

NCT Title: **Resin Infiltration to Arrest Early Tooth Decay**

NCT Number: NCT01584024

IRB Approval Date: 10/18/2011

Content:

1. Clinical Investigation Plan

2. Statistical Analysis Plan

CLINICAL INVESTIGATION PLAN (2011)

Study Title:

Infiltration of Caries Lesions

Full Study Title:

Radiographic Progression of
Infiltrated Approximal Caries Lesions *in-vivo*

Study Sites:

- A. University of [REDACTED] – single session management
- B. [REDACTED] – two-session management

CIP – Version 2011-10-04

[REDACTED]

[REDACTED]

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[REDACTED] (2011)

1 SYNOPSIS OF THE CLINICAL INVESTIGATION

Introduction

Dental caries is the most widespread of all diseases. Caries is coming to be more broadly understood as a chronic bacterial infection. The resultant caries lesion causes destruction of tooth structure by dissolving the enamel on the outside of the tooth first. If not effectively arrested by remineralization therapy, it continues with dissolution progressing into the dentin. While it is possible to use traditional dental fillings to replace diseased tooth structure, it is far better to slow down or reverse the disease process so that no fillings are needed. One of the most difficult places to use preventive or non-surgical treatment is at the contact area between teeth. Recently there is evolving interest in using plastic resins to infiltrate enamel and dentin for teeth that have suffered some initial damage from caries but have their proximal surfaces intact. For uncavitated proximal surfaces, the infiltration arrests the disease progression and assists in repair of the damage already done.

Infiltration lesion management would be indicated when remineralization efforts either didn't provide the expected result or have a high likeliness of failure due to lack of monitoring and follow-up, or due to potentially drastical changes in attention to oral health.

Objective

The purpose of this study is to assess the *clinical effectiveness of using resin to infiltrate initial caries lesions* below the uncavitated tooth surfaces that exist on the contact surfaces between posterior teeth *as a means of stabilizing diseased tooth structure and arresting further lesion development.*

Materials and Methods

Young volunteers (14-35 years old) with two early lesions in posterior teeth will be enrolled into a clinical trial to evaluate the clinical effectiveness of arresting lesion progression by infiltrating the lesions as compared to current watch-and-wait approaches that are combined with good oral hygiene and fluoride supplementation. Each subject will have a treated lesion and a control lesion. Only small early lesions without clinical signs of surface cavitation will be selected. The control lesions will be stabilized through a normal preventive regimen, while the treatment lesions will be infiltrated with a resin. Lesion status will be monitored at six month intervals for the first year by clinical examination and bitewing radiographs. If serial radiographic and clinical

recall demonstrates no lesion progression then the next bitewings will be taken at annual intervals for the remaining two years of surveillance.

Clinical Significance

Infiltrating a caries lesion is a potentially effective strategy to strengthen damaged tooth structure and to arrest caries progression without any surgical intervention, while protecting the surface against renewed caries attacks.

The present CIP is the most recent version of the **Clinical Investigation Plan (2011)** for the infiltration trial. It supersedes the former version including the [REDACTED] trial. Where applicable, the current CIP includes an update of the [REDACTED] study site (enrollment concluded, 1-yr recall ongoing).

Advancing insight in the novel procedure and emergence of the first short-term clinical data using a similar technique, warranted the start of a new patient group. Hence, a new supplemental part of this study investigating the infiltration technique is proposed. This part is based on a largely similar clinical protocol. The slight modifications are related to patient pool and clinical application technique as described in this CIP.

September 2011, [REDACTED]

2 OBJECTIVES OF THE CLINICAL INVESTIGATION PLAN (CIP)

The objectives of the CIP are to provide a full description of the planned clinical trial.

The preceding short narrative (Synopsis) introduced the goal of the project and its approach to investigate the clinical effectiveness of management of early caries lesions by resin infiltration.

The Background and Rationale section addresses the relevance of the project to oral health and the rationale for the proposed clinical trial. The existing knowledge is briefly stated, including literature citations and highlights of relevant data, indicating the early progressive caries management gap that the project is intended to fill. The research plan includes the Study Design and Methods addressing the hypotheses to be tested, followed by Specific Aims. The data collection and analysis (including assessment of statistical significance) will be described and used to prove or disprove the hypotheses.

Previous experience with the materials involved is described including attention to risk analysis. Expected results, potential difficulties and limitations are discussed and solutions or alternative approaches indicated.

Project Overview and Professional Support

Based on internationally accepted protocols we have designed a prospective, randomized controlled clinical trial (RCT) to investigate the effect of a novel infiltration method as an alternative management option for the treatment of early, progressing, non-cavitated caries lesions.

The Clinical Investigation Protocol (CIP) for this study includes all components and documentation as required to conform to international standards for clinical research (CONSORT^[1, 2, 3], ISO/DIS^[4], and Good Clinical Practice Guidelines^[5]). An overview of terms, definitions and acronyms used in this document are included in Appendix 9.

3 THE STUDY ORGANIZATION

The trial organization is located at the Core Data Center (CDC), Department of Cariology, Restorative Sciences and Endodontics (CRSE), School of Dentistry at the University of Michigan, Ann Arbor, USA. The investigation is supported by an established research team, that conducts clinical studies in search for alternative management options for dental caries.

Study Teams: • *Core Data Center:*

(MI)

• Clinical Sites:

(OH)

(NY)

The study team in [REDACTED] is involved in preparation, monitoring and oversight of the clinical study and provides progress reports to the Sponsor. The actual treatments will be provided by the clinicians in the clinics at their respective institutions. The teams are assisted in their endeavors for this trial by a web-based clinical data system and statistical support from the U of Michigan.

Core Data Center (CDC)

██████████, Director of CRSE International Clinical Research, has ample experience in clinical research being productively engaged in patient-oriented research for over 25 years. She will be the main contact for CDC communication.

Study team¹:

Program Director/Principal Investigator (PD/PI)

¹ The titles and positions as described in this document are in accordance with the ISO 14155 guidelines

The Core Data Center (CDC) in ██████████, MI at the ██████████ is the administrative center for the study. It is supported by a customized web-based system DigiClin (DigiDent, ██████████). The DigiClin software provides a dynamic data analysis environment. This resource presents an optimal setting for the investigation creating a productive and cost-efficient way of communication between the CDC, the clinical site and the Monitor. In addition, the Center for Statistical Consultation and Research (CSCAR), U of Michigan, provides statistical support for final data analysis.

A) Clinical Site [REDACTED] (OH)

The clinical investigation site in [REDACTED] USA is located in [REDACTED]
[REDACTED]
[REDACTED] will provide oversight and will be assisted
by [REDACTED]
[REDACTED]
The [REDACTED] serves a stable population of patients of all
ages, and includes a [REDACTED]
[REDACTED] Their patient pool represents patients fitting the inclusion criteria for his study.
Previous successful collaboration with the faculty in clinical research at a different location
provides a sound basis for efficient management and effective teamwork leading for the current
study.

On-site team members:

[REDACTED]

[REDACTED]

B) Clinical Site West Point (NY)

The clinical investigation site is located at the [REDACTED] NY.

The surveillance protocol will be provided under responsibility and oversight of [REDACTED]. He will be assisted by one or two clinicians. This site serves a stable population of young adults with a relatively high frequency of dental caries and thus a population fitting the inclusion criteria for this investigation and study design. The proposed student population will be present at West Point for recall, post-protocol assessment and any additional treatment deemed appropriate for four years after the infiltration interventions are provided.

On-site team members:

[REDACTED]

Trial locations

[REDACTED]

West Point: The study will be conducted in the dental clinics at [REDACTED]. [REDACTED] will be the main study clinician with assistance of attending dentists.

Timing of the study

The clinical study will start as soon as the required ethical IRB approvals (U of Michigan, U [REDACTED]) have been received and Training & Calibration has been provided to the clinical teams.

NOTE: Status Sep 2011:

[REDACTED]

B) West Point: In preparation phase (planning, organizational and IRB aprovals pending).
Projected time line: Clinical treatment phase [REDACTED] 2012.

Sponsor**DMG**

Chemisch-Pharmazeutische Fabrik GmbH
Elbgaustraße 248
22547 Hamburg
www.dmg-dental.com

[REDACTED] [REDACTED]

Study contact:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Standby study contact:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Monitoring arrangements

The study will be monitored during the clinical investigation by an External Monitor. The External Monitor will be proposed by the program director/principal investigator (PD/PI) of the CDC [REDACTED] [REDACTED] and has to be approved by the Sponsor (DMG) and the Site-PCI [REDACTED] [REDACTED]. The Monitor will be accompanied by a representative of the Sponsor and by the PD/PI.

The Monitor will check the local arrangements for the study and assess whether the Site-PCI is compliant with the most current Clinical Investigation Plan. The Monitor reports directly to the PD/PI at the CDC in Ann Arbor. If serious deviations are reported the PD/PI will determine corrective actions together with the sponsor.

Unexpected inspection visits by the Monitor who may be accompanied by the representative of the Sponsor may take place during all of the clinical phases of the trial. Such visits must receive the prior approval of the PD/PI.

The representative of the Sponsor may request access to the site of the investigation and may accompany the Monitor during periodic visits. The representative may also request access to all

trial documentation at the clinical site and at the CDC under the condition that confidentiality concerning the identification of subjects is guaranteed. Access to clinical records and clinical areas can only be granted with the permission of the PCI, PD/PI and in accordance with the recognized procedure of the University of Michigan. Reasonable requests will not normally be refused.

Oversight of human subject research

Approval of the appropriate ethics committees is required (see Human Subjects appendix: A3). In addition to approval of the investigation by the ethics committee of the central administrative core at the University of Michigan (IRBMED), the application for the clinical site will be submitted for the opinion and approval by the local governing ethics committee.

Approval by both central and local ethics committee is required to initiate the clinical phase and the start of patient recruitment.

The Human Subjects appendix (A3) describes the issues involved in human subjects research. This includes target recruitment tables, certifications and FDA information of the materials that will be used in the investigation. The Data Safety and Monitoring Plan (DSMP; A3.4) describes the reporting of clinical complications (Adverse Events (AE) and Other Reportable Information and Occurrences (ORIO): A3.5) and the data quality and management.

4 PRELIMINARY INVESTIGATIONS AND JUSTIFICATION

4.1 BACKGROUND AND RATIONALE

Fissure sealing has been shown to inhibit not only the formation of occlusal caries but also to impede the progression of existing caries lesions^[6, 7, 8]. Pit-and-fissure sealants are an effective way of preventing caries in children and adults—even in early noncavitated (incipient) lesions, according to a new set of ADA evidence-based clinical recommendations^[9, 10, 11].

Lately, the concept of sealing caries to arrest lesion progression has been transferred to approximal surfaces^[12, 13]. In a clinical study sealed approximal lesions showed significantly reduced progression after 18 month compared with those that were treated only with preventive measures^[13]. In addition, it has been shown in contemporary European populations that lesions, radiographically progressed into dentin, were not cavitated in 60% of the cases^[14]. The literature suggests that, when appropriate, a less-invasive management of progressing, non-cavitated caries lesions may be reasonably preferred above currently utilized “conventional” but, more invasive operative-restorative management options.

The pores of enamel caries lesions provide diffusion pathways for acids and dissolved minerals. The aim of lesion infiltration is to occlude these pores by infiltration with light curing resins in order to block the diffusion of acids into the lesion body^[15, 16]. In contrast to the sealing of caries, caries lesion infiltration aims to occlude the pores *within* the lesion rather than placing a diffusion barrier on the lesion surface. Several *in-vitro* studies show significantly reduced lesion progression within and peripheral to infiltrated enamel lesions in demineralizing environments^[15, 16]. Emerging early data from clinical trials are promising. Resin infiltration in combination with self-applied non-invasive measures was shown to be more efficacious in reducing lesion progression compared with selfapplied non-invasive measures alone.^[16A]

Clinical Significance: Infiltrating a caries lesion is a potentially effective strategy to strengthen damaged tooth structure and to arrest caries progression without any surgical intervention. Successful management of early progressing, non-cavitated caries lesions by resin infiltration instead of immediate or or postponed restorative treatment may have a great impact in improving oral health care by means of its non-invasive nature. It may drastically lengthen the

life-cycle of an at-risk tooth. Confirmation of the clinical efficacy of infiltration resins would yield a simple and cost-effective caries management treatment option with the least anticipated iatrogenic effect and a diminished need for future re-treatment due to the deterioration of conventional restoration margins.

There are currently no USA-based clinical data reported comparing the recently available option to infiltrate lesions with a standard preventive regimen. Therefore, a randomized controlled clinical trial is warranted to study lesion progression with and without resin infiltration, while the participating patients concurrently receive standard-of-care hygiene treatment, diet counselling and the appropriate fluoride regimen.

4.2 HYPOTHESES

The objectives of the investigation are to study the short-term clinical performance of resin-infiltrated teeth in a caries-active environment. We hypothesize that, in a high caries risk population and with a regular preventive regimen as control management, the infiltration of early approximal caries lesions leads to arrest of the lesion and a reduction of lesion progression.

4.2.1 HYPOTHESIS 1

Infiltrated early caries lesions in a high caries risk population have a *lower incidence of lesion progression* when compared to lesions managed by regular preventive regimen.

4.2.2 HYPOTHESIS 2

Infiltrated early caries lesions in a high caries risk population have a *lower rate of lesion progression* when compared to lesions managed by regular preventive regimens.

To confirm or reject the hypotheses a prospective, randomized controlled trial (RCT) is designed to investigate the clinical performance of resin-infiltration as early caries management in a caries-prone population.

Definitions

Caries detection and diagnosis is an important part of the dentist's daily work. *Caries risk assessment* is the assessment of a patient's risk of developing new lesions in the near future^[17],

^{18]}. At present, the literature shows inconsistent use of criteria defining “high caries risk”. The target population for the current study is a caries-prone population. Recruitment and selection will focus on previous disease (DMFT). During the study the oral environment will be monitored by DMFT assessment using fibre-optic transillumination. The local environment at the embrasure of the included approximal lesion surfaces will be assessed in terms of (1) presence of plaque and gingivitis, and (2) visually using collapsed ICDAS-II scores (see Clinical Evaluation Criteria).

In this clinical study the term “*high caries-risk*” is defined by clinical evidence of previous disease. The caries prevalence is expressed in DMFT. In this study, a **DMFT ≥ 3** is chosen to define a patient’s status of “*high caries-risk*”.

4.3 PREVIOUS EXPERIENCE WITH STUDY MATERIALS

The proposed components of the infiltration kit are substantially equivalent to a variety of currently marketed dental materials in terms of physical and mechanical properties.

4.3.1 INFILTRATION PROCEDURE MATERIALS (KIT)

Infiltrant

The infiltration resin is substantially equivalent to an FDA-cleared – 510(k) K992326 – light-curing sealant material.

Etching gel

The HCl Etching Gel (15%) is substantially equivalent to an FDA-cleared – 510(k) K891536 – enamel microabrasion compound.

The *indication for use* of the DMG “Infiltration kit for caries lesions” is micro-invasive treatment of early approximal caries. The materials will be used according to the label.

4.3.2 PRECLINICAL TESTING

The materials to be used for infiltration (etchant and infiltrant) have received EEC market authorization for medical devices on 2007/04/03. Therefore, complete documentation of preclinical testing and biological evaluation of the device and its results has passed the appropriate regulatory bodies. Documentation and approvals are on file with the sponsor.

4.3.3 PREVIOUS CLINICAL EXPERIENCE

The devices used in this study have seen clinical application for several years for sealant indication with excellent results. The materials in the infiltration kit will be used according to label and for approved indication (micro-invasive treatment of early approximal caries). The materials have a low incidence of adverse events and no prior serious adverse events are known. A recently reported *in-vitro* study showed that active management of incipient lesions with sealant application reduced lesion size^[20]. Investigations of clinical performance of sealed approximal lesions^[12, 13] revealed that application of a sealant acted as a physical barrier and reduced lesion size. An 18-month clinical study demonstrated that only 22% of the sealed incipient proximal caries lesions progressed, compared with the 47% of the group left with no intervention other than instructions for patients to floss regularly^[13]. However, only limited in-vivo data is available evaluating the clinical performance of *infiltrated* early caries lesions in a cariogenic oral environment. A recently published abstract concluded that for proximal caries lesions extending around the enamel-dentin junction (E2, D1) resin infiltration in combination with self-applied non-invasive measures was more efficacious in reducing lesion progression compared with self-applied non-invasive measures alone.^[16A]

4.3.4 DEVICE RISK ANALYSIS AND RISK ASSESSMENT

There is „no more than minimal“ risk associated with the device itself and the procedures involved in its use, as identified by risk assessment and post-market experience of substantially equivalent materials, beyond the common risks related to standard dental treatment. The FDA 510(k) information of the products used is included in A3.4: FDA–510(k) Database Excerpts.

Definition: **Minimal risk** is the probability and magnitude of harm or discomfort anticipated in the research and not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(i)).

The entire treatment in *each aspect*, including lesion size and location, all materials, equipment and techniques used, is part of regular daily life (see also A3.1 Risks). Dentist visits, like in this study, resulting in caries detection, diagnosis and management by regular preventive regimen or sealant are not at all out of the ordinary. It is –alas– rather ubiquitous and a common part of daily oral health care provisions that our profession provides to the public. **Therefore, the risk is**

NOT greater than routine dental practice. The care provided meets this definition of minimal risk.

Although the exclusion criteria mention allergy to methylmethacrylate (a commonly used monomer as a component in many commercial medical, dental, and non-medical applications), this allergy has a low prevalence and materials containing methylmethacrylate or its analogues are managed routinely in dental practices around the world every day. In case of the rare occurrence of an allergy, patients are isolated immediately from contact, treated using well-known emergency procedures, and recover quickly. In almost every case, a patient knows in advance that they have these types of allergies because they must avoid contacts with a huge number of acrylic materials present normally in the world as parts of garments, containers, and common household items. No other adverse effects are known, and none are anticipated.

5 OBJECTIVES OF THE CLINICAL INVESTIGATION

5.1 OBJECTIVES

The aim of the study is to evaluate the efficacy of infiltrating early approximal caries lesions in a caries-prone environment.

5.2 SPECIFIC AIMS (PRIMARY ENDPOINTS)

The investigation will address the following specific aims (primary endpoints):

5.2.1 SPECIFIC AIM 1

To investigate in a high caries risk population of young volunteers (14-35 years old) the *incidence of radiographic progression* of infiltrated early caries lesions, when compared to lesions managed by a standard preventive regimen, evaluated by dental subtraction radiography after 12, 24 and 36 months.

5.2.2 SPECIFIC AIM 2

To investigate in a high caries risk population of young volunteers (14-35 years old) the *rate of radiographic progression* of infiltrated early caries lesions, when compared to lesions managed by a standard preventive regimen, evaluated by dental subtraction radiography after 12, 24 and 36 months.

5.3 SECONDARY ENDPOINTS

In addition to the Specific Aims that describe the use of subtraction radiography, the digital radiographs also will be evaluated *visually* under *standardized conditions* (using low-level magnification (magnifier, loupes) on a computer screen (that can be magnified with the program). The details of the digitizing process and use of procedures involved in image enhancement techniques are described later.

- Radiographic *size* of lesions, evaluated visually by independent assessment of *single* bitewing radiographs taken at baseline and after 12, 24 and 36 months
- Radiographic *progression* of lesions (incidence and rate), evaluated visually by direct pair-wise comparison of *sets of two bitewing radiographs* taken at different intervals (at baseline and after 12, 24 and 36 months).

5.4 STUDY OVERVIEW

In view of prevalence of the type of early lesions to be included in this study and the availability for recalls for a 3-year period, our focus for recruitment will be adolescents/young adults (age range of 14-35 years) with a high caries risk status. After receiving introductory study information at the start of the screening visit the parent/guardian and/or the patient will sign the appropriate consent/assent form. A dental examination including a caries risk assessment will confirm eligibility for the study and individually standardized bitewing radiographs will be taken. The subjects will receive the standard preventive regimen for high caries risk patients. The risk status will be monitored throughout the study using determinants as DMFT, plaque and gingiva status and ICDAS-II scores.

Clinical and radiographic examinations of the study teeth are indispensable components of clinical caries studies in order to diagnose and properly monitor change in approximal caries lesions. ^[21, 22, 23, 24] Clinical evaluations will include history taking and diet counseling, and clinical examination (plaque, gingiva and caries status).

The infiltration procedure will be conducted at the second visit. Contact with the patient will be assured twice a year following a regular 6-months recall schedule, to monitor the study lesions by clinical examination, to update demographic registration information and to maintain

participants' interest in the study. Standard preventive measures will be provided at each recall and individually standardized bitewing radiographs will be taken annually.

It is expected that after 3 years of clinical service the safety and efficacy is maintained and both study teeth are considered satisfactory for continued clinical service.

NOTE — Status Sep 2011:

This protocol was originally designed for a clinical site [REDACTED]. However, the study had to be moved due to unexpected change in local circumstances [REDACTED] (administrative changes, not study-related). Subsequently the CIP was adapted for the clinical site in [REDACTED].

Advancing insights and emerging data led to a new study group, now planned for the **clinical site in** [REDACTED]. The [REDACTED] study includes minor adjustments to the CIP. The most important differences compared to the [REDACTED] study group are:

- Study population:
 - Patients attending the Dental Clinic at [REDACTED]
 - Young adults (age range 18-24 yrs) previously identified having two approximal early caries lesions
- Clinical protocol modifications:
 - Instead of a one-session treatment (incl 20 min separation), the treatment will take place during two sessions (insertion of small tooth-separating elastics at 3 days prior to treatment session).
 - A small pre-treatment impression (included approximal surfaces only) will be taken to confirm 'non-cavitation' status
 - In cases where – after tooth separation – cavitation is diagnosed (and infiltration is no longer indicated), the tooth surface will be conditioned and GIC will be applied. These surfaces will be evaluated during recall as well.
 - At conclusion of treatment the occlusal surface will be sealed.

6 DESIGN OF THE CLINICAL INVESTIGATION

6.1 CLINICAL INVESTIGATION PROTOCOL

This CIP describes a three-year longitudinal, prospective, randomized controlled trial incorporating a bilateral intra-oral design. The investigation is designed as a proof-of-principle trial in anticipation of a future multi-site controlled trial. The study includes a clinical team involving one on-site Principal Clinical Investigator (Site-PCI)/operator and one or two Clinical Investigator (CI).

The clinical site will enroll 50 subjects (in the age range of 14-35 years (U [REDACTED] and 18-24 ([REDACTED])) with two study lesions. If the lesion management provided in the study appears to be insufficient within the investigation period ([REDACTED]; [REDACTED]), the standard traditional restoration will be provided. The patients will be evaluated at six time points over a period of 3 years. Lesion status and caries risk will be radiographically and clinically monitored at 6-month intervals during the first year, with radiographic evaluation then conducted at 12-month intervals (at 1-, 2- and 3-year recall visits).

6.2 PARTICIPANT SELECTION

6.2.1 INCLUSION CRITERIA

Subject level

- Young adolescents/adults with good general health
- High caries risk status based on past experience: DMFT ≥ 3
- Reliable for recall attendance for a 3-year follow-up period
- At least two early caries lesions in approximal posterior surfaces

Tooth level

- Vital, non-symptomatic tooth
- Approximal caries lesion into the inner enamel or outer dentin (E2/D1 lesion)
- Lesion visible on radiograph
- Tooth routinely in contact with adjacent tooth
- Tooth with independent lesion or restoration (PRR, sealant, amalgam) at another surface is allowed

Lesion level

- Location: Lesion not adjacent to a lesion to be treated,

- Depth: Radiographic score R2-R3 (lesion depth around EDJ)

6.2.2 EXCLUSION CRITERIA

Subject level

- Current participation in another clinical study
- Medically compromised subjects
- Hyposalivation
- Pregnancy
- Allergic to methylmethacrylates

Tooth level

- Symptomatic tooth

Lesion level

- Location and size outside targeted lesion description

If patients, teeth or lesions fall outside the scope of this study the patient will be referred back to their regular dental provider. The enrollment will continue until the required number of subjects for study population has been met.

6.3 RANDOMIZATION AND BIAS

Using a computer-generated random list, the treatment (infiltration or control) is randomly assigned to each tooth between the screening visit and the intervention visit. The randomization is recorded at the Patient-Code link list and at the Case Report Form (CRF).

The operator will not be blinded. To avoid bias during the evaluation phase the assessment of the patient's radiographs after the 1-, 2- and 3- year recall will be performed by non-operator examiners/evaluators. The evaluators will be masked to the treatment provided.

6.4 ENDPOINTS

The primary endpoints will be:

- Incidence of lesion progression as analyzed by subtraction radiography
- Rate of lesion progression as analyzed by subtraction radiography

The secondary endpoints will be:

- Radiographic lesion size as evaluated visually by independent reading of digital radiographs

- Radiographic lesion progression (incidence and rate) as evaluated visually by direct pair-wise comparison of sets of digital radiographs taken at different intervals

7 CLINICAL EVALUATION

At the screening visit and at each 6-month recall a clinical evaluation will be conducted. The patient will be interviewed and receive a clinical examination. Additionally, at the screening, 6-month [REDACTED] and at 1-, 2- and 3-year recall visits a bitewing radiograph will be taken.

7.1 RADIOGRAPHS

Additional radiographs will not be taken for purpose of the trial only. The policy described below reflects the widely accepted, current best practice regarding detection, diagnosis and monitoring of approximal lesions. Standardized diagnostic BW-radiographs will be taken using an individualized aiming device. The device facilitates optimal direction of the x-ray beam and thus leads to optimal diagnostic representation of the caries lesion.

Radiographic evaluation of the lesions and the quality of the adjacent enamel contact surface by standardized bite-wing radiographs (BW's) at baseline will be used to detect and diagnose the caries and monitor lesion change. An extensive review of the scientific evidence^[21] supports the following recommendations for the interval between initial bitewings and first radiographic recall. Both, the guidelines by Pitts and Kidd^[25] widely used in Europe, and the ADA/FDA-coordinated US guidelines^[26] advise that in a high risk teenage population the interval should be 6-12 months. The proposed timing of bitewings in our study including young adults (baseline, 6-month and at yearly intervals) falls within these guidelines. It represents a minimum of the advised frequency for a caries-prone study population of adolescents and young adults..

Detection of approximal carious lesions is greatly facilitated by digital processing of the radiographs^[27]. The advantage of using digital images is that electronic contrast enhancement may aid in visualization of the complex image^[28, 29]. Recently, subtraction radiography was reported to be more accurate and reproducible for detecting mineral loss than subjective comparison of paired digital images^[30]. A digital subtraction program will be used to detect the differences in extent and density of the lesions. These programs have been successfully used to detect simulated and clinical caries progression^[30, 31, 32].

7.2 CLINIC VISITS

Table 1 provides an overview of the procedures during each visit.

Table 1: Measurements and procedures during screening, intervention and follow-up.

Clinic sessions	Visit S	Visit BL	Visit 0.5	Visit 1	Visit 1.5	Visit 2	Visit 2.5	Visit 3
Type of visit	Screening, Consenting, Placement of Separators	Inter- vention	Monitor- ing	1-Year Recall	Monitor- ing	2-Year Recall	Monitor- ing	3-Year Recall
Study Time	60 min	30 min	Regular recall	30 min	Regular recall	30 min	Regular recall	30 min
Patient Information	✓							
Signing of Informed Consent / Re-confirmation of Consent	✓		✓	✓	✓	✓	✓	✓
Medical/Dental history incl. diet, F-history, restorative dentistry experience for last 3 years / Re-check changes in health	✓	✓	✓	✓	✓	✓	✓	✓
Checking of inclusion and exclusion criteria (incl DMFT) / Re-confirmation of criteria	✓		✓	✓	✓	✓	✓	✓
Dental examination (incl plaque and gingiva assessment)	✓		✓	✓	✓	✓	✓	✓
Caries risk assessment / Reconfirmation of lesion status	✓		✓	✓	✓	✓	✓	✓
Standardized radiographic examination (bitewing; incl individualized sensor holder)	✓			✓		✓		✓
Selection of eligible lesions	✓							
Placement/removal of separators	✓	✓						
Oral health care instructions	✓		✓	✓	✓	✓	✓	✓
Randomization of treatment	✓							
Clinical Intervention (Infiltration/Control)		✓						
Record of adverse events or other reportable information and occurrences	✓	✓	✓	✓	✓	✓	✓	✓
Oral health care measures (F- varnish)		✓	✓	✓	✓	✓	✓	✓
Patient compensation (Toledo)	✓	✓		✓		✓		✓

7.3 EVALUATION CATEGORIES

Following is a description of the different evaluation categories that will be used to determine caries risk status, to monitor the lesions and to determine the primary and secondary endpoints of this investigation.

7.3.1 HISTORY TAKING (INTERVIEW)

- Fluoride history
- Hyposalivation
- Restorations for the last 3 years

7.3.2 DIET

- Snacking: frequency and content
- Softdrinks: frequency and sipping

7.3.3 LOCAL ECOLOGY OF LESION ENVIRONMENT (ADJACENT EMBRASURE)

- Plaque score
- Gingiva score
- [REDACTED]: A separate, local periodontal examination of study teeth and adjacent teeth will be performed by a periodontist specialist at baseline and 3-month post-treatment

7.3.4 CARIES EXPERIENCE

- DMFT (using fibre-optic transillumination)
- Collapsed ICDAS score for included approximal lesion surfaces

7.3.5 INDIVIDUALLY STANDARDIZED RADIOGRAPHS

- Early caries lesions at approximal surfaces (E2/D1)

7.3.6 CONFIRMATION OF LESION STATUS

- [REDACTED]: After tooth separation and prior to treatment a small impression will be taken of the approximal surface to confirm the clinical diagnosis of 'non-cavitated' lesion.

7.4 EVALUATION CRITERIA

7.4.1 ELIGIBILITY CRITERIA

Hyposalivation

Due to the impact of hyposalivation on the oral environment and caries risk, subjects who suffer from a dry mouth are excluded. Some questions that can be asked to determine hyposalivation are:

- Does your mouth feel dry when eating a meal?
- Do you have difficulty swallowing food?
- Do you have to sip liquids needed to aid in swallowing?
- Is the amount of saliva in your mouth “too little” most of the time?

Patients may report symptoms associated with dry mouth as “burning mouth” and “loss or diminished taste”. As several medications are causing or contributing to hyposalivation the regular use of known hyposalivatory medications for at least 6 months should be noted.

Caries Prevalence – DMFT score 0-28

DMFT value: calculate number of Decayed (D), Missing-due-to-caries (M) and Filled (F) teeth (T). Third molars are excluded. Sealants do *not* count towards DMFT.

Radiographic scores

Description	Score	INCLUSION CRITERIA
Radiolucency in the outer half of enamel (E1)	R1	
Radiolucency in the inner half of enamel (E2) up to the EDJ	R2	
Radiolucency in the outer third of dentin (D1)	R3	
Radiolucency in the middle third of dentin (D2)	R4	
Radiolucency in the inner third of dentin (D3)	R5	

Caries experience

The International Caries Detection and Assessment System (ICDAS) has been adjusted to facilitate recording in this study. The ICDAS-II Caries Detection Criteria ^[33, 34, 35] will be used in a simplified form: the original scores 1 and 2 and scores 3 and 4 have been collapsed to one score each.

This leads to the following “collapsed” scores^[35]:

Approximal Enamel Surface	Score	Description
Sound	0	Sound, no evidence of caries
Early enamel caries, non-cavitated	1	Visual change in enamel opacity and/or color due to caries (not fluorosis, or marginal stain)
Early dentin caries, non-cavitated (cariou defect $\leq 0.5\text{mm}$)	2	Cariou dentin shadow underneath intact enamel or: Cariou loss of surface integrity $\leq 0.5\text{ mm}$
Advanced caries, cavitation $>0.5\text{mm}$	3	Distinct cavity with visible cariou dentin and gap $> 0.5\text{ mm}$

Histologically, these collapsed scores can be classified^[33, 36] as follows:

Approximal Enamel Surface	Score	Histological Classification
Sound	0	No demineralization
Early enamel caries, non-cavitated	1	Demineralization between inner enamel and outer dentin
Early dentin caries, non-cavitated (cariou defect $\leq 0.5\text{mm}$)	2	Demineralization in middle third of dentin
Advanced caries, cavitation $>0.5\text{mm}$	3	Demineralization in inner third of dentin

Most lesions that are eligible to be included in this study will receive a score 1 or 2. Lesions with a score 3 are excluded.

7.4.2 LOCAL ECOLOGY OF LESION ENVIRONMENT (ADJACENT EMBRASURE)

Gingival Status^[37]

Papilla Bleeding Index (PBI)	Score
Sound	0
Redness – no bleeding after probing	1
Redness – bleeding after probing	2
Bleeding after air blowing	3

Plaque Status^[37]

The occurrence of plaque is recorded under clinically dry conditions. A periodontal probe is used to gather any plaque present beneath the contact point by inserting it buccally or lingually, cervical to the contact point. Evidence of plaque is classified as follows:

Plaque accumulation	Score
No visible plaque on the probe	0
Thin visible plaque on the probe	1
Thick visible plaque on the probe	2
Heavily visible plaque in the embrasure	3

8 CLINICAL MEASUREMENTS AND PROCEDURES

8.1 SCREENING VISIT

Patient Information

Consenting procedure – Enrollment

Screening results are documented in Case Report Form (CRF).

Patient Interview

Clinical examination

Caries risk assessment

Individual caries risk is assessed on the basis of the following parameters:

- Past caries experience DMF-T
- Plaque stagnation and gingiva scores
- Diet (frequency and content)
- Fluoride history
- Restorative dentistry history for last 3 years

Standard-of-care caries risk management

Screening and all recall visits will include specific instructions for good oral hygiene and fluoride treatments will be provided.

Radiographic Procedures

For screening as well as follow up examinations a pair of standard bitewing radiographs is taken of the enrolled lesions using individualized bitewing sensor holders (similar to holder in figures 1 and 2). Sensor holders will be personalized with PVS-impression (polyvinylsiloxane). Digital radiography will be employed using phosphor plates and scanner or digital sensors.



Fig. 1: Bitewing film holder with acrylic impressions

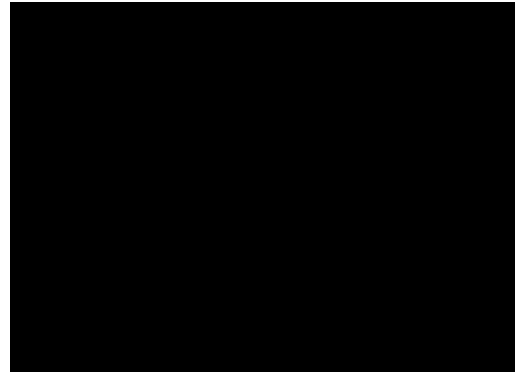


Fig. 2: Radiographic examination

8.2 PLACEMENT OF SEPARATORS

██████████ protocol: To facilitate proper diagnosis of non-cavitated lesion the approximal contact surface of the study tooth will be separated using orthodontic elastics. The elastic separators will remain in place until just prior to treatment intervention (next session).

8.3 SELECTION OF LESIONS (SCREENING VISIT ONLY)

Using the study radiographs **two lesions will be selected** for inclusion in the study:

- 1) The bitewing radiographs are evaluated by the clinical investigator
- 2) Of those approximal caries lesions with radiographic scores R2 (inner enamel – E2) and R3 (outer dentin – D1) the study investigator selects two eligible lesions.
- 3) If more than two lesions are present, the following priorities will be applied to determine those to be included in the study: (1) lesion depth R2/R3 (E2 or D1); (2) tooth type (premolar or molar); (3) lesion location (preference for same arch left and right over two arches left and right over same quadrant).

8.4 RANDOMIZATION

Randomization for this study is associated only with the allocation of lesions to the two management groups. Prior to the intervention visit, the two study lesions will be randomized and assigned to either 'infiltration' or 'control' group by means of a predetermined randomization table.

8.5 INTERVENTION VISIT

To facilitate proper placement of the applicator foil, the teeth will be separated using orthodontic elastics. The elastic separators will be in place for 20 min prior to treatment intervention ([REDACTED] only).

After checking potential changes in medical history, the separators will be removed.

A small PVS impression will be taken of the lesion surface to confirm diagnosis of 'non-cavitation' ([REDACTED] only)

The lesion will be checked for correct diagnosis (contact surface now visually accessible) of non-cavitated early caries lesions.

[REDACTED] In cases where – after tooth separation – cavitation is diagnosed (and infiltration is not indicated), the tooth surface will be conditioned and GIC will be applied.

These single treated surfaces will be evaluated during recall as well.

If 3 or more eligible lesions are present the patient could be enrolled for another pair of study lesions, starting with preparation visit to assure personalized x-ray and tooth separation for 3rd lesion as well.

The selected tooth pair will receive the randomly assigned treatment (as follows).

8.5.1 INTERVENTION SITE: 'INFILTRATION'

The lesion allocated to 'infiltration' is treated using the 'kit for infiltration' (DMG-Dental, Hamburg, Germany) and follows the procedure in Table 2 (next page).

8.5.2 INTERVENTION SITE: 'CONTROL'

The lesion allocated to 'control' receives every step in Table 2 except application of etchant and infiltrant (both replaced by tap water using the triple syringe). This still has the advantage of permitting the best clinical observation of the subject lesion.

At the end of the session fluoride varnish will be applied to the control lesion as part of standard preventive remineralization protocol. The control surface will receive two more fluoride varnish applications within one month.

Table 2 Infiltration protocol

CLINICAL STEPS:

1. Apply a topical anesthetic gel to tooth to be clamped and papilla to be wedged.
2. [REDACTED] Remove orthodontic separator.
([REDACTED] Pre-wedging: Expand the interdental space using a wedge.)
3. Clean the affected tooth and adjacent tooth with non-fluoride containing slurry/paste.
4. [REDACTED] Take a small impression of lesion surface
([REDACTED] Remove wedge.)
5. Apply rubber dam. Remove any residue with water spray.
6. Expand the interdental space using a flattened wedge and place the applicator.
7. Apply HCl gel on the lesion (1.5-2 turns) using the foil applicator and let set for **2 minutes.**
8. While rinsing, remove foil applicator. Rinse-off HCl gel immediately with water spray for at least **30 seconds.**
9. Then dry with oil-free and water-free air.
 - * The etched enamel should have a chalky white appearance. If this is not the case, the etching process must be repeated.
 - * The etched surface must not be touched or contaminated with saliva until the treatment resumes. If contamination occurs after drying re-etch for approx. **10 seconds.**
10. Apply approximately half of the syringe content of ethanol (96%) on the lesion for **30 seconds.** Dry with oil-free and water-free air for **30 seconds.**
11. Place a fresh foil applicator between the separated teeth.
12. Apply infiltrant on the lesion using the foil applicator and let set for **3 minutes.**
13. Remove excess material using air (triple syringe) and high-vacuum suction.
14. Remove foil applicator and wedge.
15. Remove excess material with floss.
16. Light-cure infiltrant for **≥ 40 seconds** total from buccal and lingual direction
Place the light-tip as close to the material as possible.
17. Repeat the application (using a fresh foil applicator and wedge; **1 minute** setting time) and **≥40 s** light-curing of the infiltrant (steps 11 – 16).
18. [REDACTED] Application of sealant to or perform PRR in occlusal surface
19. Remove rubber dam.

* Light-curing unit should have a minimum standard output of 450 nm and should be checked regularly with a handheld calibrated radiometer. The light intensity should be at least 400 mW/cm².

8.6 FOLLOW-UP EVALUATIONS

All procedures for the yearly follow-up examinations are itemized in Table 1. In addition, intervening 6-month recalls will be conducted to reinforce oral hygiene and to monitor lesion status. Specific standard instructions for good oral hygiene and fluoride varnish will be provided at each recall to both study teeth. Due to the non-invasive preventive approach for controls, the patient will be on a strict 6-month recall schedule to closely monitor any changes in caries lesion status and caries risk assessment.

At the 6-month intervals any visual signs of lesion progression are noted and an additional set of 2BW radiographs will be taken to confirm any change in lesion status by radiographical assessment and diagnosis. This procedure is current standard-of-care clinical practice.

8.7 CONCOMITANT TREATMENT

The clinical study is concerned with two lesions per patient. Within the study *no additional concomitant* treatment will be offered to the subjects outside the normal clinical routines.

At the recall appointments, normal recall procedures will be applied.

If lesion progression is suspected or detected by clinical examination during the 1.5 or 2.5 year recall, 2 BW radiographs will be taken to confirm the diagnosis.

If lesion progression is detected at any interval, intervention with a management response that is in the best interest of the patient will be indicated and performed. If this intervention deviates from the study's hygiene or fluoride measures (fluoride varnish application) the patient will be transferred out of the study. The treatment provided will be recorded and the patient's study participation is completed.

9 BIOSTATISTICAL DESIGN

9.1 PROSPECTIVE BI-LATERAL INTRA-ORAL DESIGN

Study designs, as proposed, where the patient serves as her/his own control are recognized as having the ability to greatly facilitate the interpretation of trials by minimizing the effects of inter-patient variability^[38]. In such a design it is possible to subtract out the influence of individual patient characteristics and obtain a more powerful estimate of treatment effect with smaller sample size.

9.2 DETERMINATION OF SAMPLE SIZE

Sample size calculations were calculated based on clinical data from^[13].

Input data for the power analysis:

- two-sided test (paired responses McNemar Chi-square test)
- alpha: 1%
- power 90%

Sample size calculation

Parameters:

- p_0 : 0.841
- p_1 : 0.435

- θ : 0.211
- α : 0.01
- $1-\beta$: 0.9
- n : 29

Initial sample size: 41 pairs (41 patients). At the estimated drop-out rate of 30%, the number of lesion pairs expected is 29.

In view of the specific study population, i.e. high caries risk, it seemed appropriate to estimate 30% attrition after *three* years. Taking attrition into account the study design was based on a sample size of 41 subjects (in total 82 lesions) and 41 lesion pairs at the start of the investigation. This provides some leeway in terms of other unexpected losses from the study. To achieve a final enrollment of 41 patients it is expected that about 50 patients need to be screened. The maximum number of subjects to be enrolled to achieve more than 90% power remains 50 subjects.

NOTE: Sep 2011

██████ site: Study enrollment has been concluded at 22 pairs (██████ 2011).

██████ site: Planned for enrollment of 50 lesion pairs. With a low estimated drop-out rate of 10% over three years the number of lesion pairs expected will be 45. This will allow for some losses while the power of the study remains high.

9.3 STATISTICAL ANALYSES

9.3.1 DESCRIPTIVE STATISTICS

Screening and Baseline data will be reported using descriptive statistics (patient population characteristics, frequencies).

9.3.2 BLINDING

The clinical investigation involves blinding of the patients and the evaluators to the lesion management provided. The operators are not blinded.

If access and breaking of the code is necessary, information regarding the lesion management provided can be retrieved from the Patient-Code List.

The teeth will be randomly allocated to either the „infiltration“ or „control“ group. The study materials are used “on-label”, and have been on the market for a considerable period of time. It is unlikely that the study needs to be terminated on statistical grounds as the safety and efficacy of the materials have already been established. We do expect to find similar or larger differences between the two management approaches in this study when compared to the Martignon study^[13]. Based on emerging clinical data (2011) a higher difference in discordant pairs is to be expected.

9.3.3 EVALUATION OF RADIOGRAPHS

The radiographs will be examined and assessed by evaluators who are blinded to both sequence of radiographs and allocation of lesions to ‘infiltration’ and ‘control’ group.

9.3.4 DIGITAL SUBTRACTION RADIOGRAPHY – LESION EXTENSION AND DENSITY

After image enhancement the digital radiographical image will be assessed for positive, none or negative change in size and density using digital subtraction radiography.

Digital subtraction using a set threshold will be performed by two independent examiners who are masked to the origin of the radiographs. The images are read independently and discrepancies between the readings will be solved by consensus. The examiners determine the size of the lesion and record whether the lesion progressed, did not change or regressed. Chronological and other sets of radiographs will be compared: BL vs. 1Y, 1Y vs. 2Y and 2Y vs. 3Y; and also BL vs. 2Y, BL vs. 3Y and 1Y vs. 3Y.

9.3.5 INDEPENDENT VISUAL READING – LESION SIZE

The radiographs are read independently using the standard radiographic scoring system as described in Evaluation Criteria (7.3).

9.3.6 DIRECT VISUAL COMPARISON – LESION EXTENSION

At least one week later the bitewing radiographs are read pair-wise (Scores: “A deeper than B”; “B deeper than A”; “A and B same lesion extension”). The examiner is blinded regarding the date of record (baseline or follow-up).

9.3.7 MISSING DATA

Missing data due to dropouts have been accounted for in adjusted sample size. The missing data will be at random.

9.3.8 STATISTICAL SOFTWARE

All analyses will be carried out using PASW (SPSS 18), STATA (11.0 SE) and SAS (9.2)^[39, 40, 41].

10 METHOD OF REPORTING

10.1 PERIODIC REPORTS TO THE SPONSOR

Reports will be written by the PD/PI [REDACTED] at the Core Data Center based on the analyses of the baseline and recall data (see Appendix 8). The Final Report will mark the official end of the trial. Each report will include summary data sheets, and an evaluation of the results with clinical conclusions and will be signed by the PD/PI and the Site-PCI.

10.1.1 FINAL REPORT

The Final Report of the clinical investigation will include a description of the methodology and design, data analysis together with a critical evaluation, a clinical appraisal signed by the PD/PI and the Site-PCI, together with statistical analyses. The final report will take into account all data for all enrolled subjects; no subject will be identifiable either from the Final Report or published results. The data will be securely stored for 5 years after completion of the study.

10.2 DEVIATIONS FROM THE CLINICAL INVESTIGATION PLAN (CIP)

10.2.1 DEVIATIONS FROM THE CIP

Any deviation from the CIP will be documented together with an explanation for the deviation. Deviations will be reported to the PD/PI who is responsible for analyzing the deviations and assessing their significance.

Other Reportable Information and Occurrences (ORIO's: such as protocol deviations, accidents/incidents, and complaints) will be reported to the IRB in the form of an ORIO Report:

- within 7 days when urgent subject safety or regulatory concerns exist and /or oversight letter is received
- within 15 days when situations or event potentially alters risk-benefit assessment and/or may jeopardize integrity of study results and/or potential benefits to subjects
- with scheduled continuation review or concurrently with report to oversight body, whichever comes first, when ORIO falls outside of other IRB timeframe parameters.

The reasons for withdrawal and discontinuation of any subject from the investigation will be recorded on the most recent CRF or CEF form. The PD/PI at the Core Data Center will assess their significance.

10.2.2 *WITHDRAWAL / DROPOUT OF SUBJECTS*

Table 3: Withdrawal and drop-out of subjects

WITHDRAWAL / DROP-OUT		
LEVEL	CAUSE	CONSEQUENCE
Lesion	An allocated lesion progresses radiographically into the middle or inner 1/3 of dentin (scores 4 and 5).	The lesion is treated invasively by removing the caries and placing a filling. The case is scored as "progressed" and "failure".
	The patient shows signs of reversible or irreversible pulpitis in an allocated tooth.	The tooth is treated. The case is scored as "progressed" and "failure".
Patient	The patient shows adverse reactions for one of the study materials.	Counteractive measures are taken. Unwanted effects are documented in CRF or CEF. The patient is scored as "drop out".
	The patient can not be examined (i. e. x-ray during pregnancy)	The patient is scored as "drop out".
	One or more allocated lesions have been treated by an external dentist.	The patient is scored as "drop out".
	The patient can not be contacted to make appointments	The patient is scored as "drop out".
	The patient decides to withdraw his informed consent or study participation.	The patient is scored as "drop out".
Study	One or more patients show severe unwanted side effects to treatment.	Individual counteractive measures are taken. The study is halted.
	More than four patients show unwanted side effects to one treatment or material used.	Individual counteractive measures are taken. The study is halted.

10.2.3 *AMENDMENTS TO THE CIP*

All amendments to the CIP shall be agreed to by the PD/PI and the Site-PCI and be recorded with a justification for the amendments. Deviations will be reviewed to determine the need to amend the CIP or to terminate the investigation.

However, when there are changes to the initial list of clinical investigators this list will not be formally updated by amendments at each change; the PD/PI will maintain an updated list, which will be available on request. The definitive list of all investigators shall be provided with the final report.

10.2.4 ADVERSE EVENTS

Emergency contact details for reporting of serious adverse events (Appendix 4) are included in the CIP (see A4: work and residential addresses and phone numbers of PCIs).

All materials and devices used in this study have been approved by local regulatory bodies (including FDA) and are currently on the market in various parts of the world. Their clinical use is according to label. Therefore, no foreseeable adverse events are expected.

In case of a serious adverse event and subsequent need for un-blinding the name-code list can be accessed immediately and breaking the code will not cause any further problem. The data recorded until the report of adverse event will remain included in the dataset.

10.2.5 EARLY TERMINATION OR SUSPENSION OF THE INVESTIGATION

All materials and devices used in this study have been approved by local regulatory bodies and are currently on the market in various parts of the world. Their clinical use in this investigation is according to label. Therefore, early termination or suspension of the investigation due to problems with the restorative materials is not anticipated.

If the investigation is terminated prematurely or suspended, the PD/PI will promptly inform the clinical investigators/investigation center of the termination or suspension and the reason(s) for this. The ethics committees will also be informed promptly and provided with the reason(s) for the termination or suspension by the PD/PI or by the Site-PCI.

10.2.6 LENGTH OF FOLLOW-UP (3 YEARS) – POTENTIAL STUDY EXTENSION

At the 3-year recall the number of subjects and the outcomes of the study will be assessed specifically in view of study continuation. Based on an informed discussion concerning patient retention data and available results an assessment regarding continuation or closing of the investigation will be made by the PD/PI. The PD/PI will inform the Sponsor whether continuation

of the evaluation period to the 4- or 5-year recall is expected to provide scientific valuable results. The decision for continuation will be made by the Sponsor.

11 ETHICAL CONSIDERATIONS

The Human Subjects appendix (Appendix 3) describes the issues involved in human subjects research.

Institutional ethics applications, including proper informed consent (parents/guardians) with informed assent (teenagers 14-17 years old) or adult informed consent (18-35 years), will be submitted for approval according to the international rules and regulations for Federal-Wide Assurances of Protection for Human Subjects (FWAs). See also webpage:

http://www.hhs.gov/ohrp/assurances/assurances_index.html . The study protocol will be submitted to the ethics committee (Institutional Review Board: IRBMED) at the University of Michigan (location of the central administrative core) and the respective IRBs in [REDACTED] and [REDACTED] IRB-KACH). The participating clinical centers [REDACTED] have each an established, registered IRB and FWA (or equivalent).

Current information: *Michigan: FWA00004969*

[REDACTED] *FWA00007742*

[REDACTED] *USAMEDDAC assurance: DoD A10027*

Full registration information of the governing Assurances and IRBs is included in Appendix 3.8. All investigators involved are required to complete the PEERRS certification (or equivalent) prior to the start of the study (*Appendix 11*).

12.1 THE RESEARCH TEAM AND ITS RESPONSIBILITIES

12.2PROJECTED TIME FRAME

Table 4: Projected time frames

[illegible]

PLANNED			(NY)
		Study Preparation – CIP and IRBs completed	
		Training and Clinical site preparation	
		Calibration session (clinical team)	
		IRBMED and IRB-KACH approval	
		Clinical study initiation, start treatments in	
		Patient screening and enrollment	
		Clinical phase: screening and treatment sessions	
		Baseline Report	
		One-year recall	
		One-year Report	
		Two-year recall	
		Two-year Report	
		Three-year recall	
		<i>Decision regarding potential extension to 5-yr recall</i>	
		Three-year Report – Study Completion: Final Report	

12.3FINANCING

Financial agreements regarding funding of the different aspects of the investigation are part of separate contracts between the Sponsor and the Study Team / University of Michigan.

12.4REIMBURSEMENT TO SUBJECTS

Subject compensation and incentives being part of the subject retention package for the clinical site will be part of a separate contract and fall outside the scope of the CIP. (not applicable in



12.5INSURANCE OF THE SUBJECTS

The study materials in this investigation are cleared by the FDA (USA) and available on the market. Therefore, the subjects taking part in the trial are insured by the Sponsor against any injury caused by the study materials under investigation.

12.6CONFIDENTIALITY

All unpublished information concerning this trial and the materials supplied to the PD/PI and the Investigators by the Sponsor will be treated confidentially by all parties involved until the Sponsor gives written consent that the information may be published or handed over to third parties.

The Sponsor has the rights on all data and information acquired during the investigation.

12.7PUBLICATIONS

Publication of (parts of) the trial by the Study Team will take place only with the written consent of the Sponsor, or following a period of one year from the date the Sponsor receives the related report.

13 REFERENCES

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Statistical Analysis Plan

Study Title: **Infiltration of Caries Lesions**

NCT Number: **NCT01584024**

NCT Title: **Resin Infiltration to Arrest Early Tooth Decay**

Sample size calculation

Sample size calculation for paired observations (split-mouth design, McNemar's test) was based on the following parameters from a previous infiltration study of Martignon et al. [25]. Assuming a difference of proportions of 41% in lesion progression between control (84%) vs. test (43%) group, and a proportion of discordant pairs of 56%, $\alpha = 0.05$, and $1 - \beta = 0.8$, the calculated sample size was 22 lesion pairs. Allowing for a potentially high attrition rate over a period of 3 years, 42 participants were enrolled to find significant differences using McNemar's test.

Statistical analysis

Intra/inter-examiner reliability for independent radiograph evaluations was analyzed with Kappa statistics. The primary outcome was proportion of lesion progression (comparative pairwise assessment: continuous progression), whereas change in categorical lesion depth (progression to next depth category) was considered a secondary outcome. Differences between groups were tested using Chi-square test and Fisher's exact test. Differences in proportion of progressing lesions were analyzed with McNemar's test with 95% confidence interval (95% CI) and $P = .05$ for significance level using SAS software. Pairwise comparison data and cumulative lesion progression were used to calculate the therapeutic effect (absolute value) and the relative risk reduction (RRR) that indicates efficacy of treatment.