation table and recorded in the trial's files at each investigating center. They undertake to comply with the rules for completion set out in the specific manual handed out during the set-up visit.

In this trial, no directly identifying information (identity, address, social security number) or sensitive information will be collected.

The health data collected concerns only:

- patient demographics (gender, age),
- relevant history and treatments taken at the time of enrolment,
- data relating to the tooth to be treated: tooth number, pulpal and periapical pathology, number of canals to be treated,
- pre— and post-operative X-ray image(s); these will all be anonymous, distinguishable by the subject's identifier number.

6.6.2. Identification of all source data not contained in the medical file

The following data may be collected directly in the eCRF, without being notified in the source file: data relating to operating techniques.

6.6.3. Right of access to source data and documents

By definition, a source document is any original document or object that can be used to prove the existence or accuracy of data, such as patient medical records.

The investigator will make the documents and individual data, which is strictly necessary for the monitoring, quality control and audit of the trial, available to persons with access to these documents in accordance with current applicable legislative and regulatory provisions (Articles L.1121-3 and R.5121-13 of the Public Health Code and Annex XV of Regulation (EU) 2017/745 on medical devices). The medical data relating to each subject collected for this trial and coded will only be transmitted to the Sponsor or any person duly authorized by them, and, where applicable, to authorized health authorities, under conditions guaranteeing confidentiality.

In accordance with applicable legislative provisions (Articles L.1121-3 and R.5121-13 of the Public Health Code and Annex XV of Regulation (EU) 2017/745 on medical devices), persons with direct access to the source data will take all necessary precautions to ensure the confidentiality of information relating to the trial, to the persons who take part in it and in particular with regard to their identity and to the results obtained.

The Sponsor and regulatory authorities may request direct access to the medical file in order to verify the clinical trial's procedures and/or data, without breaching confidentiality and within the limits authorized by law and by the regulations.

The data collected during the study may be processed electronically, in compliance with the General Data Protection Regulation (GDPR, EU Regulation 2016/679) and the requirements of the CNIL, in accordance with the reference methodology MR-001 (deliberation no. 2016-262 dated 21 July 2016 amending the reference methodology for the processing of personal data carried out in the context of biomedical research; Declaration of compliance provided in Appendix 4).

To ensure the confidentiality of the personal data relating to subjects participating in the trial, a 5-character alphanumeric code will be assigned to each subject (see below).

Persons authorized to access medical records are bound by professional secrecy.

6.6.4. Data encoding:

Identifier of trial patient:

By signing this protocol, the investigator and their collaborators undertake to keep confidential the identities of the subjects taking part in this clinical trial.

The observation booklet, the follow-up booklet and all other source documents attached to the CRF (including X-ray images) will be pseudonymized: each included patient will receive a four-digit identification code and a letter in the following format (NNN-CN). This alphanumeric code will be the only information to appear in the case report book and will enable the CRF to be linked to the patient *at a later date*.

N N N — CN

N: center number (from 1 to 7)

NN: center enrolment number (in chronological order of enrolment)

C: treatment arm: N = PA1704; R = BioRoot™ RCS

N: stratum number: 1 = Initial Endodontic Treatment (ET); 2 = Re-treatment (ER).

Examples:

Code of 1st patient enrolled at center 4 with indication of ET and treated with PA1704: 401-N1

Code of 12th patient enrolled at center 2 with indication of ER and treated with BioRoot™ RCS = 212-R2

The list of matching identification numbers and patient identities will be managed and kept by the investigator in paper format and archived with the trial documents specific to his/her center **only** at his/her premises.

Encoding of adverse events and device defects:

The IMDRF terminology (appendices A to G) will be used to encode adverse events related to medical devices and device defects (see details in chapter 14 on vigilance).

6.6.5. Data quality & monitoring

Data monitoring will be carried out by the CRO's CRAs, in accordance with Good Clinical Practice aimed at guaranteeing the quality of the trial. As the OPTIFILL trial is a category 1 RIPH involving a class IIa medical device that is not CE marked, the level of control will be high.

The CRAs will carry out regular remote monitoring *via* the ENNOV Clinical software application to track recruitment and check the integrity of the data entered into the eCRF. Requests for corrections or clarification of data will be sent to the investigator electronically.

In addition, the CRO's CRAs will regularly visit the investigating centres; 6 site visits are planned: 1 visit soon after the first enrolments, then a site visit after each follow-up visit provided for in the protocol, for up to 5 years of patient follow-up. The CRAs will check and verify consent forms, the consistency of critical data (PEC clinical criteria, AEs, patient record data, device defects) and equipment.
Visits will be organized after making an appointment with the investigator. The CRA must be able to consult:
— Consent forms,
— Observation and monitoring records,
— Patient source files (paper and/or electronic format),
— Medical devices made available (PA1704 and Bioroot™ RCS)
— Investigator file provided by the CRO.

7. Statistical considerations

7.1. Software used:

- Creation of the input template for the electronic CRF and patient record, database media: Ennov Clinical version 8.0,
- Statistical analysis: JMP® version 15.0.0 or later (SAS Institute) on Windows 10 Pro.

7.2. Size of sample:

Based on the assumption that there is no difference in efficacy at 2 years between the 2 filling materials (PA1704 and BioRoot™ RCS) and that the expected efficacy rate of BioRoot™ RCS after initial and repeated endodontic treatment is 90% (Zavattini et al., 2019; Chybowski et al., 2018, Bardini et al., 2016), we calculate that a minimum of 66 subjects per group must be enrolled **to show non-inferiority of PA1704 over BioRoot™ RCS** with a confidence interval of 80%, a unilateral alpha risk of 5% and a 13% difference in efficacy tolerance between the 2 products (Ng 2007; Ng 2008; Eyuboglu 2016). By enrolling an additional 20% of patients in order to take into account those lost to or withdrawn from the trial, **the number of patients who must be included is 80 in each group, or 160 patients in total.**

Patients will be enrolled either due to an indication for initial endodontic treatment or due to indication for repeat treatment; the proportion of repeat treatments will be 30%.

7.3. Degree of significance and power of the clinical trial

The main analysis will be carried out using a one-tailed statistical test with a significance threshold α set at 5%. The clinical trial is designed to ensure 80% power for the main analysis test. Secondary analyses will be carried out using two-tailed statistical tests with a significance threshold α set at 5%.

7.4. Expected drop-out rates

The study includes a 24-month follow-up for patients in the BioRoot RCS arm, and a 5-year follow-up for patients in the PA1704 arm, which may mean that some patients will withdraw or be dropped from the study. These patients will not be replaced. The calculation of the number of subjects to be enrolled allowed for a 20% increase in this number, in order to anticipate the drop-out rate at 2 years.

7.5. Procedures for taking all data into account:

Data review and database freezing: Before each statistical analysis (intermediate and final), a data review meeting will be held, attended by *at least* the sponsor and the CRO's biostatistician in charge of the statistical analysis. This will enable deviations from the protocol to be identified and categorized, so that samples of patients can be evaluated for statistical analysis. This will provide an opportunity to identify factors not initially considered that could influence the trial results and which would be worth taking into account in the analysis. At the end of the last data review meeting, the clinical database will be frozen.

Once the clinical database has been frozen, statistical analyses will be carried out by the CRO in accordance with the trial's Statistical Analysis Plan.

7.6. Definition of analysis populations:

The Tolerance population is the entire population treated with the investigational MD or the comparator MD. Patients will be analyzed according to the medical device they actually received (if a patient is randomized to one arm but receives the medical device from the other arm (allocation error), they will be analyzed according to the medical device they actually received).

The modified ITT (mITT) population is the set of patients included in the clinical trial, meeting the major eligibility criteria (see below), having been treated with one of the MDs, and for whom at least one set of performance data is available (efficacy at 6 months, 12 months or 24 months based on clinical and radiological criteria). Evaluation of breaches of the eligibility criteria will be carried out blind to whichever medical device was allocated and to post-randomization data. Patients will be analyzed according to the intention-to-treat principle, i.e. according to the medical device for which they have been randomized.

The Per Protocol (PP) population is the entire mITT population that perfectly complied with the protocol. Thus, subjects with major protocol violations, including major false inclusions (see below), and subjects for whom the primary criterion was not available, will be excluded from the PP population.

Major enrolment breaches include:

- No signed consent,
- Enrolment of a vulnerable subject,
- Enrolment of a patient with a contraindication to endodontic treatment or a known contraindication to the use of BioRoot™ RCS or PA1704 filling material,

Major deviations from the protocol include:

- Error in allocating the medical device,
- Failure to comply with the procedure for using the medical device,
- Coronal restoration procedure contraindicated or insufficient,
- Lost contact,
- No performance data,

Particular care will be taken to describe any deviations from the protocol.

All major deviations will be validated by the coordinating investigator, ideally during clinical implementation and monitoring visits, or at the latest at the time of data review; the evaluation will be carried out blind to the data relating to whichever medical device was allocated and data collected after randomization.

It should be noted that non-compliance with the schedule of visits scheduled at 6, 12 and 24 months (with a tolerance of ± 1 month) will be considered a minor deviation from the protocol; the same applies in the case of a coronal restoration carried out after more than 45 days.

7.7. Statistical methods

The statistical methods are based on the following elements and will be detailed in the Statistical Analysis Plan.

7.7.1. Sample description:

The description of the subjects enrolled who completed the trial and those enrolled who left prematurely will be presented using a table of absolute (N) and relative (%) frequency. Reasons for premature discharge and deviations from the protocol will be listed.

7.7.2. Descriptive analyses:

Clinical data collected at enrolment and at each visit will be described. Descriptive statistics will be presented according to the nature of the criterion analyzed:

- Quantitative variable: sample size, number of missing data sets, mean, standard deviation, median, minimum and maximum;
- Qualitative variable: absolute frequencies (N) and relative frequencies (%) per class in each group, number of missing data.

Graphs will be provided for each variable.

7.7.3. Comparative analyses:

A comparison of 2 independent means will be made using the Student's t-test; if the variances are unequal (verified by the Fisher's test), use the Welch's test instead of the Student's test. If the conditions for applying the Student test are not met ($n < 30$), the non-parametric Wilcoxon test is used.

2 independent percentages are compared using Pearson's Chi-2 test. If the conditions for application are not met (at least one theoretical number < 5), Fisher's exact test is used.

7.7.4. Analysis of primary performance criterion:

As a reminder, the primary performance criterion is the efficacy rate at 24 months of treatment based on clinical criteria assessed by the investigator (tooth functionality and pain level) AND radiological criteria assessed blind by independent reviewers (complete healing, reduction of lesions, failure). In the event of failure at 6 or 12 months, the patient will be considered to have failed at 24 months.

The primary criterion will be analyzed using 2 approaches, in accordance with the literature:

- **Primary analysis of soft criteria**: treatment rates with complete or incomplete cure are compared against failure rates;
- **Secondary analysis of strict criteria**: treatment rates with complete healing are compared against rates of failure or incomplete healing (complete healing can take up to 4 or 5 years).

The comparison of efficacy rates between the 2 groups will be carried out using the Dunnett and Gent χ^2 test (Dunnett CW and Gent M 1977; Elie C et al 2008).

In addition, the difference in the 2-year efficacy rate between the 2 materials are to be calculated; its unilateral confidence interval of 95% will be provided and the lower limit is will be compared against the non-inferiority limit.

The main performance analysis will be carried out on the PP population, in accordance with the recommendations for non-inferiority studies. This will be complemented by an analysis of the mITT population to check the stability of the results.

7.7.5. Analysis of secondary performance criteria:

Efficacy rate at 6 months based on radiological and clinical criteria: Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the 6-month efficacy rate by Pearson's Chi-2 test or Fisher's exact test.

Efficacy rate at 12 months based on radiological and clinical criteria: Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the 12-month efficacy rate by Pearson's Chi-2 test or Fisher's exact test.

Quality of apical obturation at T0 (complete obturation, under-filling or over-filling): Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the proportions of apical obturation quality by Pearson's Chi-2 test or Fisher's exact test.

Density of root canal filling at T0, 6 months, 12 months, 24 months: Description and comparison at each time point, between the PA1704 arm and the BioRoot™ RCS arm, of the proportions of canals with an

obturation density deemed sufficient and the proportions of canals free of voids, by Pearson's Chi-2 tests or Fisher's exact tests.

Progress of material resorption over 24 months, in the event of over-filling at T0 (6 months, 12 months and 24 months): Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the proportions of patients with resorbed materials among patients who were over-filled at T0 by Pearson's Chi-2 test or Fisher's exact test.

Pre-operative and post-operative pain experienced by the patient (VAS 0-100 mm) at T0 (end of surgery), 12h, 24h, 48h, 72h and 7 days: For each time point, description and comparison of the pain, between the PA1704 arm and the BioRoot™ RCS arm, by a Student, Welch or Wilcoxon test. A figure representing average pain as a function of assessment times per arm will be provided. The causes of the pain will be described.

Maximum pain in the first 7 days and time to onset of maximum pain: Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the maximum pain experienced during the 7 post-operative days and its time to onset by a Student, Welch or Wilcoxon test.

Intra-operative pain relief between T0 and D7: Description of painkiller classes, reasons for use, frequency of use and cumulative dose per patient over 7 days. Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the proportion of patients who used *oral* pain medication between T0 and D7 by Pearson's Chi-2 test or Fisher's exact test.

Description of the surgical technique: Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of the type of anesthesia, the technique used to remove the old filling material (if root canal re-treatment only), the technique used to shape the canal, the type of disinfectant and rinse solutions used and irrigation techniques, the method of application of filling material and gutta-percha condensation, and the coronal restoration technique, by Pearson's Chi-squared test or Fisher's exact test. Intraoperative complications will be described where appropriate.

Operator comfort and satisfaction: Description and comparison, between the PA1704 arm and the BioRoot™ RCS arm, of operator comfort criteria. Satisfaction will be described at T0 and 2 years, and the proportions of satisfied operators will be compared.

For the performance criteria (efficacy rate, filling density, and material resorption) evaluated at 3.5 years and 5 years in the PA1704 arm: These criteria will only be described.

7.7.6. Safety/tolerance analysis:

The tolerance analysis will focus on the Tolerance population. Tolerance data is to be expressed as the number of adverse events (AEs) and the number of patients reporting at least one AE. Severity, cause (filling material or surgical technique) and the time of occurrence shall be described. The proportions of AEs and patients with AEs will be compared between the 2 groups. The proportions of patients who used an additional dental consultation for significant post-operative complication or pain will be described and compared, between the PA1704 arm and the BioRoot™ RCS arm, by Pearson's Chi-squared test or Fisher's exact test.

Defects in the devices will be described in the form of a list and proportions will be compared between the 2 groups.

7.7.7. Intermediate analyses:

No interim analysis of the primary criterion is planned. The main analysis will only be carried out after the 2-year follow-up of all patients enrolled.

Two interim analyses of the secondary criteria have been planned. These will be carried out after 6 and 12 months' follow-up for all included patients.

The alpha risk will not be inflated, as the main criterion will not be analyzed in the interim analyses. Therefore, no alpha risk adjustment method is required. The final analysis will focus on the primary and secondary criteria.

For patients treated with the PA1704 ready-to-use filling material and who agree to be followed-up with for up to 5 years, a non-comparative descriptive analysis of secondary performance and safety criteria at 3.5 years and 5 years will be carried out at the end of their participation.

7.7.8. Criteria for stopping the clinical trial from a statistical point of view:

None. Interim analyses are only used to collect data on secondary criteria before the end of the study. The conclusion on the non-inferiority of PA1704 compared to BioRoot™ RCS will only be made on the final analysis at 2 years.

7.7.9. Changes to the statistical analysis plan:

The statistical analysis plan will be drawn up before the first interim analysis is carried out. The initial analysis strategy may undergo minor modifications following each data review, and the new statistical analysis plan will be described in detail at that time.

7.7.10. Specification of sub-groups for further analysis:

The following sub-group analyses will be carried out, at least on the PP population, during the final analysis at 2 years. Other factors not considered in this protocol may be added in the Statistical Analysis Plan.

- For the primary criterion, the rate of effective treatment at 2 years:
    - Prognostic factors at enrolment
        - Presence or absence of a periapical lesion,
        - Indication for endodontic treatment: initial versus repeat endodontic treatment,
    - Factors related to the surgical procedure
        - Type of rinse solution used to finalize root canal disinfection,
        - Operating techniques used: technical platform used (whether or not a microscope was used), manual files versus continuous rotation versus alternative rotation.
- Post-operative pain:
    - Operating techniques used: manual files versus continuous rotation versus alternative rotation.
    - Initial pulp pathology (pre-existing inflammatory situation or necrosis or live pulp),
    - Preoperative pain (symptomatic tooth at enrolment, preoperative VAS).

7.7.11. Handling missing, unused or erroneous data, including drop-outs and withdrawals:

No imputation method is planned. However, as stated above, patients with treatment failure at 6 or 12 months will be withdrawn from the study and will be considered to have treatment failure at 24 months.

7.7.12. Exclusion of certain information from the hypothesis tests, if relevant:

None.

7.7.13. In the case of multi-center investigations, minimum and maximum number of subjects to be included for each center:

Each center will include 22 to 24 patients with an indication for initial or repeat endodontic treatment. The number of repeat treatments may vary between centers, but will total 30% in the sample. Some investigators, because of their specialty in endodontics, will include a majority of patients with an indication for repeat treatment, whereas GP investigators will probably have more indications for first-line treatment.

8. Data management

Procedures for examining data, cleaning databases, issuing and resolving data queries:

See Chapter 6.6, Data quality and monitoring section.

Procedures for verification, validation and securing of the electronic clinical data systems, where applicable:

The data collected in electronic CRFs is recorded directly in an electronic database using ENNOV software and hosted on a secure health data server in accordance with current regulations. The data collected in the paper logbooks is entered by the CRO into the electronic database using ENNOV software.

Data retention:

See the Archiving section in Chapter 12.4.

9. Amendments to the clinical investigation plan

Requests for substantial modifications will be sent by the CRO, on behalf of the sponsor, to the relevant ethics committees for their opinion and to the competent authorities for authorization, in accordance with law 2004-806 of 9 August 2004 and its implementing decrees in force.

Similarly, non-substantial modifications will be sent for information.

An updated version of the amended protocol must be dated. This new version will be sent to the investigators.

The patient information leaflet should be amended if necessary.

10. Deviations from the clinical investigation plan

The investigator undertakes to comply with this Clinical Investigation Plan (CIP). It is not authorized to deviate from the CIP except in urgent circumstances, in order to protect the rights, safety and health of patients. In this case, deviations may be carried out without the prior agreement of the sponsor, the CRO and the CPP.

Documentation of deviations: each deviation from the protocol must be documented in the CRF or in the data review report.

The investigator must inform SLB Pharma as soon as he/she is aware of any deviation in an eligibility criterion or early study withdrawal.

In order to limit deviations, SLB Pharma will present the CIP in detail to the entire investigating team during the study set-up visit.

11. Counting the devices

Used and unused PA1704 syringes will be counted during site monitoring visits. As a reminder, all used or defective syringes must be stored by the investigator in a collection box provided at the set-up visit (see chapters 2.9 and 0).

At the end of the clinical run, the remaining medical devices will be collected by the CRO for counting before destruction (unused, used or faulty PA1704 syringes, additional equipment, BioRoot™ RCS boxes).

12. Declarations of conformity — Regulatory obligations

12.1. Compliance

The sponsor, the investigators and the CRO undertake to carry out this trial in accordance with the protocol and the ethical, legal and regulatory provisions in force: the principles of the "Helsinki Declaration", national legislation and regulations relating to clinical trials in France and Belgium (Jardé Law and its implementing decrees, Belgian law of 7 May 2004 on human experimentation and Royal Decree 1999-03-18/34 relating to medical devices) and in accordance with regulations relating to medical devices (Regulation (EU) 2017/745 on medical devices, Standard EN ISO 14155:2011 relating to the clinical investigation of medical devices for human subjects — Good clinical practice).

The Clinical Investigation Protocol is drawn up in accordance with Annex A of Standard EN ISO 14155:2011.

12.2. Obligations before starting the trial:

Ethics Committees

In France:

The CRO undertakes to submit the protocol to a Committee for the Protection of Individuals on behalf of the sponsor, designated by drawing lots, to seek its prior opinion, in accordance with the procedures defined by Article 24-II of Decree no. 2016-1537 of 16 November 2016. The information provided concerns the nature of the trial and the safeguards provided for patients taking part in this clinical trial.

In Belgium:

The CRO undertakes to submit the protocol to the Cliniques Universitaires Saint-Luc Hospital-Faculty Ethics Committee (CEHF) on behalf of the sponsor to seek its prior opinion, in accordance with the regulations in force (Belgian Law of 7 May 2004 on human experimentation and Article 2N10.2 of the Royal Decree 1999-03-18/34 relating to medical devices).

The trial will not be initiated in the investigating centers until a favorable opinion has been obtained from the relevant ethics committee in each country.

Competent authorities

As the study is category 1 research involving humans, the CRO undertakes to submit an application for clinical trial authorization on behalf of the sponsor to the competent authority in each country where the trial is taking place: the ANSM in France and the AFMPS in Belgium.

The procedures in France are carried out as part of the Pilot Phase for clinical trials (phase prior to the application of EU Regulation no. 2017/745) proposed by ANSM and the CPPs(Practical information guide for applicants 2019).

Personal data protection authorities (CNIL and APD)

This trial complies with the French law on information technology, files and freedoms (law no. 78-17 of 6 January 1978 amended by law no. 2018-493 of 20 June 2018 on the protection of personal data, and the General Data Protection Regulation (RGPD— Regulation (EU) 2016/679 of 27 April 2016). This trial meets the requirements of the MR001 reference methodology for consent-based research (Annexe 4).

This trial complies with the Belgian law of 8 December 1992 on the protection of privacy with regard to the processing of personal data, the specific rules of chapter 2 of the Royal Decree of 13 February 2001.

Financing & insurance

The sponsor, Septodont, is financing the clinical study.

Septodont has taken out a Sponsor Civil Liability policy for research with the insurance company HDI-Global SE in France and Belgium on 8 and 9 July 2020, in accordance with French and Belgian legal and regulatory provisions on research involving the human person and in particular the provisions of Law 88.1138 of 20/12/1988, amended by subsequent texts, in particular Law no. 2012-300 of 5 March 2012 and its implementing decree no. 2016-1537 of 16 November 2016 and Article 29 of the Belgian Law of 7 May 2004. The twoinitial insurance certificates are available at Annexe 5.

Subject allowances

No compensation is provided for participation in this study.

12.3. Obligations after the start of the trial:

From the first enrolment, the CRO on behalf of the sponsor will inform the competent authority and the CPP without delay of the effective start date of the investigation (Effective start date = signature of the consent form by the first person to take part in the trial).

The date of completion of the clinical trial will be sent by the CRO on behalf of the sponsor to the ANSM and the CPP within 90 days. The end date of the trial corresponds to the end of the follow-up of the last person followed as part of the protocol (date of receipt of the last 6-month follow-up questionnaire).

12.4. Archiving

All correspondence relating to the clinical study, regulatory authorizations, source documents and data collection documents must be filed and kept by the Sponsor and the investigators at each center for 15 years, in accordance with current regulations. The CRO will keep the data collection documents for a limited period after the end of the study (until the results are published).

12.5. Inspection / Audit

As part of this study, an inspection or audit may be carried out, as defined by the rules of Good Clinical Practice. Inspectors are entitled to check the documents, logistics, records and any other resources that the authorities consider to be associated with the clinical study and which may be located at the research site itself, at the sponsor's premises or at other establishments deemed relevant.

13. Process for obtaining informed consent

The investigator undertakes to inform the patient, orally and in writing, in a clear and fair manner, of the terms and conditions of participation in the OPTIFILL protocol; in particular, he/she will provide the patient with an information note.

The information given by the investigator to the patient will concern:

- the objectives, methodology and duration of the research,
- presentation of the system under investigation,
- the expected benefits, inconveniences and risks of the trial,
- the opinion of a CPP and authorization from the competent authority (ANSM or AFPMS),
- a ban on taking part in other trials at the same time.

Patients should also know:

- that they may refuse to take part in the trial,
- that they may withdraw their consent at any time for any reason,
- that they will not incur any additional financial burden as a result of their participation in the trial,
- that he/she must not participate simultaneously in another research project for one month following the end of the current research project,
- that they have rights of access, rectification, opposition and limitation of processing with regard to their personal data, in accordance with the General Data Protection Regulation (Regulation (EU) 2016/679 of 27 April 2016).

The investigator must answer any additional questions that the patient may have about the study at the time of selection and throughout the duration of the research.
Prior to enrolment in the study, the subject's informed, free and express consent will be obtained in writing. The consent form will be signed and dated by the patient and the investigator. Participation in the OPTIFILL protocol will be specified in the patient's medical record; a copy of the consent form will be given to the patient, another will be kept by the sponsor in a sealed envelope, and the original will be kept by the investigator.

14. Adverse events, device-related adverse events and device defects

General provisions:

As part of this clinical trial, it is the investigator's responsibility to report all device defects and adverse events in the CRF on the pages reserved for this purpose (reporting process detailed in the following sections).

Tolerance monitoring begins as soon as the patient's consent is obtained and will continue until the end of the patient's participation in the protocol. Adverse events will beactively sought on the basis of patient declarations (follow-up logbook) and during clinical examinations and interviews carried out by the investigating team at each follow-up visit and until the end of the study.

The investigator will be on call during office opening hours so that patients can inform the investigator of any adverse events.

If the adverse event leads to the subject's participation being terminated, the "End of Clinical Investigation Form" at the end of the CRF will be completed by the investigator.

14.1. Definitions

The definitions below are in line with EN ISO 14155:2011 and Regulation (EU) 2017/745 on medical devices (including guide MDCG 2020-10/1) and current national regulations:

Device failure

Any defect in the identity, quality, durability, reliability, safety or performance of a device under investigation, including any malfunction, any error in use, or any defect in the information provided by the manufacturer.

Adverse event (AE)

Any adverse clinical event, unintended illness or injury, or any untoward clinical sign (including an abnormal laboratory finding) in participants, users or others, in the course of a clinical investigation, whether or not related to the device under clinical investigation.
NOTE 1: This definition includes events related to the medical device under investigation or to the comparator.
NOTE 2: This definition includes events linked to the procedures involved.
NOTE 3: For users or other persons, the definition concerns only events linked to devices under investigation and comparator.

Adverse device effect (ADE)

Adverse event linked to the use of medical devices under investigation and comparator.
NOTE 1: This definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, deployment, implantation, installation and operation, or any malfunction of the medical device.
NOTE 2: This definition includes any event resulting from an error of use or intentional improper use of the medical device.

Serious adverse event (SAE)

Any adverse event leading to:

a) death;

b) a serious deterioration in the participant's state of health:

i) a life-threatening illness or injury;

ii) a permanent impairment of an anatomical structure or function;

iii) hospitalization or prolongation of the patient's hospitalization;

iv) medical or surgical intervention to prevent any life-threatening illness or injury or any permanent impairment of an anatomical structure or function;

v) a chronic illness;

c) fetal distress, fetal death, congenital physical or mental impairment or congenital malformation;

NOTE: A planned hospitalization due to a pre-existing condition or a procedure required by the clinical investigation plan, without any serious deterioration in health, is not considered to be an SAE.

Serious adverse device effect (SADE)

Adverse effect of the device leading to one of the consequences characteristic of a serious adverse event (see previous definition).

Anticipated adverse device effect (A-ADE)

An anticipated adverse effect is one whose nature, incidence, severity and consequences have been identified in the current version of the risk analysis report or in the device's instructions for use.

Unanticipated adverse device effect (U-ADE)

An unanticipated adverse effect is an effect of the device, the nature, incidence, severity and consequences of which have not been identified in the previous version of the risk analysis report or in the instructions for use for the device.

New fact (Jardé Law) / Urgent safety measure (EU Regulation 2017/745)

A new fact is any new information that may lead to a reassessment of the benefits and risks of the research, to changes in the conduct of the trial or in the documents relating to the research, or to the suspension, interruption or modification of the research protocol. For the purposes of this trial, any serious adverse effect to the device will be considered a new fact.

An urgent safety measure, as defined in Article 2-paragraph 66 of EU Regulation 2017/745 on medical devices, is an event that is likely to result in an imminent risk of death, serious deterioration of health status or serious illness that may require prompt corrective action, and that is likely to result in significant morbidity or mortality in humans or that is unusual or unexpected in the place and time considered.

The sponsor will immediately inform the competent authorities and ethics committees of any new developments or urgent safety measures.

14.2. Process and time-frame for reporting an adverse event (including the date of the event, treatment, resolution, assessment of the seriousness and assessment of the relationship with the device under investigation).

14.2.1. Recording an adverse event

All AEs, whether or not related to the medical device under investigation or comparator, or to the endodontic treatment procedures, reported by the patient or observed by the investigator must be reported in the eCRF, specifying **1)** the nature (clinical signs, symptoms, diagnoses), **2)** the date and time of onset, **3)** the duration, **4)** end date and time, **5)** the severity, **6)** the therapeutic consequences, the ensuing evolution, and **7)** relationship with the DM under investigation or the comparator DM or the endodontic treatment procedures (according to the investigator's opinion).

Clinical signs, symptoms and diagnoses should be described by the investigator/reporter using precise terminology, avoiding ambiguity and abbreviations; the location of symptoms may be specified if relevant. Based on this information, the CRO will code each AE using the IMDRF dictionary – appendices E and F (IMDRF, 2020).

Further instructions on how to register an AE can be found in the eCRF user guide provided by the CRO.

Health conditions related to the dental pathology studied which change during the clinical trial, and which are attributable to a lack of effectiveness of the medical device (e.g. failure of the endodontic treatment), are NOT considered as AEs and should therefore not be recorded as such.

Previous or ongoing medical conditions known at study entry should NOT be considered as AEs unless worsening has occurred. In this case, if a deterioration or exacerbation of an intercurrent condition previously reported in the patient's medical history occurs, the AE must be described using appropriate terminology (e.g. deterioration, exacerbation, etc.).

In the case of surgery or diagnosis, the cause leading to such a procedure is considered to be the AE rather than the procedure itself. In the case of death, the cause of death is considered to be the AE and the death its consequence.

14.2.2. Severity of adverse events

The investigator should assess the severity of the AE (i.e. intensity) using the following scale:

Grade 1 (Mild):	Asymptomatic or with mild symptoms that do not require corrective treatment.
Grade 2 (Moderate):	Requiring minimal local or non-invasive corrective treatment.
Grade 3 (Severe):	Medically significant but not immediately life-threatening; indication for hospitalization or prolongation of hospitalization; disabling.
Grade 4:	Life-threatening, requiring emergency treatment.
Grade 5:	AE-related death.

14.2.3. Accountability for Adverse Events

In accordance with Regulation (EU) 2017/745 on medical devices, the relationship between the use of the device under investigation, including the comparator device or investigation procedures, and the occurrence of each adverse event must be assessed and classified according to 4 levels of imputability (1/ Unrelated, 2/ Possible, 3/ Probable, 4/ Causal relationship).

The sponsor and investigators will use the following definitions to assess the relationship between each adverse event (non-serious or serious) and the device under investigation or comparator or the investigational procedures:

1) **Unrelated:** the imputability of the device or protocol may be excluded when:

- The event is not known to be a side effect of the product category to which the device under investigation belongs or to a similar device and/or protocol,
- The time taken for the event to emerge appears to be incompatible with the use of the medical device under investigation or with the procedures involved.
- The event does not follow a response pattern known to the medical device (if the response pattern is already known) and is biologically implausible.
- Stopping the use of the medical device or reducing its level of use (when clinically possible) and then resuming its use or increasing its use had no impact on the event.
- The event affects a part of the body or an organ whose impact by the device or by the protocol is not expected.
- The event may be attributed to another cause (e.g. an underlying or concomitant disease/health condition, the effect of another device, another drug, another treatment or another risk factor).
- The damage suffered by the subject is clearly not due to an error in use.
- In order to establish the absence of a causal link, it is not necessary for all of the above criteria to be met; it depends on the type of device/protocol and the event.

2) **Possible:** the relationship with the use of the device is weak but cannot be totally ruled out. Alternative causes are also possible (e.g. an underlying or concomitant disease/condition and/or an effect of another device, drug or treatment). Cases in which imputability cannot be assessed or no information has been obtained should also be classified as possible.

3) **Probable:** the relationship with the use of the device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information can be obtained.

4) Causal relationship: the adverse event can be reasonably associated with the device under study, the comparator or the procedure with the protocol*(the relationship cannot be excluded*) when:

- The event is known to be a side effect of the product category to which the device under investigation belongs or to a similar device and/or protocol.
- The event has a temporal relationship with the use of the medical device under investigation or comparator, or with the procedures involved.
- The event affects a part of the body or an organ which is expected to be affected by the device or the protocol.
- The event follows a response pattern known to the medical device (if the response pattern is already known).
- Stopping the use of the medical device or reducing the level of use (when clinically possible) and then resuming its use or increasing its use had an impact on the event.
- The event cannot be attributed to any other cause (e.g. an underlying or concomitant disease/health condition, the effect of another device, another drug, another treatment or another risk factor).
- The damage suffered by the subject is clearly due to an error in use.

- The event depends on a false result given by the device under investigation used for diagnosis (if applicable).
- In order to establish a causal link, it is not necessary for all of the above criteria to be met; it depends on the type of device/protocol and the event.

14.2.4. Type and duration of follow-up of subjects after an AE

AEs will be followed by the Investigator until they are resolved (i.e. the event is resolved or the pathology is unlikely to change or the subject is lost to follow-up). All clinical and biological examinations deemed necessary by the investigator will continue until the patient returns to normal. The investigator will provide the sponsor with copies of all examination results and treatments related to the follow-up of events.

14.2.5. Reporting of serious adverse events (SAEs) to the sponsor:

As part of this category 1 research involving human beings, the investigator is obliged to notify the sponsor immediately, and for no more than 3 calendar days, of any serious adverse event occurring during the study in an included patient (MDCG 2020-10/1). The people who should be contacted are listed in the 14.5 section.

1/ Initial declaration:

This initial report should be made on a paper form entitled "Initial report of a serious adverse event" (blank form kept in the Trial Master File of the investigating site), indicating the date of occurrence, the severity, the relationship with the device under investigation or comparator (or the protocol) and the follow-up. The narrative report must be completed and sent to the CRO and the sponsor as soon as any new relevant information is obtained. Depending on the nature and seriousness of the event, anonymized copies of the patient's source documents may be attached. The information to be collected on the paper form for the initial notification of an SAE is as follows:

- Clear identification of the Investigator/Rapporteur with all contact details,
- Detailed identification of the subject (patient identifier in the study, site number, patient age at the start of the SAE, sex),
- Subject treatment group (device under investigation or comparator),
- Date of endodontic treatment (start date of treatment and date of root canal filling if different from start date),
- Description of the event (free text): nature of the symptoms observed, duration and severity of the symptoms, date of onset of the first signs of the AE (before it becomes an SAE), patient history and current treatments,
- The reason why this event is considered serious,
- The Investigator's opinion on the imputability of the medical device under investigation or the comparator or the investigation protocol (unrelated, possible, probable, certain),
- Corrective action and treatment.

The status of the SAE must be classified as follows:

- Resolved,
- Resolved with sequelae,
- In progress,
- Death.

The date on which the AE was resolved must be added; if the AE is still in progress, "Not Applicable" should be entered.

Following submission of the initial paper report form, the Investigator/Rapporteur must respond to any follow-up requests or queries from the Sponsor in relation to the SAE within the same timeframe as for the initial report. All the above contacts will be systematically copied on any exchanges concerning an SAE.

The Investigator must also report all SAEs in the eCRF by completing an AE form page.

If the SAE results in the patient being withdrawn early from the study, the Investigator must give details of the reason in the comments section of the initial paper declaration form.

2/ Follow-up declaration:

The Investigator must draw up a specific clinical report and complete and send the "follow-up SAE form" to the CRO and the sponsor within the same timeframe as mentioned above. Test results and hospital reports should be sent to the e-mail addresses listed in the 14.5 section. SAEs must be monitored until they are resolved or stabilized.

3/ After completion of the study:

All SAEs, whatever their relationship with the medical device or the protocol, occurring within 30 days of the last visit of each patient must be notified to the Sponsor in the same way as mentioned above. Any event occurring at any time after the end of the study for a subject who participated in the study and which could be related to the medical device under investigation in the opinion of the Investigator should also be reported to the CRO and the Sponsor.

14.2.6. Urgent safety problem

Any serious threat to public health (as defined in section 14.1) must be reported immediately to the sponsor (contact persons: See section 14.5).

14.2.7. Pregnancy

Pregnancies occurring after the date of signature of the informed consent and up to study discharge (whether early or not) will not be considered a serious adverse event insofar as no genotoxic effect of the medical device under investigation or comparator has been demonstrated; they will be recorded by convention in the AE pages of the eCRF.

14.2.8. Responsibility of the sponsor:

The sponsor will also comment on the relationship between each adverse event and the device under investigation or comparator or the investigation procedures as defined in paragraph 14.2.3. The sponsor will comment on the significance of the serious adverse events it reports and the consequences it draws from them, particularly with regard to the conduct of the research.

The sponsor will maintain detailed records of all adverse events reported by investigators and transmitted by the CRO.

In accordance with Article 80 of Regulation (EU) 2017/745 on medical devices, the sponsor will promptly notify all Member States in which the clinical investigation is ongoing (France and Belgium) of all SAEs and defects that could have led to an SAE in the absence of appropriate action or intervention, or if circumstances had been less favorable.

The sponsor will pass on to the study investigators any information likely to affect the safety of individuals. Serious adverse events must be monitored and documented until the disease has stabilized or returned to normal.

The Sponsor will send periodic safety reports to the Competent Authority and the Ethics Committee in accordance with the company's standard operating procedures with respect to EU regulations taking into account specific local requirements or regulations of the territory where the study is conducted. The Sponsor will respond to all requests from the Competent Authority or the Ethics Committee. The reference document for the medical device under investigation will be the latest instructions for use in force. These reference documents will need to be adapted during the course of the study, if necessary.

14.3. Process for reporting device faults.

All defects in the medical device under investigation or comparator must be recorded in the CRF by the investigator (forms provided for this purpose); defects which did not lead to an adverse effect but which could have caused a clinical event must also be recorded.

The investigator/rapporteur should describe the problems of the device as precisely as possible, avoiding ambiguities and abbreviations. On the basis of this information, the CRO will code each defect according to Appendix A of the IMDRF dictionary with a level 2 or 3 accuracy (IMDRF, 2020).

The sponsor will keep detailed records of defects which are reported by investigators and transmitted by the CRO.

Procedure to be followed by the investigator in the event of failure of the device under investigation (PA1704):

<table>
<tr><td>In the event of a defect such as (non-exhaustive list):</td><td>The investigator must:</td></tr>
<tr><td>Difficulty extruding PA1704 from the syringe</td><td>Attempt to extrude PA1704 onto a plate; if this does not work, remove the tip of the syringe and attempt to extrude onto the plate again.

Then, before use, the investigator visually assesses the texture of the PA1704 cement on the plate.

If the texture is satisfactory, apply the cement in the root canal using a new endodontic tip.

If the texture of the PA1704 is not satisfactory, do not use the device; put the faulty syringe in the syringe collection box and take another new syringe. Note the reason for the discrepancy on the defect form.</td></tr>
<tr><td>Low viscosity, the product flows by itself.</td><td rowspan="4">Do not use the device; put the faulty syringe in the syringe collection box and take another new syringe.</td></tr>
<tr><td>Product out of phase in the syringe (visual assessment of the texture of PA1704 by the investigator).</td></tr>
<tr><td>Impossible to extrude PA1704 cement, even after trying on a plate (see 1st line).</td></tr>
<tr><td>Damaged syringe (broken, cracked) after visual inspection when the box is opened.</td></tr>
</table>

Table 8: Action to be taken by the investigator in the event of device failure under investigation (PA1704)

14.4. List of foreseeable adverse events and anticipated adverse device effects, their probable incidence, means of mitigation or treatment.

List of possible AEs (linked to DMs):

Not known

List of foreseeable adverse events (linked to surgical procedures):

- Anesthetic protocol: reactions linked to high plasma uptake of the anesthetic, for example in the event of inflammation at the injection site or accidental intravascular administration (tremors, dizziness, malaise), local reactions at the injection site.
- Mechanical treatment of the canal: fracture of an instrument in the canal, ingestion of an instrument.
- Allergy, irritation following ingestion of disinfectant solution in the canal (usually hypochlorite).

14.5. Emergency contact details for reporting serious adverse events and serious adverse device effects.

The investigator must notify SLB PHARMA by telephone on [redacted] or by e-mail to the vigilance department [redacted] by e-mail to the sponsor's drug safety department [redacted]

14.6. Information on the Data Monitoring Committee, if established.

Not applicable.

15. Vulnerable population

✓ *Description of the vulnerable population concerned by the study*

Not applicable

✓ *Description of the specific process for obtaining informed consent.*

Not applicable

✓ *Description of the specific responsibility of the ethics committee.*

Not applicable

✓ *Description of any medical care provided to subjects once the clinical trial has been completed.*

Patients continue to be treated by their regular dental surgeon.

16. Premature termination or suspension of clinical trial

✓ *Criteria and provisions concerning premature termination or suspension of the clinical trial for the investigation as a whole or for one or more sites.*

The reasons for temporary or permanent early termination of the trial are as follows:

- decision of the Sponsor,
- decision by the person directing and supervising the trial (the coordinator),
- decision of the institution responsible for the trial.

- ✓ *Criteria for accessing and breaking the blinding code due to suspension or premature termination of the clinical trial, if this involves a blinding technique.*

Not applicable (no blinding of products).

- ✓ *Subject monitoring requirements.*

Patients will be monitored in accordance with standard practice.

17. Publication policy

- ✓ *Statement as to whether the results of the clinical trial will be published.*

The results may be published.

- ✓ *Statement indicating the conditions under which the results of the clinical trial will be published.*

Communications and scientific reports relating to this clinical study will be produced under the responsibility of the sponsor, with the agreement of the investigators. They will draw up a list of authors. Publication rules will follow international recommendations (N Engl J Med, 1997).

Any publication of the results will be strictly anonymous with regard to the participating subjects.

At the end of the clinical study, subjects may be informed of the overall results of the research on simple request to the investigator in charge of their follow-up.

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19. Appendices

APPENDIX 1: INSTRUCTIONS FOR USE PA1704
APPENDIX 2: CE BIOROOT™ RCS CERTIFICATE
APPENDIX 3: NOTICE D'UTILISATION BIOROOT™ RCS
APPENDIX 4: DECLARATION DE CONFORMITE AU REFERENTIEL MR-001
APPENDIX 5: ASSURANCES (FRANCE + BELGIQUE)

Appendix 1: Instructions for use PA1704

Instructions for using PA1704 filling cement and precautions.

Injection of PA1704 into the root canal:

1/ Clean the root canal and shape it using standard endodontic procedures.

2/ Select a master gutta-percha cone and check that it fits the length of the working area

3/ Rinse with sterile saline solution to remove any residual irrigation solution, then dry without completely dehydrating the root canal.

4/ Open the protective sachet and take out the syringe.

Note the patient identifier on the label (PATIENT _ _ _ — _ _).

5/ Take out the endodontic tip supplied with the PA1704

CAUTION: It is recommended to use conventional means (techniques) to hold the filling material in the canal with the endodontic tip.

6/ Remove the syringe cap and screw on an endodontic tip as far as it will go.

CAUTION: Make sure that the tip is correctly screwed on to prevent it coming off the syringe during treatment.

7/ The gripping wing can be placed on the syringe to make it easier to push the plunger.

CAUTION: Make sure that the gripping wing is correctly clipped in to prevent it coming off when the material is injected.

8/ Before injecting the cement into the canal, check that the cement is coming out of the syringe by ejecting a small quantity of material; if the syringe is blocked, do not use it, dispose of it in the syringe recovery box, and complete the defect form in the eCRF.

9/ Insert the tip into the canal, up to a maximum of the first third of its length; check that the tip is not stuck in the canal, nor being forced in, then gently inject the material, without forcing it and gradually and slowly withdraw the tip from the canal while continuing to inject the product.
10/ Complete the obturation by inserting the master gutta-percha cone (single cone technique) or several gutta-percha cones (lateral condensation technique) to the length required.

11/ Assess the quality of the root canal filling by taking a radiograph (intraoperative check),

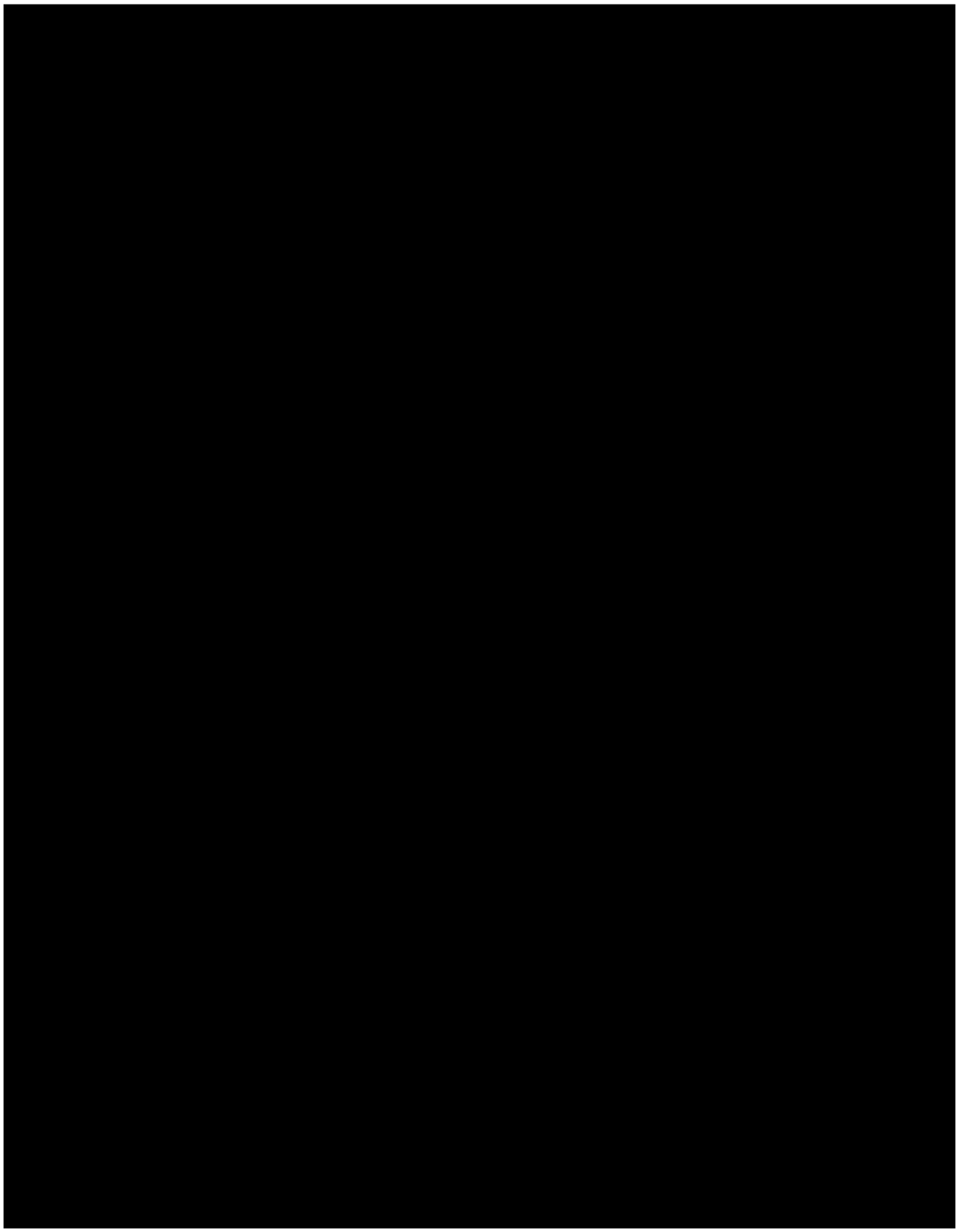
12/ Use a heat source to cut the cone at the entrance to the filled canal.

13/ Complete the procedure by lightly condensing the upper part of the gutta cone with a large-diameter vertical endodontic compactor
14/ Assess the quality of the root canal filling by taking an X-ray (postoperative check) at T0. The images obtained are to be transferred into the eCRF.

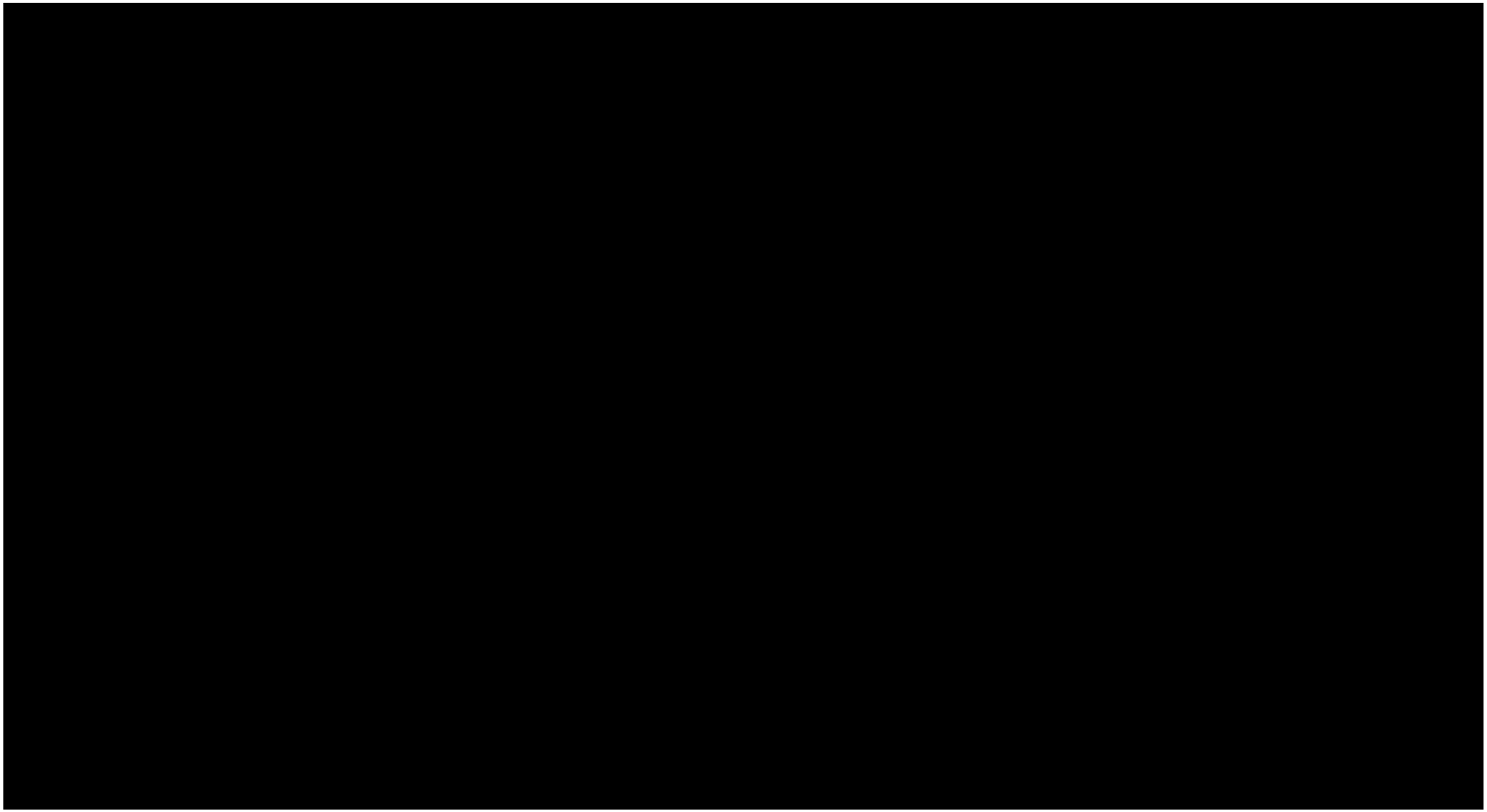
After filling with the PA1704 product:
15/ Perform a sealed coronal restoration.

16/ If it is necessary to fit an anchor pin, this should be done after the PA1704 material has fully hardened in the canal, i.e. 7 days.

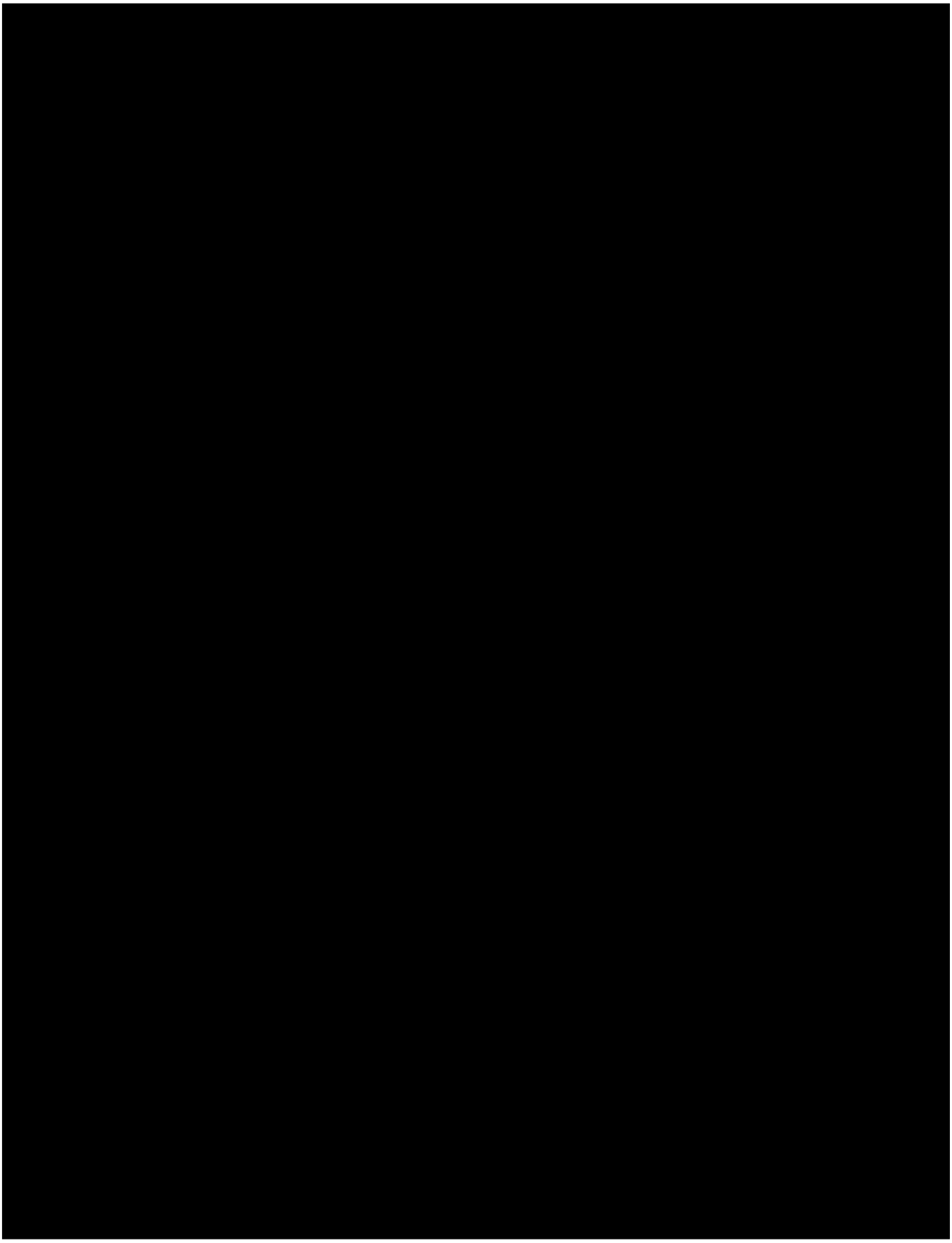
Appendix 2: CE BioRoot™ RCS certificate



Appendix 3: Notice d'utilisation BioRoot™ RCS



Appendix 4: Déclaration de conformité au référentiel MR-001



Appendix 5: Assurances (France + Belgique) – contrats initiaux, hors LDA