Clinical Investigation Protocol (incl. statistical considerations)

Clinical examination of the F-Composite 2 Systems in the direct filling therapy

(NCT03221660)

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1. Objectives and hypotheses of the clinical investigation

a) The aim of this prospective study is to evaluate the clinical performance of F-Composite 2, a proven flowable bulk material and adhesive system for the restoration of masticatory posterior fillings (Class I and II), all three materials being polymerized with Bluephase PowerCure (flash mode).

b) Primary hypotheses to be accepted or rejected by statistical data from the clinical investigation.

Prof. Dr. Valentin Rousson from the Biostatistical Department of the Institute of Social and Preventive Medicine at the University of Lausanne, Switzerland, has performed a case number calculation. Assuming that a maximum of 10% post-operative hypersensitivity is acceptable, but actually only 5% is expected, the following formula can be used to calculate the case number (80% power, using a chi-square test at 5% probability of error)
N = (1.96*sqrt(0.95*0.05)+0.84*sqrt(1*0))^2/(1-0.95)^2 = 73 participants or fillings

Furthermore, if one assumes - based on internal experience - that after one year there is a drop-out rate of 2%, 75 fillings are necessary at the beginning of the study to statistically confirm the primary endpoint (post-operative hypersensitivities).

(c) claimed and intended performance of the test product, which shall be demonstrated.
The following working hypotheses should be clarified:

- Teeth restored with the F-Composite 2 system have postoperative hypersensitivity in a maximum of 10% of cases after 1 month.
- A maximum of one tooth shows a loss of vitality within 12 months.
- With the selected application protocol, the F-Composite 2 system enables a filling quality at least comparable to F-Composite (see study "Clinical investigation of Flash Composite in direct restorative therapy" CEC-ZH No. 2011-0150/5.) After 2 years a maximum of 3 fillings should be replaced due to poor quality.

(d) The following risks shall be assessed:
- post-op discomfort. In almost all clinical studies with direct filling materials, postoperative hypersensitivity occurs in the range of a few percent of the treated teeth. Whether the probability of occurrence is increased when using the F-Composite 2 restorative system can only be estimated by a clinical study.
- Inflammation/death of the pulp (the "dental nerve"). In December 2015 a clinical study was completed after an observation period of three years (KEK-ZH No. 2011-0150/5), in which the filling material was polymerized with 10 000 mW/cm^2 for one second, but without exposing the adhesive to this light intensity. No permanent damage to the pulp due to the high light intensity or temperature gradient was observed. In addition, Bluephase PowerCure was used to investigate the temperature gradient in the pulp in in vitro studies on extracted teeth. The absolute temperature was comparable to other lamps (recorded in investigator's brochure). However, the temperature gradient was steeper.
- Cracks in the tooth structure or between tooth and restoration or marginal gaps which could lead to discoloration, secondary caries, filling fracture, filling loss or tooth fracture. In very severely hollowed cavities on extracted molar teeth with undercuts (worst-case scenario) under the cusps, horizontal cracks in the tooth structure could be observed in vitro in bulk fillings with the flowable composite (recorded in validation report examiner brochure). For this reason, special attention is also paid to this point during the clinical investigation.
- Unexpected changes in the filling surface that could lead to roughness, discoloration or increased wear of the material. As the material is similarly polishable as a conventional composite material, it is expected that no more surface discolouration will be observed.

2. General overview of the clinical investigation

The F-Composite 2 system is a coordinated system of filling materials, adhesive and polymerization unit for direct restorative therapy in dentistry.
The aim of this single-arm prospective clinical study is to investigate the F-Composite 2 system in direct filling therapy of class I and II cavities.

The following working hypotheses should be clarified:

- Teeth restored with the F-Composite 2 system have postoperative hypersensitivity in a maximum of 10% of cases after 1 month, which corresponds to a frequency as described in the literature.
- With the selected application protocol, the F-Composite 2 system enables at least comparable restorative quality to F-Composite (see study "Clinical investigation of Flash Composite in direct restorative therapy" CEC-ZH No. 2011-0150/5.) After 2 years a maximum of 3 fillings should be replaced due to poor quality.
- The rate of loss of vitality after 1 year is maximum 1%, which corresponds to a frequency as described in the literature.

The clinical investigation will be conducted with a maximum of 75 patients. No more than two restorations will be placed in any one patient. For inclusion and exclusion criteria, see item "7.3 Participants".

Recalls take place after 6, 12, 24, 60 months.

Aftercare

At the end of the study period or when patients leave the study, they will continue to be routinely cared for by their private dentist.

3. Justification for the structure of the clinical investigation

In summary, it can be concluded from the literature cited in the investigator's brochure that restorative composites are suitable for the intended indications and show a clinically acceptable performance.

Up to now, polymerization of the adhesive or a composite increment takes 5 to 40 seconds, depending on the material used and the polymerization lamp used to cure the material. Currently, the upper limit of available light intensities for direct restorations is approximately 2'000 mW/cm^2. In a recent study from Norway (Kopperud et. al, 2017), in which 740 dentists from the public sector were interviewed, it was shown that these dentists exposed each composite increment for an average of 27 s.
In the experimental fillingsystem F-Composite 2, the components are cured with the new Bluephase PowerCure polymerization light. In the special flash mode, the Bluephase PowerCure emits blue light with an intensity that is 1.7 times higher than that of the Bluephase Style 20i, the most powerful light unit from Ivoclar Vivadent AG to date. The Bluephase PowerCure polymerization light emits 3000 mW/cm^2 and thus allows the materials to be cured in 3 seconds in combination with F-Composite 2, a flowable composite and Adhese Universal.

As the laboratory tests and technical data of the F-Composite 2 system have shown promising results (recorded in investigator's brochure), clinical results are now to be collected. The main focus is on the frequency of occurrence of postoperative hypersensitivities, the investigation of edge quality and surface behaviour.

The fillings are examined and evaluated after certain times (recalls) according to defined criteria. The clinical performance and the clinical success of the restorative material are measured.

4. Investigators

The principal investigator is Dr. Lukas Enggist. Dr. Enggist and the other investigation-site team members will place resp. evaluate the restorations. An investigator-blinding is carried out during the evaluation of the fillings during recall: the examiner does not know who placed the fillings. All follow-up examinations and the baseline findings are performed by an experienced evaluator. (stated in 7.1 (b))

5. Materials

a) F-Composite 2 and the flowable composite are light-curing composite materials for direct restorative therapy in dentistry. Adhese Universal is a universal adhesive which ensures the adhesion of composites to enamel and dentin. It is indicated for direct and indirect restorative therapy. According to the EC Directive on Medical Devices 93/42/EEC, Annex IX, Rule 8, 1st indent, it is a Class IIa medical device. The flowable composite and Adhese Universal have already been on the market for some time and have proven their worth. What is new here is the polymerization in only three seconds. F-Composite 2, on the other hand, is a newly developed material that does not yet bear the CE mark.
Bluephase PowerCure is a polymerization light which emits blue light in higher intensity than the most powerful light unit Bluephase Style 20i from Ivoclar Vivadent AG (2000 mW/cm^2 in turbo mode). The Bluephase PowerCure polymerization light emits 3000 mW/cm^2 . It is also a Class IIa medical product, which is not yet CE certified.

F-Composite 2, the flowable composite, Adhese Universal and Bluephase PowerCure are a coordinated system consisting of composite restoratives and adhesive system as well as an LED polymerization unit that allows composite layers up to 4 mm thick to be cured in only 3 seconds for posterior restorations.

Details of the composites and the adhesive

- Composition
- Indication
- Contraindication
- Side effects
- Interactions

as prepared in the provisional Instructions for Use for clinical investigation of F-Composite 2, a flowable composite and Adhese Universal.

Details of the polymerization lamp

- Product overview
- Security
- Commissioning
- Operation
- Maintenance and cleaning
- Product specification

as prepared in the provisional Instructions for Use for clinical investigations of Bluephase PowerCure

b) The four products (F-Composite 2, a flowable composite, Adhese Universal and Bluephase PowerCure) are manufactured by the dental company Ivoclar Vivadent AG, Bendererstrasse 2, 9494 Schaan, Liechtenstein.

c) The batch numbers of the materials used and of the lighting unit can are recorded in CRF I.

d) Traceability during and after testing is ensured by batch numbers (filling materials) and serial numbers (equipment).

e) Intended purpose in the planned clinical investigation:
The restorative materials F-Composite 2 and the flowable composite are intended for direct restorative therapy in the posterior region (Class I and II cavities). The Bluephase PowerCure polymerization light is designed for high-energy bulk curing of the F-Composite 2 material, the flowable composite and Adhese Universal when used in Class I and II cavities.
f) populations and indications for which the test product is intended:
Any person between 18 and 65 years of age, who is eligible for the indication "Class I or II posterior filling", can be treated. The gender distribution should be 40-60% women and 40-60% men (see also point 7.3).
g) The test products F-Composite 2 and the flowable composite are composites which consist mainly of inorganic fillers and monomers. In addition, they contain additives, initiators, stabilizers and pigments. Details on the composition can be found in the Instructions for Use for F-Composite 2 and the flowable composite. When used as directed, the material comes into contact with tooth structure, i.e. with dentin and enamel. Dentin and enamel are pretreated with the established bonding agent (Adhese Universal). The products F-Composite 2 and the flowable composite do not contain any human or animal substances or derivatives and also no biologically active substances.
h) General dental training is sufficient for the application of the F-Composite 2 system. Within the framework of this training, the placement of fillings with a composite is state of the art nowadays. The handling of the Bluephase PoweCure polymerization light is trained in the course of monitoring on the basis of the provisional Instructions for Use.
i) there are no specific medical or surgical procedures associated with the use of the test device

6. Risks and benefits of the investigational product and the clinical investigation

a) Participation in this clinical investigation could have the following benefits: The F-Composite 2 system allows a shorter treatment time. On the one hand, the risk of unintentional slippage of the light guide on the filling during the reduced exposure time could be reduced, which would contribute to the safe curing of the composite. On the other hand, it could be easier for the practitioner to keep the surgical field dry during the reduced exposure time of the composite. Both factors could increase the process reliability and thus the quality of composite fillings. These benefits must be weighed against the risks mentioned below.
It is also essential that the treatment and all follow-up examinations are free of charge and that the study recalls ensure regular monitoring of the general dental findings.

b) No foreseeable adverse effect(s) of the product are known.

c) Risks associated with the test product itself are listed in the Instructions for Use F-Composite 2, the flowable composite and Adhese Universal under the heading 'Side effects' and under the heading 'Warning'. All risks also exist when conventional products are used in direct restorative therapy. Due to the high light intensity of the polymerization unit, the gradient of temperature changes in the pulp is increased. It is possible that the patient may feel this if no local anaesthesia is applied. The patient decides whether the procedure is performed under anaesthesia or not. According to in vitro experiments, the maximum temperature reached in the pulp is comparable to conventional polymerization devices. If the energy input is too high, the pulp could suffer thermal damage. Therefore, within 30 s, the Bluephase PowerCure can only be exposed twice in a row for 3 seconds each time. This lock can be manually unlocked by the dentist if the clinical situation requires it. Thermal damage to the soft tissue can be ruled out in Class I and II when used as intended, since the distance between the optical fibre and the tissue is sufficient in these situations. The polymerization of cervical fillings is not indicated.

No in vitro examination can serve to conclusively assess the risk of postoperative hypersensitivity. Therefore this study must be carried out.

d) There are no risks in connection with participation in the clinical investigation other than those mentioned under a)-c).

e) Possible interactions with concomitant medical treatments are not expected.

f) If the Instructions for Use for F-Composite 2, the flowable composite, Adhese Universal and for Bluephase PowerCure are followed, there are no further measures to be taken to control or mitigate the risks.

g) risk/benefit justification.
The F-Composite 2 system is a novel material or technology with which no clinical experience is yet available. Despite thorough laboratory tests, undesirable effects cannot be excluded. For example, post-operative discomfort or inflammation or the death of the pulp (the "tooth nerve") could occur, or cracks could appear in the tooth structure or between the tooth and the restoration, or marginal gaps could occur which could lead to discoloration, secondary caries, filling fracture, filling loss or tooth fracture.
Unexpected changes in the filling surface could result in roughness, discoloration or increased wear of the material.
Components of the restorative materials used or the adhesive could cause sensitization and allergies (information is contained in the corresponding instructions for use).
The high light energy of the Bluephase PowerCure could cause overheating or burning of the irradiated tissue, resulting in damage to the pulp, the periodontium or the gums.
Flash Composite 2 has been thoroughly tested for possible toxicological and mutagenic properties. Based on the available knowledge, there is no risk to the patient for reasons of toxicology and mutagenicity.

7. Structure of the clinical investigation

7.1 General information

a) It is a single-arm clinical investigation without a control or comparison group. This design was chosen because clinical studies ("Clinical investigation of Flash Composite in direct restorative therapy" CEC-ZH No. 2011-0150/5; "Clinical investigation of AdheSE One F Upgrade in direct restorative therapy" CEC-ZH_NR. 2012-0076) with direct fillings have already been conducted by the same dentists in the same institution. Accordingly, existing data regarding the quality of fillings can be used for comparison purposes. The chosen study design allows higher case numbers, which seems reasonable in view of the primary endpoint.

b) An investigator-blinding is carried out during the evaluation of the fillings during recall: the examiner does not know who placed the fillings. All follow-up examinations and the baseline findings are performed by an experienced evaluator.

c) Primary endpoint: postoperative hypersensitivity

Secondary end points: devitalization and therefore necessary endodontic treatment, quality of filling and therefore necessary replacement of fillings

d) The following assessment criteria shall apply:

Baseline Findings
The participants are recalled 7-10 days after placing the filling to record the baseline findings. In addition to the clinical examination, the participants are also questioned regarding sensitivity

to temperature and occlusion. The aesthetic integration of the filling is evaluated, the occlusion is checked and corrected if necessary. Photos of the restoration are also taken. For the baseline findings and for all recalls, the restorations are examined and evaluated (SQUACE and FDI criteria) using a special evaluation sheet.
On the findings sheet, the patient has to draw the sensitivity of the tooth in everyday life regarding temperature and bite sensitivity on an unscaled straight line of 10 cm. The distance from the left edge (zero point = no discomfort or pain) is measured to within 1 mm in the evaluation.
In the semi-quantitative evaluation of the fillings (SQUACE=SemiQUantitative Clinical Evaluation), the following findings are documented: secondary caries FDI 12, marginal gap FDI 6.b, marginal deficits FDI 6.c, marginal discoloration FDI 2.b and marginal fracture FDI 6.a (in each case as a percentage of the total margin)
The following FDI criteria are assessed using the FDI rating system

- Postoperative hypersensitivity or tooth vitality FDI 11
- Surface gloss FDI 1
- Surface discoloration FDI 2a
- Colour match and translucency FDI 3
- Fracture of material and filling retention FDI 5
- Proximal contact point FDI 8
- Patient satisfaction FDI 10
- Tooth integrity (tooth cracks and fractures) FDI 13

Based on the FDI System for Clinical Evaluation of Restorations (Hickel et al 2007, 2010), evaluations are assigned for each FDI criterion according to the following scheme
1= clinically ideal
2= clinically good
3= clinically acceptable
4= no longer clinically acceptable (but repairable)
5= clinically unacceptable, restoration must be replaced (repair not possible or not practical)

Horizontal cracks are plotted on the printout of oral or vestibular photographs of the tooth (before and after the filling is placed or during recall) and compared with the preoperative findings.

Follow-up examinations
Recalls take place after 6, 12, 24, 60 months. The restorations are evaluated according to the above criteria.
Photos are taken of all restorations at the examination appointments. If a patient suffers from postoperative complaints, the patient is examined again 14-20 or 30-35 days after the filling has been placed.

e) No special test equipment is used for the assessment of the test variables.

f) instructions for the exchange of participants are not required and no exchange takes place

7.2 Products and reference products

The following materials are used in the clinical study:

conditioning agents:

Total Etch - Gel for enamel etching and dentine conditioning for direct filling therapy with composites

Adhesive system: Adhese Universal - Bonding agent between dentin or enamel and composite

Composite restoratives:
- Test product: The flowable composite - light-curing flowable bulk composite filling material as first increment (maximum 4 mm).
- Test product: F-Composite 2- light-curing modellable composite filling material as obligatory covering layer of at least 1 mm

Polymerization lamp:
- Bluephase PowerCure with flash mode for polymerization of the adhesive and the composites in 3 s each.

The conditioning agent, the adhesive and the flowable composite have already been introduced to the market and have proven to be clinically effective.

7.3 Participants (In-/Exclusion criteria)

a) inclusion criteria for the selection of participants

- Age: 18-65 years
- 40-60% women, 40-60% men
- Indication for a direct filling of class I or II in permanent premolars or permanent molars
    - Replacement of insufficient fillings (e.g. due to marginal caries, fracture of the filling, poor surface quality, poor aesthetics, unwanted filling material, leaky margin, marginal gap, etc.)
    - extensive primary caries
- Vital tooth (cold test)
- Single-, double- or triple-surface fillings in the posterior region, where a maximum of 25% should be single-surface fillings (class I) with antagonists.
- The occlusally assessed area of the filling must be at least 1/3 of the total area of the tooth. This criterion is estimated.
- Participant wishes to receive care within the scope of the study (written declaration of consent after detailed explanation and study of the patient information).
- Maximum 2 restorations per patient.
- Preoperative complaints on the tooth to be restored (maximum 3 on visual analogue scale (0= no complaints, 10= maximum possible pain) due to temperature stimulus or sensitivity to bite
- Sufficient German language skills

b) exclusion criteria for the selection of the participant.

- Not completed hygiene phase or poor oral hygiene
- Sufficient drainage of the surgical field not possible
- Patients with a proven allergy to one of the ingredients of the materials used
- Patient is allergic to ingredients of the local anaesthetic Ultracain DS (active ingredient: articaine; vasoconstrictor), if anaesthesia is desired
- Patients with severe systemic diseases
- Devital or pulpit teeth
- Periodontally insufficient dentition
- Restorations with cusp abutments
- open lateral bite
- missing antagonist
- Indication for direct capping
- Pregnancy (women of child-bearing age receive a free pregnancy test for self-testing in advance, the negative result of which they document with their declaration of consent)

c) Patients discontinue the study on their own initiative or withdraw for reasons that make further assessment of the filling impossible. These include, for example, extraction of the tooth due to a cause independent of the study, the change in the opposing dentition or treatment by an external dentist.
These patients are considered to be drop-out and are reported separately with the drop-out cause (CRF V). The recall data obtained up to the time of drop-out are used in the analysis.

d) the date of recording.
After a positive ethics vote and registration at "clinicaltrials.gov", the study will start, i.e. this marks the earliest point of admission.

e) Expected total duration of the clinical investigation.
The expected total duration of the clinical investigation is 5 years and 4 months.

f) The expected duration of participation of each participant in the treatment scheme in Table 1 is 5 years (60 months).

g) The required number of participants to be included in the clinical investigation shall not exceed 75.

h) The estimated time needed to obtain this number of participants (i.e. recording time) is estimated at 4 months.

7.4 Treatments

a) Description of all treatments administered to the investigation participants during the clinical investigation Three operators place 25 fillings each.

Preparatory measures and cavity preparation

- A medical and dental anamnesis and detailed findings are taken for each patient and, if necessary, x-rays are taken. A visual analogue scale is used to record the preoperative complaints of the tooth to be restored with regard to temperature stimulus and bite sensitivity. However, no cold or bite sensation is set for this purpose. The vitality is checked with a cold spray. In addition, a therapy plan is drawn up in accordance with the restoration concept.
- A digital photo of the initial state is taken. The vestibular and oral views are printed out. The occurrence and extent of horizontal tears are drawn on it.
- If possible, rubber dams are used for drainage. If a rubber dam is not possible, an appropriate relative draining method is used (OptraGate, cotton rolls, saliva ejector).
- Then the insufficient filling or caries is removed.
- The preparations are done with 80 µm diamonds, a finish of the cavity edges with 25 µm diamonds. The cavity edges in the enamel are chamfered, but not gingivocervically.

Measurement of the cavity and renewed documentation of melt cracks

- A digital photo of the prepared cavity is taken
- The lowest point of the respective proximal boxes and occlusal pull-through is measured with a PA probe (Hu-Friedy PCPUNC 15) and documented on the CRF I. The reference for the proximal box is the proximal-occlusal cavity margin in the marginal ridge area and, for determining the occlusal pull-through depth, the occlusal cavity margin adjacent to the lowest point. The determination should be made with an accuracy of ±1 mm.
- The average width of the cavity is given in absolute terms (accuracy ±1mm). The already mentioned periodontal probe is also used as an aid here.

- Prior to conditioning, the tooth is again examined for horizontal enamel cracks, which are recorded in the printed photographs in terms of their extent and localization and recorded on the CRF I. A cold-light fibre optic (light probe by Lercher) is used as an aid.
- The residual dentin thickness above the pulp is determined with a prepometer at the site with the lowest layer thickness (Wegehaupt et al. (2009)).

The partial matrix system from Garrison (Compositight) or Triodent (V3) is used as the matrix.

Application of the etching gel and adhesive system

- According to GI in Etch&Rinse mode, exposure time of Total Etch in enamel 30 s, dentin 10-15 s. The adhesive must be rubbed in for 20 s.
- The adhesive is cured with the Bluephase PowerCure in flash mode for 3 s.

Application of the composite in the bulk fill technique

- Application of the flowable composite in a horizontal layer of maximum 4 mm, taking into account the minimum layer thickness of the top layer.
- Application of F-Composite 2 in layers of max. 4 mm. To simplify the design of the anatomy, several oblique increments are permitted as cover layer. The minimum layer thickness of the top layer is 1 mm.
- Light polymerization per layer for 3 s with Bluephase PowerCure (flash mode, 3000 mW/cm^2)
- Finishing of the filling with composite shape diamonds and final polishing with the one-step polishing system OptraPol (Ivoclar Vivadent)

b) Apart from monitoring, there are no other activities carried out by representatives of the sponsor (IvoclarVivadent AG).
c) A distortion of the results could arise from the following factors:

- Mainly older patients (> 45 years) are included in the study. Older patients are less prone to post-operative hypersensitivity than younger patients due to pulp retraction caused by secondary dentin.
- The replacement of insufficient fillings or the treatment of primary carious lesions results in shallow cavities with a residual dentine thickness of 1.5-3 mm. A greater residual dentin thickness may reduce the risk of pulp irritation caused by the high light intensity of the polymerization light and thus the number of postoperative hypersensitivities. Small to medium-sized cavities also reduce the risk of horizontal enamel cracks.
- Due to the explanatory talk of the participants or the knowledge of the operators, both participants and operators could be sensitized regarding the important clinical parameter "post-operative hypersensitivity" and thus falsify the result.

If material-dependent problems occur that require replacement of the F-Composite 2 fillings, a replacement filling made of established standard materials is placed free of charge. No further medical care is planned after the test.

7.5 Specifications for monitoring

This clinical investigation will be monitored by the sponsor at defined timely intervals. The Monitoring Plan lists the activities within the scope of monitoring.

8. Statistical considerations

a) Due to the study design, no special statistical methods are necessary.
b) The sample size is 75 fillings

c) validity of the clinical investigation: the system is suitable for the market if the acceptance criteria are met.

d) Expected drop-out rate: Analysis of older comparable studies show that an annual drop-out rate of 2% can be expected. Accordingly, three fillings could no longer be checked after 2 years.

e) Acceptance criterion for post-operative hypersensitivity after 4 weeks: ≤ 10% (=6 fillings).
Acceptance criterion for loss of vitality after 1 year: maximum 1 restored tooth
Acceptance criterion for filling replacement after 2 years: maximum 3 fillings

g) If more than 50% of the patients suffer from postoperative hypersensitivity after placing at least 20 fillings, the study would be terminated.

k) If patients discontinue the study or drop out for other reasons (including extraction of the tooth from a cause not related to the study, change of the opposing dentition or treatment by an external dentist), they are considered a drop-out and are reported separately with the drop-out cause (CRF V).
The recall data obtained up to the time of withdrawal from the study are used in the evaluation.

9. Data management

a) Data verification is carried out with plausibility checks. The data is encrypted, since the patient names do not appear in the data tables, but the cases can be assigned using case numbers and patient IDs.

c) The archiving of the data takes place on the company's secure servers. The data is stored as SPSS data sheets in anonymized form. The traceability is given by case numbers.

d) The retention period of the data after completion of the study is 10 years.

Since all persons involved in the study, especially the operators and the evaluator, are familiar with and apply the company's internal guidelines regarding "Good Documentation Practice" (SOP-00081-EN; Good Documentation Practice), the traceability of changes is ensured by the dating and sizing of corrections.

CRFs, radiographs and clinical images will be collected as source data in this study.

Authorities and the Monitor will be granted access to the original data at any time, should this be necessary.

If a participant withdraws his or her consent, the health-related personal data will be made anonymous after the data evaluation is completed. Despite revocation, the participant will be offered follow-up treatments to the extent required to protect his or her health.

10. Changes to the clinical investigation protocol

Substantial changes to the approved clinical investigation must be approved by the Ethics Committee prior to their implementation. Excepted from this obligation are measures that must be taken immediately to protect the participating persons.
The following are considered to be significant changes:

- Changes that affect the health and safety of the participating persons or their rights and obligations
- changes in the study plan, in particular changes due to new scientific evidence concerning the test design, test method, objective criteria or statistical design;
- the change of the place of execution or the execution of the clinical investigation at an additional place of execution;
  the change of sponsor, coordinating investigator or investigator-in-charge at a site.

All other changes are submitted to the Ethics Committee once a year together with the safety report.

Substantial changes to the approved clinical investigation must be approved by the Liechtenstein Office of Public Health before they are implemented. This obligation does not apply to measures that must be taken immediately to protect the participating persons.
In this context, significant changes are considered to be substantial:

- Changes to the medicinal product or its administration or use;
- Changes due to new preclinical and clinical data that may affect product safety;
- Changes concerning the manufacture of the medicinal product which may affect product safety.

Other changes concerning documents submitted to the Office of Public Health must be notified to the Office of Public Health as soon as possible.

11. Deviations from the clinical investigation protocol

The investigator is not permitted to deviate from the CIP, except under emergency conditions to protect the rights, safety and health of the participant. If safety and protective measures must be taken immediately during the conduct of the clinical investigation, the investigator must notify the Ethics Committee within two days of these measures and of the circumstances which made them necessary.
In such a case, the sponsor must also submit a report to the Office of Public Health.

12. Proof of use of the product

The proof of use of the test product shall be documented as described in 6.9 of EN ISO 14155:2011.

13. Declaration of conformity

All groups involved in the investigation, as well as their individual members, undertake at all times during the investigation to

- the Declaration of the World Medical Association of Helsinki,
- local legislation
- the EN ISO 14155:2011
- the clinical investigation plan to be observed.

The investigation may not begin before the approving opinions of the competent ethics committee and the supervisory authority have been received.

Possible additional requirements of the ethics committee or the supervisory authority must be observed.

All patients participating in the clinical examination are insured against damages caused by the examination material.

14. Procedure for obtaining consent

The patients are informed orally and in writing about the course of the experiment, the materials to be tested and any risks and sign a corresponding declaration of consent. Before the patient concerned decides on the consent, he/she is given a period of reflection of at the latest 3 working days. Every patient has the right to refuse further participation in the study at any time.
According to the patient information, the participant will be informed immediately if at any time during the conduct of the study aspects should arise that could influence the willingness of patients to participate in the study.

15. Adverse events, adverse effects of the product and product defects

All incidents that are detrimental to the patient, whether or not they are caused by the object of investigation, are undesirable incidents. If these adverse events are due to the object of investigation, they are adverse effects. Each of these adverse reactions must be documented on the follow-up examination form (CRF IV). The clinical investigator must decide whether or not the adverse reactions could have been caused by the materials under investigation and thus whether or not an adverse effect exists.

A serious adverse event (SAE = Serious Adverse Event), which cannot be ruled out as being attributable to the investigational product or to an intervention carried out in a clinical investigation, is reported to the Cantonal Ethics Committee in Zurich within 7 days. In addition, a report must be made to the Liechtenstein Office of Public Health within 7 days ("Reporting form for clinical investigations with medical devices - Serious Adverse Event").
A serious adverse event in this study is an event that
(a) resulted in death
(b) resulted in a serious adverse health effect to the participant, which was either
1) results in a life-threatening disease or injury, or
2) results in a permanent impairment of a body structure or function, or
3) results in hospitalisation or the extension of an existing hospital stay, or
4) involves a medical or surgical procedure to prevent a life-threatening disease or injury or permanent impairment of a body structure or function
Once a year, a safety report (ASR) is submitted to the Ethics Committee and the Office of Public Health, which contains a list of events (SEA) and establishes their causality for intervention and assesses the safety of the participating patients

If undesirable events occur that require treatment outside the practice, follow-up treatment is ensured by means of a detailed referral to the relevant specialist, family doctor or, if applicable, family dentist.

16. Population that can be pressured

During the planned clinical investigation, the investigational product will not be applied to populations that can be put under pressure.

17. Premature termination or suspension of the examination

The study can be terminated by the dentist, the sponsor or the manufacturer of the drugprouct. The following reasons can lead to this:

- technical problems during the manufacturing process
- Adverse events related to the testproduct that threaten the safety and health of the investigation participants (unacceptable risks)
- lack of compliance (willingness to cooperate) of a patient

Any interruption of the study must be reported to the Ethics Committee and the Office of Public Health within 15 days. An interruption or the regular end of the study must be reported to both institutions within 90 days. The final report must be submitted to the Ethics Committee and the Office of Public Health within one year of the end of the study.

No study follow-up beyond the duration of the study is foreseen.

18. Publication policy

It is desirable that the principal investigator publishes the findings for scientific purposes. A manuscript should be provided to the sponsor for review at least 30 days prior to the planned publication. Suggestions for changes should only be considered if they do not compromise the scientific character or neutrality of the publication. Exceptionally, the client may request a postponement of the publication up to a maximum of 90 days after submission of the manuscript if and to the extent that this is absolutely necessary to protect the client's intellectual property. If the client has not raised any objections within 30 days of receipt of the manuscript, the consent to publication is deemed to have been given. As this is an in-house study, conflicts of interest between the principal investigator and the sponsor are not to be expected.

19. References

Demarco FF, Correa MB, Cenci MS, Moraes RR, Opdam NJ (2012) Longevity of posterior composite restorations: not only a matter of materials Dent Mater 28 87-101.

Heintze SD, Rousson V (2012) Clinical effectiveness of direct Class II restorations - A meta-analysis J Adhes Dent 14 407-431.

Hickel, R., A. Peschke, et al. (2010). "FDI World Dental Federation: clinical criteria for the evaluation of direct and indirect restorations-update and clinical examples." Clin Oral Investig **14**(4): 349-66.

Hickel, R., J. F. Roulet, et al. (2007). "Recommendations for conducting controlled clinical studies of dental restorative materials. Science Committee Project 2/98--FDI World Dental Federation study design (Part I) and criteria for evaluation (Part II) of direct and indirect restorations including onlays and partial crowns." J Adhes Dent **9 Suppl 1**: 121-47.

Kopperud S.E., et al., (2017) Light curing procedures – performance, knowledge level and safety awareness among dentists, Journal of Dentistry58: 67-73

Manhart J, Chen H, Hamm G, Hickel R (2004) Buonocore Memorial Lecture. Review of the clinical survival of direct and indirect restorations in posterior teeth of the per manent dentition Oper Dent 29 481-508.

Opdam NJ, van de Sande FH, Bronkhorst E, Cenci MS, Bottenberg P, Pallesen U, Gaengler P, Lindberg A, Huysmans MC, van Dijken JW (2014) Longevity of Posterior Composite Restorations: A Systematic Review and Meta-analysis J Dent Res 93 943-949.

Wegehaupt F, Betke H, Solloch N, Musch U, Wiegand A, Attin T (2009) Influence of cavity lining and remaining dentin thickness on the occurrence of postoperative hypersensitivity of composite restorations J Adhes Dent 11 137-141.