NCT Title:	**Lesion Progression After Icon Treatment in Young Adults**
NCT Number:	NCT01988337
IRB Approval Date:	10/03/2014

Content:

Study Protocol

Title:	**Double Blind Randomized controlled clinical trial of lesion progression after treatment with Icon vs. Placebo in caries lesions in young adults over 36 months**
Short Title:	Lesion progression after Icon treatment in young adults
Running Title:	TOPIC_36_Study
Protocol-ID:	NCT01988337
	+ 1 Amendment valid as of 30.11.2015 (Appendix 9)
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Sponsor:	DMG Dental Material Gesellschaft mbH
	Elbgaustraße 248
	22547 Hamburg
Study Site:	University of Alabama at Birmingham
	School of Dentistry
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	Birmingham, AL 35294
	United States
Version:	StudyProtocol_NCT01988337_5.0[redacted]
Replaces Version:	StudyProtocol_NCT01988337_4.0[redacted]
Date:	21-Dec-2016

[redacted]

Content

1 Synopsis of the Clinical Investigation

Introduction

Dental caries is the most widespread of all diseases. It causes destruction of tooth structure by dissolving the enamel on the outside of the tooth first and then progressing into the inside of the tooth. 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 the contact area between teeth. Recently there is evolving interest in using composites to infiltrate enamel and dentin areas that have just begun to be destroyed by caries. The infiltration technique arrests the lesion progression by sealing the porous surface and restores the damage avoiding ongoing acidic damage of tooth structure.

Objective

Assess the clinical efficacy s of using Icon to infiltrate initial lesions below the 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

One hundred fifty volunteers (14+ years) with two early lesions in posterior teeth will be enrolled into a clinical trial to evaluate the clinical efficacy of infiltrating the lesions as compared to current watch-and-wait approaches that are combined with good oral hygiene and fluoride application. 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 every six months by clinical examination and as well using annual radiographs.

Clinical Significance

Infiltrating a caries lesion is a potential effective strategy to strengthen damaged tooth structure and to reduce caries progression without any surgical intervention.

1.1 Description of the 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 efficacy of management of early caries lesions by resin infiltration.

1.2 Sponsor

DMG

Dental Material Gesellschaft mbH

Elbgaustraße 248

22547 Hamburg

GERMANY

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+49 40 840 060

[redacted]

1.3 The Study Organization

The trial organization is located at the School of Dentistry at the University of Alabama, Birmingham, AL, USA. [redacted] has broad experiences in clinical research being engaged in patient-oriented research for years. He will be the Principal investigator and the main contact for study communications (clinical site)

1.3.1 Principal Investigator:

[redacted]

1.3.2 Head of the Clinical study (Sponsor)

[redacted]

1.3.3 Regulatory Affairs/ Clinical Monitoring

[redacted]

1.4 Abstract

This is a three year single site clinical evaluation of a FDA approved (510(k):K100062) lesion penetrating resin used to infiltrate and hamper progression of proximal carious lesions. The purpose of this study is to compare lesion progression infiltrated with (Icon, Hamburg, Germany) to a similar sized lesion in the same patient treated with a placebo. The study is designed as a randomized, controlled, prospective clinical trial with a three year follow-up evaluation period.

The clinical site will enroll 150 subjects (in the age range of 14 years or older) with 2 study lesions. The patients will be evaluated at six time points over a period of 3 years. Lesion status and caries risk will be monitored at 6-month intervals, while radiographic evaluation will be conducted at 12-month intervals at 1-, 2- and 3-year recall visits.

This controlled trial will assess the positive effects of caries lesion infiltration by Icon and may open a new therapeutic strategy in dentistry to establish a micro-invasive therapy.

[redacted]

[redacted]

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[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

[redacted]

2.2 Chemical Composition

2.2.1 Chemical Composition Infiltrant (Resin)

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

2.2.2 Chemical Composition Ethanol Solution (Dry-it)

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

2.2.3 Chemical Composition HCl Etching Gel (Hydrochloric Acid Gel)

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

2.3 Instructions for use

[redacted]

3 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 project. The existing knowledge is briefly stated, including literature citations and highlights of relevant data, indicating the 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 treatment option for early caries lesions. The Clinical Investigation Protocol for this study includes all components and documentation as required to conform to international standards for clinical research (CONSORT], ISO/DIN 14155:2011 and Good Clinical Practice Guidelines.[20-22]

4 Preliminary Investigations and Justification of the CIP

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.[27-29] Pit-and-fissure sealants are an effective way at preventing caries in children and adults—even in early noncavitated (incipient) lesions, according to a new set of ADA evidence-based clinical recommendations.[30] Lately, the concept of sealing caries to arrest lesion progression has been transferred to approximal surfaces.[31,32] In a clinical study sealed approximal lesions showed significantly reduced progression after 18 month compared with those that were treated only with preventive measures.[32] In addition, it has been shown in contemporary European populations that lesions, radiographically progressed into dentin, were not cavitated in 60% of the cases.[33] This indicates that non-invasive management of such lesions is preferred above invasive operative-restorative treatment 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.[33-34] In contrast to 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 showed significantly reduced progression of infiltrated enamel lesions in demineralizing environments.[35-36]

Caries results from a dynamic series of demineralization and remineralization cycles when demineralization dominates. Demineralization initially produces a small non-cavitated area on enamel (white spot lesion) which can progress to a cavitated lesion unless remineralization dominates. In the initial lesion development white spot lesions have an intact hyperminerialized surface with subsurface demineralization. As demineralization continues, surface enamel cavitates and this defect must be restored to create proper form and function to the tooth. Caries is a multifactoral disease caused by cariogenic bacteria established in the oral biofilm. These bacteria[23] metabolize sucrose or other cariogenic carbohydrates (fructose or glucose) and secrete organic acids (lactic, propionic, and formic) that cause mineral ion loss (calcium and phosphates) and demineralization of the tooth. Mineral lost by this method can be replaced during periods of neutral pH (remineralization) from calcium and phosphates in the saliva. Remineralization is facilitated by fluoride and can arrest carious demineralization in enamel by the formation of a hard outer surface. Periods of demineralization and remineralization make up a continuous cycle by which minerals in tooth structure are removed and replaced. If the balance is tipped toward demineralization, carious lesions develop.

The caries process in dentin is similar to enamel, except that dentin demineralization begins at a higher pH (6.4, compared to 5.5 for enamel) and proceeds about twice as rapidly; this is because dentin has only half the mineral content of enamel. Low fluoride levels[24] are insufficient to initiate dentin remineralization but are adequate to facilitate enamel remineralization. Fluoride-ion concentration in saliva is low, averaging about 0.03 ppm (1.6 pmol/L) in the normal subject. In enamel, at fluoride levels around 3 ppm[25-26], if adequate calcium is present the balance of mineral uptake and loss is shifted from net demineralization to net remineralization.

Dental decay is a slowly progressing disease taking several years to advance through the enamel into the dentin of permanent teeth. Progression of caries through enamel and dentin are variable and depend upon the amount of saliva, oral hygiene practices, fluoride use as well as the frequency of sucrose intake, however if proximal caries has reached the inner part of the enamel radiographically, it is difficult to halt further progression and many lesions having reached this stage are restored.

This is based partly on the assumption that carious lesions once reaching dentin will continue to progress and that a restoration is necessary at this stage. A Swedish longitudinal study following teenagers that participated in a rigorous oral hygiene program were clinically and radiographically followed during a 15-year period. [27] Even with this high level of preventive care, many had progressing proximal lesions. For a long time sealants have been used to prevent caries on occlusal surfaces with great success. Sealants have also been successfully used therapeutically when initial or even moderately deep occlusal caries developed.[28,29] Sealing lesions on smooth surfaces has also been tried *in vitro* and the suggestion was that such an approach might delay lesion progression rather than arrest the lesion. [30-32] The latter authors suggested adopting the sealing approach of initial carious lesions on proximal surfaces. There are many possibilities for stopping or reversing the advancement of the lesion. For non-cavitated lesions, remineralization is the natural repair process that relies on the local environment: sufficient saliva flow, availability of calcium and phosphate ions, fluoride, microflora and optimal environmental pH to rebuild a new surface after demineralization. However, if the environment favors demineralization the lesion will continue and cavitate spreading to dentin. Due to the structural difference of dentin, lesions in dentin progress more rapidly than enamel lesions requiring earlier intervention. Improvements in dental materials are promising but there is yet to be a material that carries all mechanical and physical characteristics of the natural tooth. Therefore, it is important to maintain the structure and arrest lesions before they advance. Lesion treatments of enamel caries focus on remineralization using topical applications of fluoride or amorphous calcium phosphate and emphasizing oral hygiene procedures. However, the success of these treatments is dependent on the patient's compliance which is especially difficult in the

proximal areas, where plaque removal is more difficult. Typically, most clinicians will observe small proximal lesions which are located entirely in enamel and typically recommend preventive measures rather than restoration. If the subject is lost to recall and the lesion continues, a larger lesion develops which requires restoration. Treating carious tooth pulp exposures is consequential, often requiring either extraction or root canal therapy. Both the loss of the tooth and its replacement, or endodontic treatment and tooth restoration, involve multiple appointments and considerable expense. A procedure which does not depend upon patient's compliance would be a micro-invasive treatment such as resin infiltration of the subsurface lesion which would eliminate dependence on the patient's compliance. A newly developed surface infiltrating resin has been developed by DMG (Hamburg, Germany). The infiltration technique has significant advantages since it is a non-invasive system requiring no irreversible removal of tooth structure and eliminates drilling and most pain associated with tooth restoration. Evidence is building that this system stops or slows the proximal carious lesion progression. Paris and Meyer-Lückel evaluated the effectiveness of resin infiltrated carious proximal lesions in an 18 month study using standardized radiographs and digital subtraction.[12] They concluded that a resin infiltration into the inner half of enamel or the outer third of dentin is an effective way to reduce carious lesion progression.[33] Martignon et al, using a radiographic comparison technique, reported that a caries infiltrating resin was more effective method for treating proximal enamel lesions than sealing or flossing over a two year period. [8,34] Ekstrand et al compared resin infiltration and fluoride varnish to fluoride varnish only in primary molars after one year. Resin infiltration and fluoride varnish was 35% more effective than fluoride varnish alone. [8,35] Alkilzy and Splieth reported that caries infiltration provided a simple, minimally invasive method for treating proximal initial caries.[36] The objective of this three year study is to evaluate the efficacy of sealing initial proximal lesions.

Clinical Significance

Infiltrating a caries lesion is a potentially effective strategy to strengthen damaged tooth structure and to reduce caries progression without any surgical intervention. Management of early lesions by infiltration instead of or postponing restorative treatment would have a great impact towards improving oral health care by means of its non-invasive nature. It will drastically lengthen the life-cycle of a tooth. Infiltration would provide a simple and cost-effective management option with the least possible iatrogenic effect and diminished need for future re-treatment due to deteriorating of restoration margins. There are only few clinical data reported comparing the recent development 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 patients receive standard-oral care hygiene treatment, diet counselling and 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 reduction of lesion progression.

4.2.1 Hypothesis I

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. The number of lesions requiring an invasive intervention (filling) is significantly lower than for lesions treated with standard regimens.

4.2.2 Hypothesis II

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.

4.3 Previous Experience with the Study Material

4.3.1 Description of the clinical procedure

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. The *indication for use* of the DMG “Infiltration kit for caries lesions” is micro-invasive treatment of early approximal caries. The FDA approved (510(k): K100062) 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 [redacted] 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 (510(k): K100062).

4.3.3 Previous Clinical Experience

The devices used in this study have seen clinical application for several years for infiltration 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 proximal caries).

4.3.4 Clinical Studies

Infiltrating a caries lesion is a strategy to strengthen damaged tooth structure and to reduce caries progression without any surgical intervention.[1-3] Management of early lesions by infiltrating instead of or postponing restorative treatment would have a great impact towards improving oral health care by means of its non-invasive nature. It will drastically lengthen the life-cycle of a tooth.[3] Infiltration would provide a simple and cost-effective management option with the least possible iatrogenic effect and diminished need for future re-treatment due to deteriorating of restoration margins.[4]

The promising *in vitro* results of caries infiltration on extracted teeth were underlined by different clinical trials. Several groups reported slower caries progression in infiltrated sites compared to controls: Radiographically obtained quantification reveals lesion progression in 16% of infiltrated sites compared to 53% for controls after one year and for 24% (infiltration group) and 62% (control) after two years. Recently, the three year follow-up data were published, reporting 32% progression for infiltrated lesion and 70% for controls in this split-mouth study.[5] Meyer-Lueckel et al. measured progression rates of 7% (infiltrated sites) and 37% (controls) after 18 month in young adults.[6] The currently available 3-year data of this study report 4% progression in infiltrated lesion and 42% for controls.[7] Ekstrand et al. aimed to assess the efficacy of resin-infiltrated lesions covered by fluoride varnish (FV) versus FV treatment only of proximal lesions on deciduous molar teeth in a one year

split-mouth study. Radiographically, 23% of the test lesions and 62% of the control lesions had progressed, comparable to the aforementioned results in young adults. [8]

5 Device Risk Analysis and Assessment

5.1 Risk Analysis of the Medical Device

There is a 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.

> *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. 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 professions provides to the public. Therefore, the risk is NOT greater than routine dental practice. The care provided meets this definition of minimal risk.

5.2 Risk Management of the Clinical Device

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 the 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 world as parts of garments, containers, and common household items. No other adverse effects are known, and none are anticipated.

6 Objectives of the Clinical Investigation

6.1 Objectives

The main purpose of the present study is to evaluate the efficacy of the Icon Caries Infiltration system, DMG, Hamburg, Germany) in controlling the progression of non-cavitated proximal lesions in posterior teeth.

6.2 Specific Aimes (Primary Endpoints)

6.2.1 Specific Aim I

Significant lower rate of invasive interventions (filling) compared to standard treatment

6.2.2 Specific Aim II

Change in lesion size (Radiographic analyses)

6.3 Secondary Endpoints

No sensitivity to percussion

No color change

No sensitivity to periapical palpation

No prolonged response to hot or cold

6.4 Study Overview

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

This CIP describes a three-year longitudinal, prospective, randomized controlled trial in split mouth design. The study includes a clinical team involving one on-site Principal Investigator (Site-PI)/operator and one back-up Clinical Investigator (CI)/operator.

The clinical site will enroll 150 subjects (in the age range of 14 years or older) with 2 study lesions. If the lesion management provided in the study appears to be insufficient within the investigated period, the study will provide a maximum of 2 traditional restorations for free to participants. The patients will be evaluated at six time points over a period of 3 years. Lesion status and caries risk will be monitored at 6-month intervals, while radiographic evaluation will be conducted at 12-month intervals at 1-, 2- and 3-year recall visits.

7 Design of the Clinical Investigation

The study will be designed as a controlled, double blind, randomized, prospective trial with a three year follow-up period regarding to CONSORT[22] recommendations as a single-center study to investigate the effect of caries infiltration as an alternative treatment option.

7.1 Clinical Investigation Protocol

Study enrolment phase includes patient interviews, dental screening and bite-wing radiographs taking.

7.2 Participant Selection

Subjects recruited for this investigation will be selected from patients attending the clinical research area and recruited from advertisements (Attached). 150 patients aged 14 years and older will be recruited into the study to provide 150 resin infiltrated and control (no Treatment) lesions.

7.2.1 Inclusion Criteria

To be considered appropriate for inclusion in the study a patient must:

- Be age 14 years and older
- Have at least two vital carious teeth with caries ranging from enamel to just into dentin.
  - If the lesion is not on a 3rd molar
  - If the lesion is not developmental.
  - If the lesion is not cavitated
- Be a regular dental attendee able to return for assessments
- Be in good medical health and able to tolerate the dental procedure
- Have no chronic periodontitis which could compromise tooth retention.
- Have normal salivary function.
- Have normal bone levels
- No lingering cold sensitivity
- No periapical sensitivity
- No sensitivity to percussion

7.2.2 Exclusion Criteria

Patients will be excluded from participating in the study if:

- Do not meet the inclusion criteria
- Are not able to tolerate the time required for the study
- There is a history of an adverse reaction to any materials used in the study
- They are irregular dental attendees
- They maintain an unacceptable standard of oral hygiene.
- They have chronic periodontitis
- There is severe salivary gland dysfunction or reduced salivary flow is observed
- They are unable to return for recall appointments

8 Clinical Evaluations

At the screening visit and at each yearly recall a clinical evaluation will be conducted. The patient will be interviewed and receive a clinical examination. Additionally, at the screening and at annual visits a bitewing radiograph will be taken. The data of each visit is documented in the respective clinical report forms (Appendix 1). The criteria and codes used on the forms are documented in the protocol.

8.1 Baseline Records (*Radiographs)*

This section was revised and specified in Amendment 1 valid as of 30.11.2015!

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 bitewing radiographs will be taken using a standardized position device (DMG, Hamburg, Germany). 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 bitewing radiographs at baseline will be used to detect and diagnose the caries and monitor lesion change. An extensive review of the scientific evidence supports the importance of initial bitewings and radiographic recall examinations for description of caries progression.[9-13] Both, the guidelines by Pitts and Kidd 4 widely used in Europe, and the ADA/FDA-coordinated guidelines [14] advise that in high risk children (age 10-16) the interval should be 6-12 month. The proposed timing of bitewings in our study (screening and at yearly intervals) falls well within these guidelines. They rather represent a minimum of the advised frequency for a caries-prone study population of young adults in the age range of 14+ years.

Quantification of caries lesions is greatly facilitated by digital processing of the radiographs.[15] The advantage of using digital images is that electronic contrast enhancement may aid in visualization of the complex image.[16] Recently, subtraction radiography was reported to be more accurate and reproducible for detecting mineral loss than subjective comparison of paired digital images.[17] A digital subtraction program will be used to detect the differences in extent and density of the lesion. These programs have been successfully used to detect simulated and clinical caries progression.[17-19]

8.2 Clinic visits

Table 8.2 Overview of the procedures during each visit

Procedure	Preoperative	Baseline and Intervention	6 moth Follow-up	12 month Follow-up	24 month Follow-up	36 month Follow-up
Time	D-1	D-0	M 6	M 12	M 24	M 36
Patient information	x					
Oral examination	x	x	x	x	x	x
Informed consent	x					
Medical history	x					
Inclusion and exclusion criteria	x					
Selection of eligible lesions		x				
Caries risk assessment	x					
Hot-cold sensitivity assessment	x	x	x	x	x	x
Dental examination	x	x	x	x	x	x
Radiographic examination		x		x	x	x
Assessment of lesion activity						
Randomization		x				
Intervention (Infiltration)		x				
Photographic documentation of lesions	x	x	x	x	x	x
Record of adverse effects			x	x	x	x
Instruction for oral health care		x	x	x	x	x
Color match		x	x	x	x	X
Discoloration		x	x	x	x	x
Surface Integrity		x	x	x	x	x
Secondary Caries		x	x	x	x	x

8.3 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.

8.3.1 History Taking (Interview)

- Oral Health care behavior

8.3.2 Diet

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

8.3.3 Local Ecology

- salivary function
- bone levels
- cold sensitivity
- periapical sensitivity
- sensitivity to percussion

8.3.4 Caries Experience

- DMFT/ WHO Standard

8.3.5 Individually standardized record (*Radiographs*)

- DMG criteria for Icon treatment

8.4 Evaluation Criteria

8.4.1 Pre-Ambule

To avoid confusion due to multi-continental data sharing the European form for dates is provided (dd/mm/yyyy).

8.4.2 Inclusion Criteria

In order to be eligible for the study, each participant must meet preliminary eligibility criteria and the participant or the guardian must be willing to sign a statement of informed consent. This will document the agreement of the participant to participate in the study activities. The patient must have two lesions which meet criteria as listed in Table 8.4.2, shown below.

Additionally, participants will be asked by study personnel not to participate in any other therapeutic research studies during the participant´s follow-up period from baseline to the 36 month visit.

Table 8.4.2. Criteria used in the radiograph examination

E1	Radiolucency confined to the outer half of enamel
E2	Radiolucency involving the inner half of enamel
D1	Radiolucency in the outer third of dentin
D2	Radiolucency in the middle third of dentin
D3	Radiolucency in the inner third of dentin
D4	Tooth must have proximal contact
D5	Patient must be able to tolerate procedure (ie – Jaw-opening must be adequate)
D6	Tooth must have adequate attachment
D7	Tooth must be vital and not sensitive to palpation or percussion
D8	Tooth to be restored must occlude with an articulating surface
D9	Tooth must not be fractured or otherwise “non-restorable”

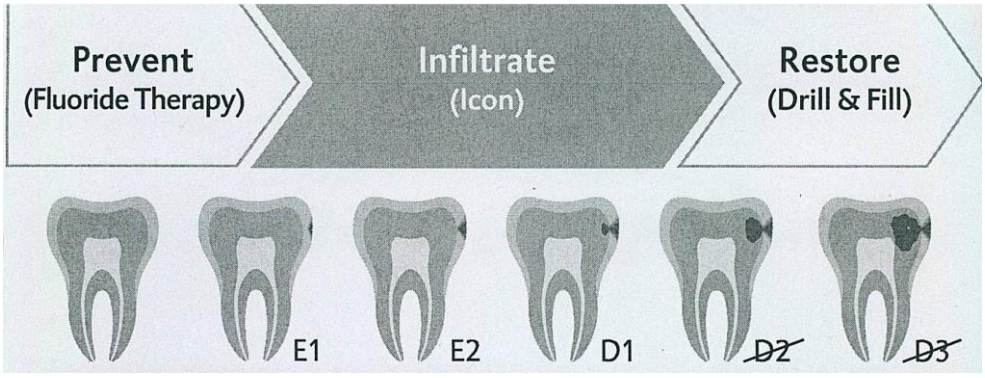


Figure 3: DMG criteria for treatment planning for Icon infiltration therapy. Adopted from DMG, Hamburg, Germany.

8.4.3 Local ecology

Sensitivity (Cold response/Biting response)

Sensitivity will be measured using a visual analogue scale.

Preoperatively –Cold response on the selected carious tooth will be measured by applying a cotton pellet soaked in Endo Ice to the tooth for 3 seconds and asking the subject to place an X on a 10 cm line labeled 1 on the left and 10 on the right. They will be told that 10 represents the worst pain they can imagine (childbirth, major surgery or kidney stones) and 1 represents no sensation at all. Stimuli – biting pressure (biting on a cotton tip applicator) and cold tests will be measured using the same scale.

Saliva function

Saliva function will use stimulated saliva flow measurement. Patient will chew paraffin for 2 minutes, hold saliva in their mouth, and then expectorate into a graduated cylinder. Amount of saliva flow will be expressed as ml.

DMFT Score

Teeth will be scored as D = decayed, M = missing, F = filled and T = teeth and the final DMFT value will be calculated as recently described.[37]

9 Clinical Measurements and Procedures

9.1 Screening Visit

The screening phase allows confirmation of subject eligibility for the trial based on inclusion and exclusion criteria. Screening includes patient information, eligible lesion are evaluated by a study investigator and randomly selection of caries lesions for treatment.

9.2 Selection of Lesions (Screening visit only)

After allowing each subject an opportunity to read and consider the consent form and answering any questions concerning the study, each subject will be asked to complete and sign the consent form. Appropriate vitality and radiographic assessments will be completed and any pathology noted and recorded. A radiograph will be made of each carious tooth lesion to be included in the study. The depth of the carious lesions will be measured and recorded (E1-2 or D1). Periapical lesions will be recorded. Digital images of the tooth will be made and filed. Cold and hot response will be recorded and the time after the stimulus is applied for any pain to stop will be recorded. Patient age and tooth number will be recorded.

9.3 Randomization

A random assignment of the treatment to teeth is based on equal distribution of the two treatments; each subject will receive both a placebo controlled or an Icon resin treatment for the two proximal carious teeth, assigned by beginning with the tooth with the lowest number, the specific procedure applied to each tooth will be determined by selecting from a box containing two choices (A or B) by the clinician doing the procedure. One tooth (the one with the lowest tooth number in the universal numbering system) will receive the treatment drawn from a box containing the names placebo or Icon. The universal numbering system begins with #1 - the maxillary right third molar and proceeds to #16 the maxillary left molar. In this system the mandibular left third molar is # 17 and the mandibular right third molar is tooth number #32. The treatment (the first one drawn) will be placed on the tooth with the lowest number. The remaining tooth will receive the second treatment. Clinicians and patients

receiving the two treatments will be blinded as to the treatment applied to the specific tooth.

9.4 Intervention Visit

9.4.1 Intervention Site "TREATMENT"

During the screening examination and after informed consent has been obtained from the subject, bite wing radiographs will be made using a customized holder for the digital sensor using VPS impression material. The subject position will be controlled in 3 dimensions by placing holders in the subject's ears and placing their chin in a holder. The positions used for the initial set of radiographs will be recorded and used for all subsequent x rays to standardize their position at each recall. At a separate appointment, each selected subject will be instructed in oral hygiene procedures to include brushing, flossing and the use of a fluoride containing toothpaste. To be included in this study the subject must have two teeth with similar sized lesions. After the lesions are selected, one of two treatments will be selected from a box by the clinician doing the procedure. One of the "treatment tooth" will randomly receive the infiltrating resin (Icon). Teeth will be isolated with a rubber dam, the tooth surface cleaned with non-fluoride prophylactic paste and pumice. The Icon material will be applied following the manufacturer's instructions and light cured with S 10 curing light (3M ESPE, St Paul, MN). Output from the curing light will be measured and recorded weekly. The Icon infiltrating resin will be polished using interproximal finishing/polishing strips (Sof Lex, 3M ESPE, St Paul, MN). Subjects will be given a letter to take to their local dentist asking them not to treat the selected lesions without informing the investigator first. Subjects will be recalled at 6, 12, 24 and 36 month intervals and at radiographs will be made of the control and test lesions after 12, 24 and 36 month . During all visits, oral hygiene will be reinforced.

9.4.2 Intervention Site "CONTROL"

During the screening examination and after informed consent has been obtained from the subject, bite wing radiographs will be made using a customized holder for the digital sensor using VPS impression material. The subject position will be controlled in 3 dimensions by placing holders in the subject's ears and placing their chin in a holder. The positions on the initial set of radiographs will be recorded and used for all subsequent x rays to standardize their position at each recall. At a separate appointment, each selected subject will be instructed in oral hygiene procedures to include brushing,

flossing and the use of a fluoride containing toothpaste. To be included in this study the subject must have two teeth with similar sized lesions. After the lesions are selected, one of two treatments will be selected from a box by the clinician doing the procedure. One tooth will randomly receive the infiltrating resin (Icon) while the other will receive a placebo. Teeth will be isolated with a rubber dam, the tooth surface cleaned with non-fluoride prophylactic paste and pumice. Syringes identical to the Icon materials will be supplied by DMG for the placebo procedure. The syringes will be filled with the solutions having the same consistency and color as the Icon material. The placebo material will be applied following the manufacturer's instructions and light cured with an S 10 curing light (3M ESPE, St Paul, MN). Output from the curing light will be measured and recorded weekly. The placebo material and the Icon infiltrating resin will be polished using interproximal finishing/polishing strips (Sof Lex, 3M ESPE, St Paul, MN). Subjects will be given a letter to take to their local dentist asking them not to treat the selected lesions without informing the investigator first. Subjects will be recalled at 6, 12, 24 and 36 month intervals and at each recall radiographs will be made of the control and test lesions. During these visits, oral hygiene will be reinforced.

9.5 Follow-up Evaluations

At each recall (baseline, 6-month, one, two and three years) all lesions will be assessed according to the asked criteria. In addition to the clinical and radiographic assessment (see below), each evaluation will include an evaluation of surface roughness, color match, post-operative sensitivity/discomfort, and presence or absence of secondary caries. Every attempt will be made to schedule the six month, one and two year recalls within ±2 weeks of the recall interval. When assessors differ, a consensus will be reached before the patient is dismissed. In the event an Icon resin is unsatisfactory, details of the mode of failure will be documented and the necessary replacement / repair made.

9.6 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 local clinical routines. At the recall appointments, normal recall procedures will be applied.

10 Data Management

10.1 Data Management Plan

10.1.1 Data collection

Data collection is done using the CRF that exists in the form of a paper version. The method is to employ paper CRFs to collect the data responses, which are subsequently translated to the monitoring database. These paper CRFs are compiled by the investigator according to the protocol.

10.1.2 CRF tracking

The entries made in the CRF will be monitored by the designated DMG clinical monitor to confirm all requested info and completed CRFs are entered into the database. CRFs are tracked for missing pages and illegible data manually to assure that the data are not lost. In case of missing or illegible data, a clarification is obtained from the investigator and the issue is resolved.

10.1.3 Data validation

Data validation is the process of testing the validity of data in accordance with the protocol specifications. Discrepancy is defined as a data point that fails to pass a validation check. Discrepancy may be due to inconsistent data, missing data, range checks, and deviations from the protocol. Ongoing quality control of data processing is undertaken by the monitor at regular intervals during the course of clinical trial.

10.1.4 Discrepancy management/query resolution

Discrepancy management includes reviewing discrepancies, investigating the reason, and resolving them with documentary proof or declaring them as irresolvable. Discrepancy management helps in cleaning the data and gathers enough evidence for the deviations observed in data. For discrepancies that require clarifications from the investigator, the monitor will discuss the query with the investigator or will be sent to the site. The Investigators will correct the resolution or explain the circumstances that led to the discrepancy in data.

10.2 Data Privacy Protection

Electronic study files will be password protected and reside on a computer that is also password protected. Paper records will be maintained in a locked cabinet in a space that has locked entryways.

10.3 Study Database

Electronic study files as well as paper records, such as CRFs, will be collected and checked for completeness by the clinical monitor during the on-site visits.

A copy of the paper records will be stored at sponsor site. Moreover study data will be transferred into a monitoring specific database.

11 Biostatistical Design

11.1 Prospective Design

Controlled, randomized, double blind study, single center design.

11.2 Determination of Sample Size

Subjects recruited for this investigation will be selected from patients attending the clinical research area and recruited from advertisements (Attached). 150 patients aged 14 years and older will be recruited into the study to provide 150 resin infiltrated and control (no Treatment) lesions. Based on previous studies approximately 20% loss of these subjects will occur over the three year period producing a subject population of 120 who will be available for the 3 year recall.

11.3 Evaluation Strategy

Four trained operators will complete the direct and indirect evaluations of the carious teeth and seal the carious lesions. Two trained and calibrated examiners will complete the evaluation process at each recall. The PI will select all lesions for this study.

11.4 Statistical Analysis

11.4.1 Descriptive Statistics

For the digital subtraction procedure, the ANOVA for Repeated Measures, will be used to determine significance between the two groups (p=.05). The remaining endpoints will be listed as percentages rather than subjected to statistical analyses.

11.4.2 Blinding

Both the placebo and the Icon materials are same in their delivery system, material color, and viscosity. Therefore, the investigators are blinded as to the material used, as are the patient and the evaluators.

11.4.3 Evaluation of Records

This section was revised and specified in Amendment 1 valid as of 30.11.2015!

The outcome variable will be the caries progression status (regression, no changes or progression) for the selected lesions after 3 years. The radiographs will be read by 2 methods (1) visual independent reading and (2) subtraction radiography of digitized images.

For visual readings the depth of each selected lesion will be visually assessed and recorded by the PI independently on the conventional baseline and follow-up radiographs, respectively. The depth of the selected lesion will be classified into the following scales 1- lesion regressed, 2- lesion expanded, 3 no change in lesion size. A score of 4 (missing surface, generally fractured) and 5 (presence of a restoration) may be assigned when needed. For all visual readings, the examiner will be blinded as to whether the examined radiograph was a radiograph of the lesion was Icon sealed or a control. The examiner will be asked to determine the status (1 to 5) of the right positioned image against the left positioned image of the radiograph.

To assess the progression status on subtraction images the conventional radiographs will be first digitized (Epson Expression 1680 Pro scanner, Photoshop software) in a standard way (TPU format, 8-bit, 3,200 resolution), and contrast and gamma levels will be pre-adjusted pair-wise in the baseline and follow-up images. The images will be stored uncompressed (TIFF 3,650 x 2,425 grayscale) at an individual size of 9–14 Mb. Next, the images will be converted to a readable format for the subtraction software in Adobe Photoshop 6.0 and stored as TIFF 600 x 400 files, with a code corresponding to case number, test/control lesion, baseline or follow-up and involved surface.

The digital subtraction of the digitized images will be undertaken by one of the examiners by means of the Compare software (Dental Health Unit, University of Manchester, UK), which runs as a plug-in to the Image Tool software, version 1.23 [University of Texas Health Science Center at San Antonio,

Texas, 2002]. The subtraction images will be obtained by subtracting the follow-up from the baseline images of each lesion. First, the two images will be automatically aligned to obtain a relationship with the least difference between them. The difference in density between the two images will then be normalized. Subtraction of images will be conducted, and the contrast stretched. The subtraction images will be coded and randomly organized, as described above, then saved in a Microsoft Powerpoint presentation. For their reading, the subtraction images will be viewed by an external trained examiner 10 days after the visual assessment of conventional radiographs. The presentation will be viewed on a 43.2-cm Hewlett Packard monitor in one session. Additionally, the examiner will be able to access the conventional baseline radiograph to confirm the vertical location of the lesion within the proximal surface. The subtraction progression will be observed as the presence of black points corresponding to an extension of the proximal lesion. Conversely, regression will correspond to the presence of white points and stabilization as an evenly grayish appearance on the image.

Intraexaminer reproducibility will be obtained by rereading 25% of the independent and paired radiographs and of the subtraction images 2 days after the first reading.

11.4.4 Missing Data

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

11.4.5 Statistical Software

The statistical software that will be used for this study is Statview.

12 Method of Reporting

12.1 Periodic Reports to the Sponsor/Monitoring

Periodic reports will be given to the sponsor in line with the frequently held monitoring visits.

The activities/reporting by the monitor that take place during the on-site visit include, but are not limited to the following:

- Only subjects who meet the study eligibility criteria are enrolled
- Informed consent process was conducted appropriately and that informed consent will be obtained prior to proceeding with any study procedures
- Data was collected and analysed as specified in the protocol
- Adverse events were reviewed promptly and reported as required
- Privacy and confidentiality of subjects was maintained
- Documentation of dropouts
- Evaluation of primary and secondary endpoints
- During an annual visit, the Monitor focuses on the areas where the majority of the deficiencies were identified or addresses other problems or issues noted since the last visit.
- The Monitor identifies and reports any suspected fraud and scientific misconduct if discovered during the review.

The clinical monitoring process of the sponsor can be classified into the following periodical visits:

Study initiation visit

The monitor conducts the study initiation visit after the sponsor submits the protocol to its IRB and in advance of study activation.

The study initiation visit is held at the study site. The monitor prepares a clinical study initiation visit report to document the study initiation visit. The PIs, Sub-Investigators, and Site Coordinators must be prepared to discuss the procedural as well as the scientific aspects of the protocol during the initiation visit.

Annual Monitoring Visit

The monitor schedules and conducts on-site monitoring visits. The first annual monitoring visit to the study site occurs 12 months after a study opens; then annually thereafter until study closure.

The monitor may conduct interim visits as requested. An interim visit can be conducted as a follow-up to an annual visit where a number of deficiencies were identified, or it can be requested for reasons such as the complexity of the study, staff changes, or number of subjects enrolled.

The annual visit is generally scheduled for two days. The monitor prepares a follow-up-monitoring report to document the visit.

Close-Out Visit

The monitor schedules the close-out visit. The close-out visit usually takes one full day. If accrual is exceptionally large, an additional day can be required.

The activities/assessments by the monitor during the close-out visit include, but are not limited to, the following:

- Complete any outstanding site monitoring tasks (e.g., regulatory review and/or review of participant records) through the date of study termination or completion;
- Confirm that the IRB has been informed of the study closure
- Ensure the PI understands follow-up requirements for reporting AEs for subjects who have completed the study
- Conduct a summary meeting with Study Principals to discuss findings and plans for resolution of outstanding issues

A final report will be prepared after finishing all monitoring activities.

13 Changes of the Clinical Investigation Plan

13.1 Amendments to the CIP

All amendments to the CIP shall be agreed to by the principal clinical investigator 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.

14 Deviations from the Clinical Investigation Plan (CIP)

14.1 Deviations from the CIP

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

Other Reportable Information and Occurrences (ORIOs: such as protocol deviations, accidents/incidents, and compliants) will be reported to IRB in the form of an ORIO report:

- Within 7 days when urgent subjects safety or regulatory concerns exist and/or oversights 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

14.2 Withdrawal / Dropout of Subjects

Table 14.2 Withdrawal and drop-out of subjects separated by level, reason consequences

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 and CEF. The patient is scored as "drop out".
	The patient cannot 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 cannot 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 patient(s) 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.

14.3 Length of follow-up – Potential Study Extension

Based on the actual study design there is no extension planned. If obtained data indicate a necessity for follow-up investigations this issue will be discussed with the sponsor and documented in the study files.

15 Confirmation of Study Material Application

Application of study material will be documented in the Study Material Application form (Appendix A2) including patient ID, investigator, date of application, material batch number and signature.

16 Ethical Considerations

This protocol was approved by the IRB from the Federal University of Alabama (Appendix 3). Parents or guardians will sign an informed consent (Appendix 4). Operative dental treatment will be provided to the participants when necessary.

17 Relevant Standards and Guidelines

The Clinical Investigation Protocol for this study includes all components and documentation as required to conform to international standards for clinical research (CONSORT, ISO/DIN and Good Clinical Practice Guidelines).[20-22]

18 Adverse Events

18.1 Adverse Events

An adverse event (AE) is defined as any unintended adverse experience associated with the study materials or study procedures that results in an unplanned medical assessment or treatment, or changes the risk to subjects. Any adverse reaction to the treatment provided as part of the study will be fully investigated and reported to the IRB. AEs will be reported according to the IRB defined timelines using appropriate forms.

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 is according to label. Therefore, no foreseeable adverse events are expected.

18.2 Serious Adverse Events

Emergency contact details for reporting of serious adverse events are included in the CIP (Appendix A5).

Serious Adverse Events are adverse events that:

a) led to a death,

b) led to a serious deterioration in health that either:

1) resulted in a life-threatening illness or injury, or

2) resulted in a permanent impairment of a body structure or a body function, or

3) required in-patient hospitalization or prolongation of existing hospitalization, or

4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

In case of a serious adverse event and subsequent need for un-blinding the name-code list can be assessed 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.

18.3 Report by the investigator to the sponsor

DMG has implemented and maintains a system to ensure that the reporting of the reportable events will be provided by the investigator to the sponsor in acceptable timely conditions using the Adverse Event/ Adverse Device Effect (AE/ADE) Report Form (Appendix A6).

18.4 Report by the sponsor to the National Competent Authorities

Reportable events will be reported at the same time to all National Competent Authorities where the clinical investigation has commenced.

- a SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than **2 calendar** days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- any other reportable events or a new finding/update to it: immediately, but not later than **7 calendar** days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

19 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 principal clinical investigator will promptly inform the clinical investigators of the termination or suspension and the reason(s) for this.

The IRB will also be informed promptly and provided with the reason(s) for the termination or suspension by the principal clinical investigator.

20 Publication Policy

Publication of (parts of) the trial by the Research 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.

21 Administrative Arrangements

21.1 The Research Team and its Responsibilities

Site

University of Alabama at Birmingham (UAB)

School of Dentistry

1919 7th Avenue South

Birmingham, Alabama 35294

United States

Principal Investigator:

[redacted]

Study Coordinator

[redacted]

Clinical Investigator

[redacted]

[redacted]

Biometrics/Statistics [redacted]

21.2 Head of the Clinical study (Sponsor)

[redacted]

21.3 Regulatory Affairs/ Clinical Monitoring

[redacted]

21.4 Clinical Study Contact (Sponsor)

[redacted]

21.5 Projected Time Frame

The clinical study will start as soon as the required ethical approvals have been received and Training has been provided to the clinical team. [redacted]

The time frame is summarized in table 22.5

Table 22.5 Overview of the study´s time frame

time	Study part
[redacted]	Study preparation – CIP and IRBs completed
[redacted]	Training of clinical team Clinical site preparation
[redacted]	**Clinical study initiation** - Patient screening and enrollment - Clinical phase: screening and baseline sessions **Baseline report**
[redacted]	Six-month recall **Six-month report**
[redacted]	One-year recall **One-year report**
[redacted]	Two-year recall **Two-year report**
[redacted]	Three-year recall **Three-year report**
[redacted]	**Completion of three-year study- Final report**

21.6 Financing

Financial agreements regarding funding of the different aspects of the investigation are part of separate contracts between the Sponsor and the Research Team / University of Alabama at Birmingham, Alabama, US.

21.7 Reimbursement 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.

21.8 Insurance of the Subjects

The study materials in this investigation are cleared by the governing bodies of the participating countries (US, Germany). Therefore, the subjects taking part in the trial are insured by the Sponsor against any injury caused by the study materials under investigation. If applicable, additional regulatory requirements in participating countries will be observed and are part of a separate contract.

21.9 Confidentiality

All unpublished information concerning this trial and the materials supplied to the principal clinical investigator and the investigators by the Sponsor will be treated confidentially by all parties involved until the sponsor gives written consents that the information may be published or handed over to third parties.

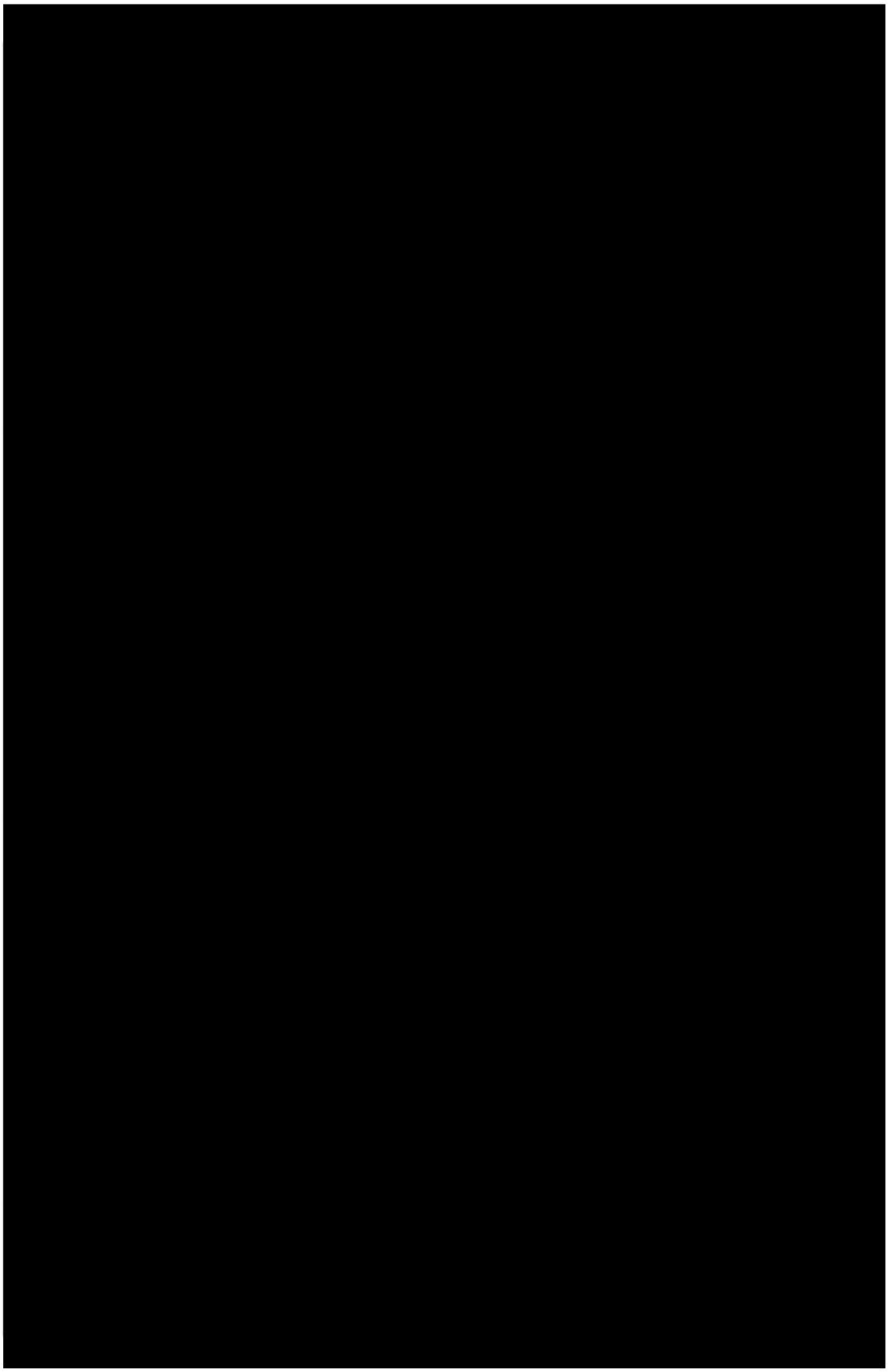
The Sponsor has the rights on all data and information acquired during the investigation.

22 Appendices

A1 Case Report Form

[redacted]

[redacted]



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A2 Study Material Application Form

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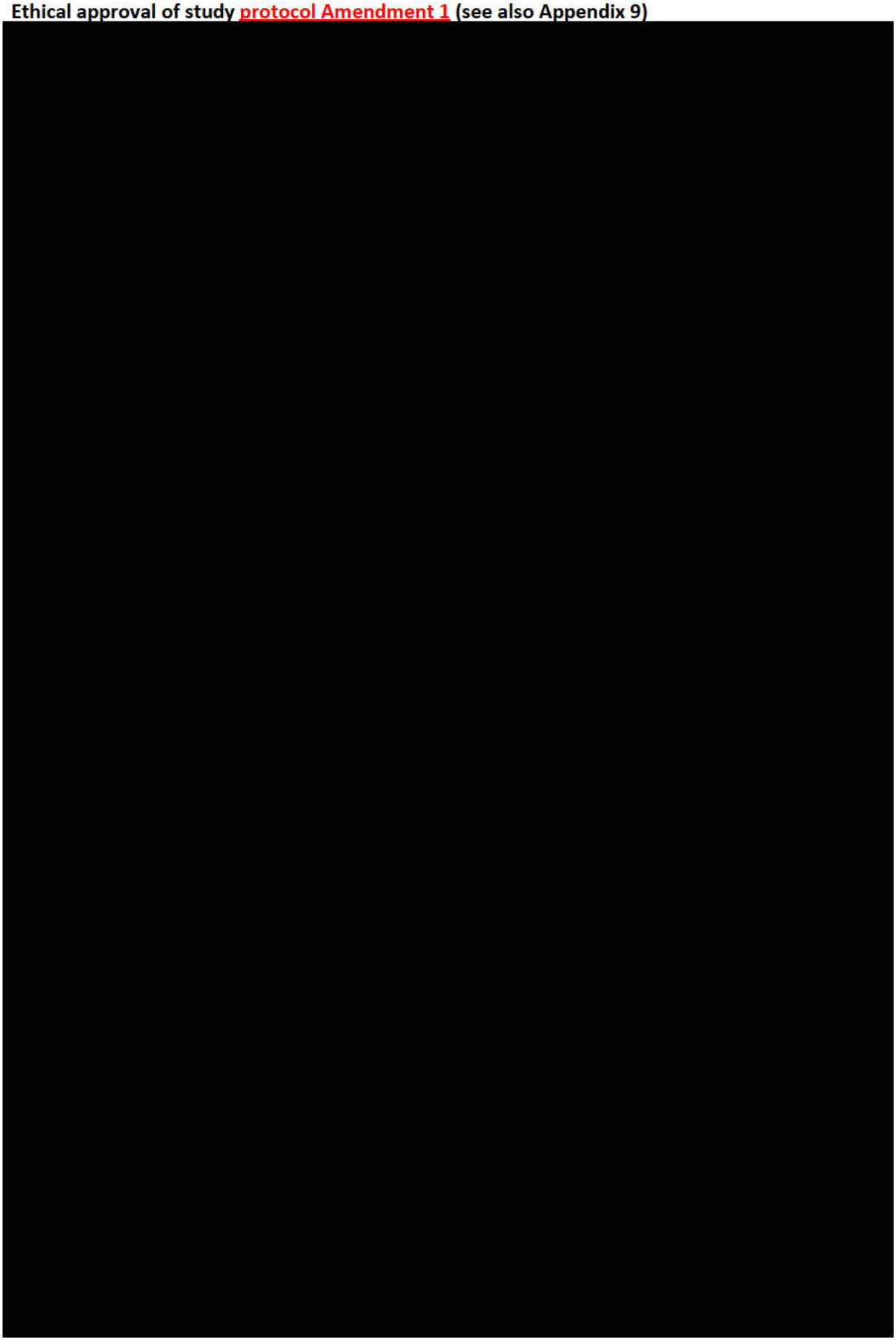
Ethical approval of study protocol Amendment 1 (see also Appendix 9)



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A4 Informed consent form

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A5 Emergency contact information

In any case of emergency please contact:

[redacted]

and/or

[redacted]

APPENDIX 6 ADVERSE EVENT / ADVERSE DEVICE EFFECT (AE/ADE) FORM

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Appendix 9

Study protocol Amendment 1 valid as of 30.11.2015

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Appendix 10

Study protocol Amendment 2 valid as of 21.12.2016

[redacted]

[redacted]

[redacted]

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Statistical Analysis Plan

NCT Number: **Lesion Progression After Icon Treatment in Young Adults**

NCT Number: NCT01988337

Sample Size Determination

A previous infiltration study by Martignon et al. [5] reported a 3-year difference of proportions of 37.8% (95%CI: 20.5-55.2%) with (resin infiltration (68%) vs. control (30%)). Based on this and with alfa = 0.05 and a power of 80% the calculated sample size (t-test; matched pairs) would be 23 lesion pairs (thus 23 participants) to find significant differences. However, this study aimed to enroll 150 participants to not only allow for a potentially high attrition rate (20%) over a period of 3 years, but also aiming to better quantify the efficiency of the treatment effect.

Statistical Analysis

All evaluations are performed by two trained and calibrated examiners. The primary outcome is proportion of lesions that required restorative treatment (filling) after 3 years as measured via dental examination. Differences between groups will be tested using Fisher's exact test and ANOVA for Repeated Measures for subgroup analysis based on caries risk. Secondary outcomes are change in categorical lesion depth (progression to next depth category lesion; E1->E2->D1->D2->filling) after 6 months and 1, 2 and 3 years as measured by pairwise comparison of radiographs as well as the influence of Icon treatment on clinical parameters. Differences will be analyzed with McNemar's test with 95% confidence interval (95% CI) and P = .05.