Clinical Study Protocol

Clinical evaluation of a new flowable composite for direct restorative treatment of non-carious cervical lesions: A prospective randomized split-mouth study

Type of investigation:	Clinical investigation concerning medical devices (MD).
Categorisation:	Category according to Art 6 ClinO-MD: C2
Registration:	Registry at ClinicalTrials.gov of the U.S. National Library of Medicine (http://www.clinicaltrials.gov) The trial gets registered in the supplementary federal database (Portal for clinical trials in Switzerland - SNCTP, https://www.kofam.ch/en/snctp-portal/) upon its submission on BASEC. Furthermore, as soon as the new electronic system EUDAMED is operational, the clinical investigation will be retrospectively registered, if required (unique single identification number: CIV-LI-23-12-045054)
Identifier:	OTCS 36419419 (Document ID: OTCS 36427036)
Principal Investigator and Sponsor, or Sponsor-Investigator:	Principal Investigator (PI): Dr. med. dent. Carola Pentelescu Internal Clinic of Ivoclar Vivadent AG Bendererstrasse 2 9494 Schaan Liechtenstein Tel. [redacted] Mail: [redacted] Sponsor: Ivoclar Vivadent AG Patrizia Elkuch-Hoch Team Leader Study Management Bendererstrasse 2 9494 Schaan Liechtenstein Tel.: [redacted] Mail: [redacted]
Sponsor representative (if the Sponsor is not located in Switzerland)	n.a.
Medical Device:	TM Flow (Ivoclar Vivadent AG)
CIP Version and Date:	Version 3.0, 17.01.2024

Signature Page(s)

ID number of the investigation:	OTCS 36419419 Registry at ClinicalTrials.gov of the U.S. National Library of Medicine (http://www.clinicaltrials.gov) The trial additionally registers in the supplementary federal database (Portal for clinical trials in Switzerland - SNCTP, https://www.kofam.ch/en/snctp-portal/) with its submission on BASEC. Furthermore, as soon as the new electronic system EUDAMED is operational, the clinical investigation will be retrospectively registered, if required (unique single identification number: CIV-LI-23-12-045054).
Title:	Clinical evaluation of a new flowable composite for direct restorative treatment of non-carious cervical lesions: A prospective randomized split-mouth study

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 3.0 (dated 17.01.2024) and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor: Patrizia Elkuch-Hoch

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SYNOPSIS

Sponsor / Sponsor-Investigator	Ivoclar Vivadent AG
Title:	Clinical evaluation of a new flowable composite for direct restorative treatment of non-carious cervical lesions: A prospective randomized split-mouth study
Short title / Investigation ID:	Split-mouth study of a new flowable composite in carious cervical lesions OTCS 36419419
Clinical Investigation Plan, version and date:	Version 3.0, 17.1.2024
Registration:	Registry at ClinicalTrials.gov of the U.S. National Library of Medicine (http://www.clinicaltrials.gov) The trial gets registered in the supplementary federal database (Portal for clinical trials in Switzerland - SNCTP, https://www.kofam.ch/en/snctp-portal/) upon its submission on BASEC. As soon as the new electronic system EUDAMED is operational, the clinical investigation will be retrospectively registered, if required (unique single identification number: CIV-LI-23-12-045054).
Category and its rationale:	Category C2 (Art. 6 ClinO-MD) The medical device has no conformity marking.
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	TM Flow UDI not available Ivoclar Vivadent AG Benderer Strasse 2 9494 Schaan SRN-number: LI-MF-000000522
Stage of development:	Pivotal stage The clinical investigation is conducted for a conformity assessment purpose.
Background and rationale:	Non-carious cervical lesions (NCCLs) are dish-shaped or wedge-shaped lesions, with well-defined margins and hard dentin on the surface. They are located in the cervical third of the tooth close to the cemento-enamel junction involving in the majority of cases the buccal face of teeth. They are widespread among middle age and older people. The cementoenamel junction proves to be more prone to loss of substance because the thickness of the enamel is greatly reduced. Also, the cervical area is considered the fulcrum of the tooth, where the stress accumulation during pressing, clenching or grinding parafunctions is the highest. These two factors lead to the loss of enamel and dentin in this area.

Objective(s):	The overall objective of this clinical investigation is to evaluate the clinical safety and performance of the new flowable composite TM Flow. The primary objective is to assess the rate of postoperative hypersensitivity after treatment of non-carious cervical lesions with TM Flow and compare it to the treatment with the well-established flowable composite Tetric EvoFlow. The secondary objective of this study is to assess the long-term clinical efficacy of the materials under investigation in terms of marginal quality retention/fracture rate of the restorations and vitality. The color match, surface lustre and texture, contour and form, are also assessed. These outcomes provide information about the clinical performance of the material including the aesthetic performance.
Outcome(s):	The primary outcome of this clinical investigation is the rate of postoperative hypersensitivity after restoration of non-carious cervical lesions with TM Flow and respectively Tetric EvoFlow. The secondary outcomes focus on the clinical performance of the composites by evaluation of functional (e.g. fracture of the material and retention), biological (e.g. caries at restoration margins) and aesthetic (e.g. color match) properties of the restorations. The primary and the secondary outcomes are assessed using the FDI criteria (Hickel et al., 2022).
Design:	Randomized, controlled, prospective, double-blinded (patient and evaluator) split-mouth study design (test material: TM Flow, control material: Tetric EvoFlow in the same patient)
Inclusion / exclusion criteria:	Inclusion criteria: • Informed Consent signed by the subject • Age: 18-65 years • 2 NCCL needing treatment, comparable in extend and size, preferably located in different quadrants • Vital teeth, regular sensitivity • Sufficient language skills • No active periodontitis • Preoperative VAS values < 3 regarding tooth sensitivity on biting. Tooth sensitivity on temperature or touching (tooth brushing, probing) originating in the area of the NCCL is accepted. • Subject wishes to have a restoration as part of the study (written declaration of consent after detailed explanation) Exclusion criteria: • Not completed hygiene phase or poor oral hygiene • Sufficient isolation of the cavity not possible • Patients with a proven allergy to one of the ingredients (methacrylates) • Patients with severe systemic diseases • Periodontally insufficient dentition • Pregnancy • Part of the development project team of TM Flow • Staff of the study management team • Staff of the internal clinic
Measurements and procedures:	Each participant receives two different fillings (test- and control material) in two different teeth. The fillings are assessed according to selected FDI criteria at baseline (7-10 days after filling placement) and after 1, 6, 12, 24, 36 and 60 months. At each of these times points, the sensitivity is recorded using a visual analogue scale. The results are documented by intraoral images.
Intervention:	The newly developed flowable composite TM Flow will be used for the restoration of NCCLs in the test group. The treatment workflow is very similar to other flowable composites.

Control intervention (if applicable):	The well-established Tetric EvoFlow will be used for the restorations of NCCLs in the control group. This material has been routinely used for such treatments in the internal clinic of Ivoclar Vivadent AG for many years.
Number of subjects with rationale:	66 patients are receiving 2 restorations because of the split-mouth study design.
Duration of the investigation:	60 months for each patient (recruiting phase 4 months)
Investigation schedule:	January 2024 First-subject-In December 2029 Last-subject-Out
Investigator(s):	- Dr. Enggist Lukas, Benderer strasse 2, 9494 Schaan [redacted] - Dr. Carola-Sonia Pentelescu, Benderer strasse 2, 9494 Schaan [redacted] - Dr. Peschke Arnd, Benderer strasse 2, 9494 Schaan [redacted] - Dr. Hu Ming, Benderer strasse 2, 9494 Schaan [redacted] - Dr. Glebova Tatiana, Benderer strasse 2, 9494 Schaan [redacted] - Dr. Lydia Eberhard, Benderer strasse 2, 9494 Schaan [redacted] - Dr. Ronny Watzke, Benderer strasse 2, 9494 Schaan [redacted]
Investigational Site(s):	This is a single center study. R&D Clinic Ivoclar Vivadent AG Benderer strasse 2 9494 Schaan Liechtenstein
Statistical considerations:	The sample size was calculated for a split-mouth design with a one-sided non-inferiority hypothesis (target alpha 5%; power 80%). The obtained data of the test group will be compared with the data from the control group.
Compliance statement:	This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
ASR	Annual Safety Report
CA	Competent Authority (e.g. Amt für Gesundheit, Liechtenstein)
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV, in French Oclin, in Italian OSRUm)*
ClinO-MD	Ordinance on Clinical Trials with Medical Devices *(in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed)*
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
DD	Device Deficiency
DMC / DSMC	Data Monitoring Committee, Data Safety Monitoring Committee
FDI	Fédération Dentaire Internationale
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
IFU	Instruction For Use
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MedDO	Medical Devices Ordinance *(in German: MepV, in French: Odim, in Italian: Odmed)*
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
NCCL	Non-carious cervical lesions
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

INVESTIGATION SCHEDULE

Study Periods	Screening	Treatment, Intervention Period	Follow-up						
Visit	0	1	2	3	4	5	6	7	8
Time (hour, day, week)	-3- (-30) d	0 d	7-10 d	1 m	6 m	12 m	24 m	36 m	60 m
Patient Information and Informed Consent	x								
Medical History	x								
In- /Exclusion Criteria	x								
Tooth Examination	x								
Pregnancy Test (only in case of uncertainty)	x								
Vitality test	x	x	x	x	x	x	x	x	x
VAS for tooth sensitivity		x	x	x	x*	x*	x*	x*	x*
Preparation of tooth,		x							
Randomization		x							
Placement of restoration (test or control)		x							
Primary Variables			x	x	x	x	x	x	x
Secondary Variables			x	x**	x	x	x	x	x
Photographs	x	x	x	x	x	x	x	x	x
Adverse events and device deficiencies		x	x	x	x	x	x	x	x

* Assessment will only be done if there is a patient complaint for paraesthesia or pain

** Not all variables will be assessed (only fracture of material, surface luster, color match)

1. BACKGROUND AND RATIONALE

1.1 Background and Rationale for the clinical investigation

Non-carious cervical lesions (NCCLs) consist of irreversible loss of mineralized tissue unrelated to carious pathology (Walter et al., 2014). NCCLs are located in the cervical third of the tooth close to the cemento-enamel junction involving in the majority of cases the buccal face of teeth. The cementoenamel junction proves to be more prone to loss of substance because the thickness of the enamel is greatly reduced and, consequently, the enamel–dentin bond is much weaker (Walter et al., 2014). Also, the cervical area is considered the fulcrum of the tooth, where the stress accumulation during pressing, clenching or grinding parafunctions is the highest. These two factors lead to the loss of enamel and dentin in this area. Indeed, it has been seen that NCCLs are lesions present at all ages; however, epidemiological studies have pointed out a significant increase in their incidence at older ages (Borcic et al., 2004; Yang et al., 2016). Kolak et al. found that in a group of patients older than 55 years, 94.7 percent of them had NCCLs, and one-third of them had more than three lesions (Kolak et al., 2018; Patano et al., 2023). Among the causes that lead to NCCL are abfraction, erosion, attrition and abrasion or combinations of those factors. NCCL are dish-shaped or wedge-shaped lesions, with well-defined margins and hard dentin on the surface. During the formation of the NCCL the dental pulp reacts and produces tertiary sclerotic dentin that obliterates the dentinal tubes and is found in the deeper areas of the NCCL. NCCL often associate with dentinal hypersensitivity due to the exposed dentin surfaces and the open dentinal tubuli. While small NCCL are treated by desensitising therapeutic procedures and the treatment of the aetiological factor the therapeutic approach changes when confronted with large NCCL. The presence of dentinal hypersensitivity, the increased plaque accumulation, the decreased mechanical tooth resistance and the aesthetic impairment (when the lesions are located in the frontal teeth) impose the necessity of a direct restorative therapeutic procedure.

The materials that can be used for direct restorations of NCCL are either glass ionomer cement (GIC), resin modified GIC (RMGIC), compomers, giomers or dental composites. While RMGIC show a higher retention rate then flowable dental composites they show a poorer aesthetic and an increased water sorbtion (Patano et al., 2023). Either flowable or packable dental composites can be used for the restoration of NCCL. When restored with a stiff hybrid composite resin, the clinical success rate was only 70% (McCoy et al., 1998). The high failure rate was attributed to the stiffness of the composite used. Thus, using a flowable composite resin with a lower flexural strength than traditional hybrid composites was assumed to improve the clinical success of these restorations. A one year clinical study evaluating Class V restorations using a flowable composite demonstrated that all restorations were intact and showed no signs of postoperative sensitivity after one year (Estafan et al., 1999). Many studies have concluded that the use of flowable composites for non-carious cervical lesions is a good choice (Kubo et al., 2010). There is only one research to compare the clinical efficacy of a flowable bulk-fill composite to a standard nano-filled composite in the management of NCCLs. Its findings showed that both composites had acceptable clinical performances, despite minor changes in surface roughness, anatomic shape, and marginal adaptation after 1 year (Canali et al., 2019). So far, no clinical trial was found that compares the clinical performance of a bulk flowable composite and a regular flowable composite in the restoration of NCCL.

Due to the shape of the cavities without any macro retentive element the retention is mainly dependent on the adhesion of the restoration to the tooth substance. This is above all dependent on the performance of the adhesive system used. The polymerization shrinkage and shrinkage stress also influence the adhesion of the restorations to the tooth structure as well as the C-factor (ratio bonded surfaces to unbonded surfaces of a restoration). Since the C factor is low in such a cavity it is reasonable to consider this type of direct restorative approach a suitable one.

TM Flow is a bulk-flow dental composite that can be applied, and light cured in 4 mm thick layers with the exception of the shade A3,5 plus which can be polymerized in 3,5 mm layers. It can be cured in 10 seconds at a light intensity of 1200 mW/cm^2, 5 seconds at a light intensity of 2000 mW/cm^2 or 3 seconds at a light intensity of 3000 mW/cm^2. Not all polymerization modes are allowed to be used for each indication. The higher the light intensity may leads to a faster increase of the pulp temperature. The pulp temperature increase during polymerization might provoke a reaction of the dental pulp that is manifested clinically as postoperative hypersensitivity (pain) as a consequence of an inflammation. If the temperature increase is too high, the pulp tissue might undergo a sterile necrosis. Additionally, the exothermal polymerization reaction of dental composites is delivering also heat to the tooth contributing to the increase of the pulpal temperature. In general, flowable composites show a higher exothermal polymerization reaction then packable composites due to the higher monomer content. However, pre-clinical investigations showed that the pulpal temperature increase after placing TM Flow fillings cured with 3000 mW/cm^2 and 2000 mW/cm^2 was not higher than that of the fillings cured with 1200 mW/cm^2

(OTCS 7218593). Therefore, it can be concluded that the use of higher light intensities for the polymerisation seem to be uncritical.

Postoperative hypersensitivity can be caused by the incomplete seal of the dentinal tubuli, either due to the wrong application technique or the poor quality of the adhesive, or due to the high shrinkage of the dental composites, that pull of the material and the adhesive from the surface of the prepared cavity opening the dentinal tubuli. Another mechanism that might induce postoperative hypersensitivity during this CT is the high energy input delivered to the tooth during light curing of the materials in the Turbo mode plus the exothermic polymerization reaction of the materials. The sudden increase in the temperature represents a strong stimulus for the dental pulp that reacts by reversible or irreversible inflammation, clinically translated in postoperative hypersensitivity (pain).

TM Flow is not bearing a CE mark and is not yet available on the market. No clinical studies have been conducted so far. The primary aim of this randomized controlled split-mouth clinical trial is to assess the incidence rate of postoperative hypersensitivity, when NCCL are directly restored with TM Flow respectively Tetric EvoFlow both light cured in the 5 seconds curing mode (Turbo Mode, 2000mW/cm^2), since this is the mode with the highest energy output that is allowed for the use in NCCL. The use of TM Flow applied in a single layer of up to 4mm (3,5 mm in the case of the shade A3.5 plus) is considered the worst-case scenario, due to the higher exotherm polymerization reaction of the flowable composite regarding the incidence of postoperative hypersensitivity. Furthermore, the shrinkage stress is the highest during this approach, so it represents the worst case scenario in terms of marginal quality and retention rate. In this clinical investigation the clinical performance and safety of TM Flow will be compared with Tetric EvoFlow (a nano-hybrid flowable dental composite) in terms of pulp response of the teeth to the materials in combination with the 5 sec light curing mode (2000mW/cm^2), marginal quality, retention rate, fracture of material, surface lustre and texture and other aesthetic properties.

1.2 Identification and description of the Investigational Medical Device

This information is provided within the Investigator's Brochure (IB) and the Instructions for Use (IFU).

2. CLINICAL INVESTIGATION OBJECTIVES

2.1 Overall Objective

The aim of this clinical trial is to assess the clinical performance and safety of the new medical device TM Flow in direct restorative treatment (class V restorations).

2.2 Primary Objective

The primary objective is to assess the rate of postoperative hypersensitivity after treatment of NCCLs with the new composite TM Flow and compare it to the treatment with the well-established composite Tetric EvoFlow.

2.3 Secondary Objectives

The secondary objective of this study is to assess the long-term clinical efficacy of the materials under investigation in terms of marginal quality and retention/fracture rate of the restorations and vitality. The color match, surface lustre and texture, contour and form, dental hard tissue defects at the restoration margins are also assessed. These outcomes provide information about the clinical performance of the material including the aesthetic performance.

2.4 Safety Objectives

This study aims to assess the long-term safety of TM Flow in terms of tooth vitality and failure rate of placed restorations. Tooth vitality is an indicator for the health status of the dental pulp. A vitality test is performed to acquire information about the vitality of teeth. A healthy dental pulp offers a positive response to the vitality test. Once the dental pulp is severely injured an irreversible inflammatory reaction starts with the endpoint of a necrosis of the dental pulp. Pulpal necrosis is followed by a negative response to the vitality test.

3. CLINICAL INVESTIGATION OUTCOMES

3.1 Primary Outcome

The primary outcome in this clinical trial is the FDI criteria - B3 pulpal hypersensitivity and pulpal status (Hickel et al. 2022) 1 month after placing of the fillings. Postoperative hypersensitivity is considered an indicator of the response of a tooth (pulp) to the therapeutic procedure applied. Postoperative hypersensitivity can be observed within a short time after the treatment. Therefore, it is assessed for the first time at the baseline recall (after 7-10 days). The assessment of postoperative hypersensitivity includes questions about type and duration of pain, intensity of pain and on the stimulus inducing the pain. The subjective perception of the intensity of postoperative hypersensitivity caused by thermal stimuli and caused by occlusal forces (during biting) will be determined by the aid of a Visual Analog Scale (VAS). The VAS values are brought into relationship to the preoperative values. In the table below a description of the correlation between FDI grade and VAS values and clinical signs and symptoms is shown. Not all signs need to be present at one stage. The exact VAS values vary widely from patient to patient, depending on each individual's pain tolerance. Therefore, it is one of the factors influencing the FDI grade, but it is not directly correlated. Not all the described conditions have to be fulfilled to attribute an FDI score. Depending on the intensity and character of the pain, further therapy will be determined. Usually, postoperative hypersensitivity subsides spontaneously and no treatment is necessary. In case of very intense pain an immediate treatment is required. The application of a fluoride varnish is the first procedure of choice. If no improvement is achieved by this method, then the replacement of the restoration would be the next step. In the worst case, the pulp is severely inflamed, requiring endodontic treatment. If the postoperative hypersensitivity does not subside spontaneously or worsens after the applied treatment, the highest assessed FDI value is used for the statistical analysis.

For all participants a 1-month recall is planned to finally assess the postoperative hypersensitivity. The clinical experience of the evaluator is of major importance in the correct assessment of the FDI grade. In general, the rule applies, that in case of uncertainties the higher score is attributed.

FDI grade	1	2	3	4	5
Intervention	none	no treatment necessary	fluoride varnish if desired	replacement of restoration or endodontic treatment with access cavity only	endodontic treatment and replacement of restoration
Patient's view / description of pain / discomfort	no complaint	minor pain	distinct pain	persistent pain for prolonged period of time, patient asks for treatment	treatment unavoidable
VAS score	0-3	<5		>5	
Pulp status	none	reversible pulpitis		reversible or irreversible pulpitis	irreversible pulpitis or pulp necrosis, with or without periapical periodontitis
Duration of symptoms	no symptoms	<1 week	>1 week	>1 month	n.a.
Vitality test	normal, short reaction		normal or more intense	intense	negative, nonvital tooth (no response)

The assessment of the pulp status is done at all recalls following the 1-month recall because the pulp is exposed to lifelong stimuli and can react any time. The methods of assessment are as described above.

VAS is only done if the patient feels any hypersensitivity.

3.2 Secondary Outcomes

A1 –Surface lustre and texture
A2 – Marginal staining
A3 – Color match
F4- Form and contour
F1- Fracture of material and retention
F2- Marginal adaptation
B1- Caries at restoration margins
B2 – Dental hard tissue defects at the restoration margins
M1 Patients view

The FDI criteria and parameter will be used to evaluate the long-term performance of TM Flow restorations. These criteria were approved by the Science Committee of the FDI World Dental Federation (FDI) in 2007 and the General Assembly in 2008 as standard criteria that were specially designed for use in clinical studies (Hickel et al., 2007, Hickel et al., 2010).
The retention/fracture rate of the restorations and the fracture rate of teeth (dental hard tissue defects at the restoration margins) are outcomes that provide information about the clinical performance of the bond of the restoration to the tooth structure and about the strength of the material and its ability to resist to the occlusal forces.
Contact point, contour and form are secondary outcomes that provide information about the physical properties of the material and its ability to maintain its form when in clinical use.
Colour match and surface lustre and texture are secondary outcomes that provide information about the aesthetic potential of the material. Surface lustre also proved information about the ability of the material to be polished to a level where plaque accumulation is reduced and the potential of the material to maintain its lustre over time.
The marginal quality including marginal staining, dental hard tissue defects at the margin, marginal adaptation, caries at the margins of the restorations provides information about the quality of the bond between tooth structure and the dental composite.
The secondary outcomes will be assessed at all recalls.

3.3 Other Outcomes of Interest

n.a.

3.4 Safety Outcomes

No other specific safety outcomes than the previous described (postoperative hypersensitivity, loss of vitality, loss of restoration, tooth fracture, tooth loss) will be evaluated.

4. CLINICAL INVESTIGATION DESIGN

4.1 General clinical investigation design and justification of design

A double blind (patient and evaluator), randomized, controlled, split mouth clinical trial is planned for TM Flow used to restore NCCL. The split mouth design allows the comparison of the two restorative materials under the same clinical circumstances. The materials are being exposed to the same oral conditions (microbiota, u oral hygiene, nutrition, saliva, chewing forces and if given parafunctions). The evaluation of postoperative hypersensitivity benefits from the study design, since this parameter is influenced by the individual perception on pain which vary widely among individuals. The risk for these interindividual variations is minimized by the use of the split mouth study design.

66 patients will be included in this clinical investigation. Each patient will receive 2 restorations. The restoration belonging to the test group will be restored with TM Flow. The second restoration belonging to the control group will be restored with Tetric EvoFlow. The clinical procedure for both flowable composites is very similar, only the material differs. The randomization process will be performed electronically by the EDC platform Castor, which will also be used for the collection of data. The restorations will pe placed by 6 trained operators. Each operator will place at least 10 fillings. The evaluation of the restorations will be performed by an evaluator, that will be blinded and that has no information about the assignments of the restorations to each group.

The duration of the clinical trial is 60 months. After the placement of the restorations, they will be evaluated at a baseline recall after 7-10 days and then after 1, 6, 12, 24, 36 and 60 months. At every recall postoperative sensitivity, teeth vitality, retention rate of restorations, color match, surface luster and texture, marginal integrity, form and contour, and contact points will be assessed according to FDI criteria (Hickel et al., 2022). Additionally, the margins of the restorations will be assessed by SQUACE (SemiQUAntitative Clinical Evaluation) according to the FDI criteria.

The participants are recruited from the existing patient pool of the internal practice of Ivoclar Vivadent AG and are thus employees of the company. No active recruiting measures are taken. Each participant has the right to refuse participation in the clinical trial at any time.

4.2 Methods for minimising bias

4.2.1 Randomisation

Randomisation is performed electronically by Castor. Castor uses a validated variable block randomization model with optional stratification.

4.2.2 Blinding procedures

The evaluator will be blinded. The evaluator has only access to the recall eCRFs which contain no information regarding assignment of the restorations to the study groups. The patient is also blinded. The operator will not communicate the material which is used to treat the lesion. As long as the patient is lying on the dental chair it does not see the material, which is applied, therefore the patient does not know which tooth has received which material.

4.2.3 Other methods for minimising bias

n.a.

4.3 Unblinding Procedures (Code break)

The operators and the PI are not blinded. Only the evaluator and the patients are blinded. If necessary, the evaluator gets information about the group allocation from the PI (for instance premature termination of the study).

5. CLINICAL INVESTIGATION INTERVENTION

5.1 Identity of the medical device under investigation

TM Flow is a flowable, light-curing, radiopaque composite (200% Al) for the direct restorative treatment of anterior and posterior teeth.TM Flow cures with light in the wavelength range of 400–500 nm and can be applied in layers of up to 4 mm.

5.1.1 Experimental Intervention (medical device)

The direct filling therapy of an NCCL with a composite often in flowable consistency is an every day procedure for most dentists. The placement of this kind of filling is part of the basic training during dental medicine study. It is also described in many videos which are freely available. In the properties relevant to the application, test and control material differ only in the fact that TM Flow can be applied in thicker increments up to 4 mm compared with Tetric EvoFlow with 2 mm increment size and in slight difference in the consistency.

For a patient it is often difficult to differentiate the exact tooth, which is responsible for a tooth ache. Therefore, experimental and control intervention can only be done at the same treatment session if the two teeth are located in different quadrants. Otherwise only one tooth can be treated in one visit. The second tooth can only be treated if the first tooth did not show any sign of postoperative sensibility or after the symptoms of postoperative sensibility have disappeared. After the first intervention at least the baseline visit needs to be waited for.

5.1.2 Control Intervention (standard/routine/comparator)

See 8.1.1

6. STATISTICAL METHODS

6.1 Hypothesis

The Null Hypothesis (H_0) is that the proportion of postoperative hypersensitivity occurrence after the treatment with the new composite (P_{treat}) will be inferior to the treatment with an already established composite ($P_{control}$). The alternative hypothesis (H_1) is that the treatment with the new composite will be non-inferior to the standard treatment.

The non-inferiority difference is a predefined margin of difference between the new treatment and the control treatment. The upper limit of the clinically acceptable proportion of postoperative hypersensitivity is 10% (proportion determined by experience). The actual proportion of patients experiencing postoperative hypersensitivity after a direct restorative treatment at the study site (internal clinic of Ivoclar Vivadent AG) is 2.4%. Therefore, the calculated non-inferiority difference is 7.6%.

Split-mouth design with a one-sided non-inferiority hypothesis:

H_1: $P_{treat} - P_{control} < 7.6\%$

H_0: $P_{treat} - P_{control} \geq 7.6\%$

6.2 Determination of Sample Size

The sample size calculation was performed by Dr. Nicole Graf (biostatistician) from the Clinical Trials Unit of the Kantonsspital St. Gallen. Her CV and calculations can be provided upon request.

The power was calculated using PASS Version 21.0.5 (PASS 2021 Power Analysis and Sample Size Software (2021). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.).

Using the parameters listed in Table below, a sample size of 63 subjects achieves 80% power at a significance level of 0.05.

Considering a drop-out of 3 patients, it is planned to include 66 patients in this study.

Parameters used for the sample size calculation.

P_{treat}	$P_{control}$	Actual difference	Non-inferiority difference	Nuisance parameter	Target alpha	Power	Sample size
0.024	0.024	0*	0.076	0.012	0.05	0.80	63

*****It is expected that the treatment with the novel composite leads to a comparable proportion of patients with postoperative hypersensitivity in comparison to the control treatment.

6.3 Statistical criteria of termination of the investigation

If 6 or more patients show a postoperative hypersensitivity of FDI grade 4 or 5 in test or control group the study will be terminated.

6.4 Planned Analyses

The IBM SPSS Version 25 software package will be used for data analysis.

The level of postoperative hypersensitivity between the control and the test group will be analysed.

6.4.1 Datasets to be analysed, analysis populations

The data collected of all eligible participants that received two final fillings will be used for the statistical data analysis.

6.4.2 Primary Analysis

Regarding the primary outcome, the interim analysis will be done at baseline. The final analysis of the primary outcome will be done after 1 month. It will be evaluated if the difference between postoperative hypersensitivity rate (FDI criterium B3) in test and control group is lower than the predefined non-inferiority margin (7.6%). The analysis will be done by the principal investigator within 3 months after

the collection of the data.

6.4.3 Secondary Analyses

Regarding the secondary outcomes, the analyses will be done after the 1, 6, 12, 24, 36 and 60 months recalls. Control and test group will be compared for each FDI criterium. The analysis will be done by the principal investigator within 3 months after the collection of the data.

6.4.4 Interim analyses

The interim analysis will be done after the collection of data at each recall. The purpose is to compare in regular time intervals the results of the control group with those of the test group.

6.4.5 Deviation(s) from the original statistical plan

Deviations from the original statistical plan must be reported to the sponsor.

6.5 Handling of missing data and drop-outs

After baseline drop-outs will not be replaced. In previous clinical trials, there were few drop-outs in the internal clinic of Ivoclar Vivadent AG. There had also been a small number of no-shows.

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