Clinical Study Protocol

Clinical evaluation of Class I and II cavities restored with the combination of a new flowable and a new sculptable universal bulk-fill composite: A prospective single arm 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 (BASEC ID: 2024-D0004). Furthermore, as soon as the new electronic system EUDAMED is operational, the clinical investigation will be retrospectively registered, if required (CIV-24-02-046014)
Identifier:	OTCS 36392568 (Document ID: OTCS 36406866)
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 Fill and TM Flow (Ivoclar Vivadent AG)
CIP Version and Date:	Version 3.0, 10.04.2024

Signature Page

ID number of the investigation:	OTCS 36392568 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.
Title:	Clinical evaluation of Class I and II cavities restored with the combination of a new flowable and a new sculptable universal bulk-fill composite: A prospective single arm study

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 3.0 (dated 10.04.2024), 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

[redacted] [redacted]

Place/Date Signature

Principal Investigator: Dr. med. dent. Carola Pentelescu

[redacted] [redacted]

Place/Date Signature

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SYNOPSIS

Sponsor / Sponsor-Investigator	Ivoclar Vivadent AG
Title:	Clinical evaluation of Class I and II cavities restored with the combination of a new flowable and a new sculptable universal bulk-fill composite: A prospective single arm study
Short title / Investigation ID:	Clinical evaluation of a new flowable and a new sculptable universal bulk-fill composite for direct restorative treatment OTCS 36392568
Clinical Investigation Plan, version and date:	Version 3.0, 10.04.2024
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 EUDAMED2 is operational, the clinical investigation will be retrospectively registered, if required.
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 Shades: A2 plus (LOT: YM0209), A3 plus (LOT: YM0210), A3.5 plus (LOT: YM0211), Bleach plus (LOT: YM0212) TM Fill UDI not available Shades: A2 plus (LOT: YM0205), A3 plus (LOT: YM0206), A3.5 plus (LOT: YM0207), Bleach plus (LOT: YM0208) Manufacturer Ivoclar Vivadent AG Benderer Strasse 2 9494 Schaan SRN-number: LI-MF-000000522 Accessories: Cannulas Luer-Lock
Stage of development:	Pivotal stage The clinical investigation is conducted for a conformity assessment purpose.

Background and rationale:	Direct restorations in the oral cavity are placed when tooth tissue is partially lost due to caries, trauma, or tooth wear in order to restore the morphology, aesthetics and function of the teeth. Nowadays resin composites used with adhesive systems that bond the restorative material to the tooth structure are most often the materials of choice. Resin composites can be classified by their viscosity in sculptable composites, and flowable composites that show a low viscosity. Resin composites are cured with a polymerization lamp which limits the thickness of material layers to 1-2 mm. Bulk-fill resin composites have been developed to facilitate clinicians' work, reduce working time and simplify the restorative procedure. They can be placed in increments of up to 4-5 mm. If a sculptable (bulk-fill) composite is used in combination with a flowable bulk-fill composite, a first layer of flowable composite can be applied in the cavity and light cured. The flowable composite has the advantage of an easy and fast application, so that the first 4 mm of the cavity are rapidly filled. Afterwards, a capping layer with a sculptable bulk-fill composite is applied and light cured. The newly developed bulk-fill composites TM Flow (flowable) and TM Fill (sculptable) can be light-cured in 3, 5 and 10 seconds (light intensity 3000, 2000 and 1200 mW/cm^2, respectively). The photons of the curing light activate the initiator for the polymerization reaction, but also create heat which could cause a pulp damage. Damage related to heat stress could lead to postoperative hypersensitivity with elevated pain to cold, heat or chewing. Class I and II cavities need to be filled most often in the daily practice since occlusal and approximal surfaces of molars and premolars are predominantly affected by caries. Class I and II restorations are in areas with the highest occlusal load, so that the material used for these types of restorations is challenged heavily by mechanical forces. I new resin composites TM Fill and TM Flow will be used for direct restorations of class I and II cavities (3 seconds light-curing mode) in premolars and molars in this clinical investigation to prove their clinical performance and safety.
Objective(s):	The overall objective of this clinical investigation is to evaluate the clinical safety and performance of the new resin composites TM Flow and TM Fill. The primary objective is to assess the rate of postoperative hypersensitivity after treatment of class I or II restorations with TM Flow in combination with TM Fill (3 seconds light-curing mode, 3000 mW/cm^2). 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, occlusion and wear 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 (acceptance criterium < 10%). The secondary outcomes focus on tooth vitality and 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:	Prospective, single-arm study

Inclusion / exclusion criteria:	Inclusion criteria: • Informed Consent signed by the subject • Age: 18-65 years • Indication Class I or II direct restorations in premolars or molars (Replacement of insufficient fillings due to secondary caries, fractures, insufficient marginal adaptation, loss of filling or primary caries) • Cavity width must be at least half of the cusp tip distance • Vital teeth, regular sensitivity • Sufficient language skills • No active periodontits • Preoperative VAS values < 3 regarding tooth sensitivity and biting Exclusion criteria: • Sufficient isolation of the cavity not possible • Not completed hygiene phase or poor oral hygiene • Missing antagonist, non-occlusion • Missing tooth adjacent to the tooth to be treated • Restorations replacing more than 1 cusp • Caries profunda or very deep cavity • Patients with a proven allergy to ingredients of the used materials (methacrylates) or local anesthetics (Articain, sulfite) • Patients with severe systemic diseases • Pregnancy • Part of the development project team of TM Flow or TM Fill • Staff of the study management team • Staff of the internal clinic
Measurements and procedures:	Each participant receives one filling in one tooth. 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 the 1 and 6 month recall the sensitivity is recorded using a visual analogue scale and at all the other recalls the sensitivity is only recorded if necessary. The results are documented by intraoral images.
Intervention:	The newly developed resin composites TM Flow and TM Fill will be used for the restoration of class I and II cavities (3 seconds light-curing mode, 3000 mW/cm^2). The treatment workflow is very similar to other resin composites, for instance the predecessor products Tetric PowerFill and Tetric PowerFlow.
Control intervention (if applicable):	Not applicable
Number of subjects with rationale:	61 subjects were calculated for the single-arm study design. Considering a drop-out rate of 5%, 65 subjects will be included in this clinical investigation.
Duration of the investigation:	60 months for each patient (recruiting phase 4 months)
Investigation schedule:	May 2024 First-subject-In April 2030 Last-subject-Out

Investigator(s):	- Dr. Enggist Lukas, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Carola-Sonia Pentelescu, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Peschke Arnd, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Hu Ming, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Ronny Watzke, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Lydia Eberhard, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Glebova Tatiana, Benderstrasse 2, 9494 Schaan [redacted]
Investigational Site(s):	This is a single center study. R&D Clinic Ivoclar Vivadent AG Benderstrasse 2 9494 Schaan Liechtenstein
Statistical considerations:	The sample size was calculated for a single-arm study design with a one-sided hypothesis (target alpha 5%; power of at least 80%). A one-sided binomial exact test is used to calculate if the probability of postoperative hypersensitivities is lower than 10% (acceptance criterium).
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 (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
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
VAS	Visual Analogue Scale

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	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							
Placement of restoration		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 deficiendcies		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

Caries lesions are a chronic disease that is widely spread among the population all over the world affecting 60-90% of children and the vast majority of adults in industrialised countries. (Pitts et al., 2017). Caries in posterior teeth (molars or premolars) occurs mostly in fissures or on approximal surfaces below the contact point of two neighboring teeth. In order to treat the disease caries affected tissue is removed. This leads either to class I cavities which have just one outer surface on the occlusal aspect of a posterior tooth or class II fillings, which are characterized with two outer filling surfaces on the occlusal and approximal aspect.

Over the last three decades, caries prevalence has decreased in all age groups in modern Western countries (Jordan et al., 2019). For example, in European, caries prevalence in adults has declined by about 20% between 1996 and 2016 (Kassebaum et al., 2017). In Germany the cumulative caries experience has decreased from 1.1 billion DMFT (decayed/missing/filled teeth) in 2000 to 867 million in 2015 and is expected to further decrease to 740 million in 2030 (Jordan et al., 2019). However, not all societal groups have benefitted equally from this decline (Jordan et al., 2019). There is evidence for an association between low socio-economic status and a higher risk of having dental caries. In addition, on an international le–el - associated with population growth and increased tooth retent–on - the number of people affected by dental caries has grown substantially, increasing the total burden globally by 37% for untreated caries (Kassebaum et al., 2017).

The evolution of carious lesion can be fast (acute) or slow (chronic). Both evolution rates are leading to loss of tooth structure over time and the morphology and function of teeth is affected. The goal of therapeutic procedures is to restore the morphology, aesthetics, and function of teeth by replacing the missing tooth substance with restorative materials. The therapeutic procedures are of two types: direct restorative procedures, where the tooth structure is restored directly in the oral cavity and indirect procedures where the restorations are manufactured either in the dental laboratory or chairside in a digital workflow.

Direct (in the oral cavity of the patient) dental restorations are placed when sound tooth tissue (enamel and/or dentin) is partially lost due to caries, trauma, or tooth wear. When carious lesions no longer can be remineralized or arrested with non-invasive methods such as fluoride applications, the defect needs to be restored. For the direct restorative procedures dental resin composites and amalgam are mostly used in the daily practice. Resin composites are tooth-colored materials. Resin composites are used with adhesive systems that bond the restorative material to the tooth structure. This allows dentists to accomplish defect-oriented preparations, limiting the removal of tooth substance to the area of the defect that needs to be restored. Composite resins are delivered in various shades, opacities and translucencies which allows aesthetically pleasing restoration of the original tooth structure.

Resin composites can be classified by their viscosity in sculptable composites, showing a high viscosity respectively flowable composites showing a low viscosity. Resin composites are cured with a polymerization lamp which limits the thickness of material layers to 1-2 mm. Therefore, resin composites must be placed in incremental layers. Bulk-fill resin composites have been developed to facilitate clinicians' work, reduce working time and simplify the restorative procedure (Kruly et al., 2018). They can be placed in increments of up to 4-5 mm as they either contain special light initiators which polymerize the resin in thicker increments or as the material is more translucent which allows the light to penetrate into deeper areas of the resin.

The sculptable (bulk fill) composites can be used either alone or in combination with flowable bulk-fill composites. If such a combination is used to restore cavities a first layer of up to 4 mm thickness of flowable composite is applied in the cavity and light cured. The flowable composite has the advantage of an easy and fast application, so that the first 4 mm of the cavity are rapidly filled. Afterwards a capping layer of sculptable bulk-fill composite is applied, modelled and light cured. In this manner the cavities are restored even more rapidly.

The modern curing lights use LED technology whose photons activate the initiators within the resin composite. Lamps with different power density are available. They vary between 700 mW/cm^2 and 5,700 mW/cm^2 (Christensen et al., 2019). The higher the power density the shorter the polymerization time. The polymerization time required for a lamp with 1.200 mw/cm^2 is 10 seconds, with 2,000 mw/cm^2 it is 5 seconds and with 3,000 mW/cm^2 it is 3 seconds. However, each increment must be cured separately which results in multiple curing shots. The photons of the curing light activate the initiator, but also create heat which has raised the concern that heat might be transmitted from the cavity to the pulp with the potential risk of pulp damage. In addition, the exothermal polymerization reaction of dental composites is delivering also heat to the tooth contributing to the increase of the pulpal temperature. The flowable

composites show a higher exothermal polymerization reaction then sculptable composites due to the higher monomer content. Possible damage related to heat stress comprises (1) reversible pulpitis with elevated pain to cold, heat or chewing after the treatment (post-operative hypersensitivity), (2) irreversible pulpitis with or without pain which makes a root canal treatment necessary or (3) internal resorption in the pulp chamber.

Post-operative hypersensitivity is reversible in most cases and lasts from one week to several months (Major et al., 2002). Besides heat stress generated by the curing lamp and by the exothermic reaction of the resin composite, many other factors may influence the occurrence of sensitivity such as the remaining dentin thickness that separates the cavity from the pulp chamber, the size of the cavity and previous damage of the tooth.

In an attempt to clarify the relationship between radiant exposure values and pulp temperature, Arrais et al. (2019) evaluated the in-vivo pulp temperature rise in premolars with cervical cavities which were exposed to 10 seconds of 2,000 mW/cm^2 or 2x3 seconds of 3,000 mW/cm^2 (Arrais et al., 2019). The teeth were extracted 2 hours after light exposure and histologically and immunochemically examined for signs of early inflammatory indicators like IL-β and TNF-α. The results showed a similar histological and immunochemical expression in both groups. A prospective clinical study on 62 posterior resin composite bulk-fill restorations that had been cured with a 3,000 mW/cm^2 curing lamp for 3 seconds found that after 12 months, none of the treated teeth had suffered loss of sensitivity (vitality). However, in two independent clinical trials the rate of post-operative hypersensitivity at baseline was slightly higher compared to restorations that had been cured with the conventional technique . Most cases of post-operative sensitivity subsided without intervention within several weeks. There were a few restorations that had manageable remnant post-operative sensitivity for which the subjects did not want intervention (Lawson et al., 2020, 2022, Enggist, 2018).

TM Fill (sculptable) and TM Flow (flowable) are dental bulk-fill composites that can be applied in up to 4 mm layers and can be light cured in 10, 5 or 3 seconds. The products are not bearing a CE mark and are not yet available on the market, so no clinical studies are available with these two products regarding the incidence rate of postoperative hypersensitivity and clinical performance of the product. The aim of this study is to assess the incidence rate of postoperative hypersensitivity, when class I and II cavities are directly restored with TM Fill in combination with TM Flow, both being light cured in the 3 seconds curing mode (3,000 mW/cm^2). The application of a first layer of up to 4 mm TM Flow is considered the worst-case scenario, due to the higher exotherm polymerization reaction of flowable composites. By this clinical study not only the pulp response of the teeth to the materials in combination with the 3 seconds-curing mode is determined, but also the clinical performance of the material by the assessment of the secondary outcomes like tooth vitality, marginal quality, fracture of material and retention loss, surface quality and aesthetics.

1.2 Identification and description of the Investigational Medical Device

This information is provided within the Investig'tor's Brochures (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 devices TM Flow and TM Fill in direct restorative treatment (class I and II restorations) polymerized in 3 seconds (3000 mW/cm^2) with Bluephase PowerCure.

2.2 Primary Objective

The primary objective is to assess the rate of postoperative hypersensitivity after treatment of class I and II cavities with the new composites TM Flow and TM Fill and to compare to the acceptance level of 10% (see chapter statistics).

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 functional (fracture of material and retention, marginal adaptation, proximal contact point, form and contour, occlusion and wear) biological (caries at the restoration margins, dental hard tissue defects at the restoration margin, pulpal status) and aesthetic properties (surface luster andsurface texture, marginal staining, colour match). 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 Fill and 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 the 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. FDI grades 3-5 are considered as postoperative hypersensitivity in this clinical investigation, since FDI grade 2 does not need any treatment, subsides spontaneously and does not have further clinical relevance. 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 rate. The clinical experience of the evaluators 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 during the 1 year recall and later is only done if the patient feels any hypersensitivity.

3.2 Secondary Outcomes

The FDI criteria are well established parameters to evaluate the long-term performance of dental restorations (Hickel et al., 2022). The following FDI criteria were selected for the evaluations of the fillings in this clinical investigation:

Tooth vitality

A1 - Surface lustre and texture

A2 - Marginal staining

A3 - Color match

F1 - Fracture of material and retention

F2 - Marginal adaptation

F3 - Proximal contact point

F4 - Form and contour

F5 - Occlusion and wear

B1- Caries at restoration margins

B2 - Dental hard tissue defects at the restoration margins

M1 - Patients view

Colour match, surface lustre and texture are secondary outcomes that provide information about the aesthetic potential of the material. Surface lustre also proves 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 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.

The marginal quality including marginal staining, marginal adaptation, caries at the margins of the restorations provides information about the quality of the bond between tooth structure and the dental composites.

Contact point, contour and form, occlusion and wearare secondary outcomes that provide information about the physical properties of the material and its ability to maintain its form when in clinical use.

The secondary outcomes will be assessed at all recalls.

3.3 Other Outcomes of Interest

Not applicable

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 single arm, prospective clinical trial is planned with TM Fill in combination with TM Flow, cured in the 3 seconds curing mode (3000mW/cm^2). In this high energy curing mode the photons of the curing light activate the initiator, but also create heat which has raised the concern that heat might be transmitted from the cavity to the pulp with the potential risk of pulp damage. TM Flow will be applied as an initial layer of up to 4 mm thickness (A3.5 mm in case of the shade A3.5 plus). The materials also have an exothermic reaction during the light polymerization that adds to the energy output of the lamp, and since the flowable material have a higher exothermal reaction when compared to sculptable materials, the application of an initial layer of flowable material in the maximal layer thickness represents a worst-case with regard to the pulp response to the temperature increase. The materials will be used for the restoration of class I and II cavities in posterior teeth (molars, premolars) since class I and II cavities are the most frequent in the daily practice and are exposed to the highest occlusal forces. This allows the assessment of the performance of the material in its main field of application.

The participants are recruited from the existing patient base 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 further participation in the clinical trial at any time.

No participant will receive more than one restoration during the clinical trial. The recruited participants who meet all inclusion criteria will have a detailed medical anamnesis (signed by dentist and participant) to evaluate diseases and a detailed dental medical report. In addition, there is a therapy plan in the sense of the complex rehabilitation concept. These details are documented in the participant file independently of the clinical study.

During the study each participant will receive one TM Filling. The restorations will consist of an initial layer TM Flow of up to 4 mm and a subsequential layer TM Fill.

The procedure for the application of the adhesive Adhese Universal is the "Etch & Rinse (E&R)" technique (previous enamel/dentine etching with phosphoric acid).

5 trained operators will insert 65 indirect restorations, so each operator will perform 13 restorations.

2 trained evaluators will perform the baseline examination (7-10 days) after placement of the restorations, and the following recalls at 1, 6, 12, 24, 36 and 60 months.

4.2 Methods for minimising bias

4.2.1 Randomisation

Not applicable since it is a single arm study.

4.2.2 Blinding procedures

Not applicable since it is a single arm study.

4.2.3 Other methods for minimising bias

This section is not applicable

4.3 Unblinding Procedures (Code break)

Not applicable since it is a single arm 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 Fill is a sculptable, light-curing, radiopaque composite (200% Al) for the direct restorative treatment of anterior and posterior teeth. TM Fill is also suitable for restoring occlusal surfaces.TM Flow and TM Fill cure 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 a class I or II with flowable and sculptable composites is an everyday procedure for most dentists. The placement of this kind of filling is part of the basic training during dental medicine study. It is described in textbooks and videos which are freely available.

5.1.2 Control Intervention (standard/routine/comparator)

Not applicable since it is a single arm study.

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 composites (P_{treat}) is higher than the clinically acceptable 10% (P_0). The Alternative Hypothesis (H_1) states that the proportion of occurring hypersensitivity in this study is less than 10%.

Single-arm study with a one-sided hypothesis:

H_0: $P_{treat} \geq 10\%$

H_1: $P_{treat} < 10\%$

The frequency of postoperative sensitivities calculated in meta-analyses with class I and II cavities vary widely between 1% and 29% (Gordan et al., 2002, Hayashi et al., 2003, Heintze et al., 2012, Arbildo et al., 2020, Reis et al., 2015) because there are many influencing factors that are difficult to standardize between different studies. Factors that influence the development of postoperative hypersensitivites include the depth and size of cavities, removal of the smear layer (adhesive strategy), type of tooth, polymerization technique, gap formation between filling material and dentin, inadequate sealing of dentinal tubules, residual caries, bacterial penetration, contractual stress and level of pain sensation. Based on their experience, the dentists of the internal clinic consider the occurrence of more than 10% postoperative hypersensitivity unacceptable. This level was already chosen for previous studies, e.g. «Klinische Untersuchung des F-Composite 2 Systems in der direkten Füllungstherapie» (BASEC-ID 2017-00904).

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 the table below, a sample size of 61 achieves 82% power to detect a difference (P_1-P_0) of -0.076 using a one-sided binomial exact test with a target significance level of 0.05. Considering a drop-out rate of 5%, it is planned to include 65 patients in this study.

Parameters used for the sample size calculation:

P_0	P_1^*	Difference P_1-P_0	Target alpha	Power	Sample size
0.10	0.024	-0.076	0.05	0.82	61

*****Proportion of patients that experienced postoperative hypersensitivity after a direct restorative treatment with already established composites at the study site (internal clinic of Ivoclar Vivadent AG).

6.3 Statistical criteria of termination of the investigation

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

6.4 Planned Analyses

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

6.4.1 Datasets to be analysed, analysis populations

The data collected of all eligible participants 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 1month. VAS values (biting and thermal stimuli) and the clinical signs and symptoms regarding tooth vitality, response to thermal tests, duration and intensity of pain are summarized in an FDI score as described by Hickel et al. (2022). It will be evaluated if the postoperative hypersensitivity rate (FDI criterium B3) is below 10% using a one-sided binomial exact test. Only FDI grades 3-5 will be considered as postoperative hypersensitivity, since FDI grade 2 does not need any treatment, subsides spontaneously, and does not have further clinical relevance. 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. A descriptive statistical 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.

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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All internally available documents with "OTCS-Numbers" will be provided upon request.