Clinical Study Protocol

Clinical evaluation of a new dual-cure universal adhesive for indirect restorative treatment

Type of investigation:	Clinical investigation concerning medical devices
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.
Study Identifier:	OTCS187088487 (Document ID: OTCS187092274)
Principal Investigator and Sponsor, or Sponsor-Investigator:	Principal Investigator (PI): Dr. med. dent. Lukas Enggist Internal Clinic of Ivoclar Vivadent AG Bendererstrasse 2 9494 Schaan Fürstentum Liechtenstein Tel. [redacted] Mail: [redacted] Sponsor: Ivoclar Vivadent AG Patrizia Elkuch-Hoch Team Leader Study Management Bendererstrasse 2 9494 Schaan Fürstentum Liechtenstein Tel.: [redacted] Mail: [redacted]
Sponsor representative (if the Sponsor is not located in Switzerland)	n.a.
Medical Device:	[redacted] (Ivoclar Vivadent AG)
CIP Version and Date:	Version 4.0, 01.10.2024

Signature Page(s)

ID number of the investigation:	OTCS187088487 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 a new dual-cure universal adhesive for indirect restorative treatment

The Sponsor, the Principal Investigator have approved the CIP version 4.0 (01.10.2024) 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. Lukas Enggist

[redacted] [redacted]

Place/Da te Signature

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SYNOPSIS

Sponsor	Ivoclar Vivadent AG
Title:	Clinical evaluation of a new dual-cure universal adhesive for indirect restorative treatment
Short title / Investigation ID:	Clinical evaluation of a new dual-cure universal adhesive OTCS187088487
Clinical Investigation Plan, version and date:	CIP Version 4.0, 01.10.2024
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.
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	[redacted] in VivaPen + VivaPen DC (dual-curing) cannula UDI not available Manufacturer: Ivoclar Vivadent AG Bendererstrasse 2 9494 Schaan Liechtenstein
Stage of development:	Pivotal stage The clinical investigation is conducted for a conformity assessment purpose.
Background and rationale:	The usage of a dental adhesive to lute ceramic inlays or onlays to teeth is necessary and state of the art to replace missing tooth structure. The investigational product [redacted] is a novel universal dual-cure adhesive. This clinical investigation is conducted to prove the clinical performance and safety of this new dental adhesive.
Objective(s):	The overall aim of this study is to evaluate the clinical performance and safety of the dental adhesive [redacted] for luting indirect ceramic restorations (inlays and onlays). The investigation seeks primarily to determine the rate of postoperative hypersensitivity occurrence after using [redacted] for the placement of indirect restorations. The secondary objective of this study is to assess the long-term clinical performance of [redacted] in terms of marginal quality, retention/fracture rate of the ceramic restorations, and vitality/fracture rate of the restored teeth.
Outcome(s):	The primary endpoint of this clinical trial is the incidence rate of postoperative hypersensitivity. The assessment of the postoperative hypersensitivity is performed and graded according to the FDI criteria (Hickel et al. 2007; Hickel et al. 2010, Hickel et al. 2022). The secondary outcomes are the vitality and fracture rate of restored teeth and the retention/fracture rate of restorations. These parameters provide information about the clinical performance of the bond of the restoration to the tooth structure. Another secondary outcome is the marginal quality of the restorations that also provides information about the quality of the bond between tooth structure and luting composite. The secondary outcomes will be assessed at all recalls with the respective FDI criteria (Hickel et al. 2022).
Design:	This is a prospective single-arm clinical investigation. The safety and performance results of [redacted] will be compared with the coded data of the control group (Adhese Universal) of an already performed clinical investigation ("Clinical evaluation of a new dual cure universal adhesive (Adhese Universal DC) in the indirect restorative therapy: A randomised, controlled clinical trial", NCT04475679). The study design of the planned clinical investigation follows the design of the previously conducted clinical investigation. The objectives, outcome parameters and methods are the same.

Inclusion / exclusion criteria:	Inclusion criteria: - Age: 18-65 years - Informed consent signed and understood by the subject - Indication for indirect restorations (inlay, onlay) in molar or premolar - replacement of insufficient fillings (e.g. due to caries at margins, filling fracture, fracture of the tooth, poor quality of the surface, leaking margin, etc.) or extensive primary caries - The occlusal area of the restoration must cover at least 1/3 of the occlusal area of the tooth. -Pre-operative discomfort of the tooth to be restored should not exceed 3 on the visual analogue scale (VAS) (0=no pain, 10=maximum conceivable pain) due to temperature stimulus or bite sensitivity - Max. 2 restorations per participant in different quadrants. - Vital tooth - Healthy periodontium, no active periodontitis - Contact with adjacent teeth (at least at one side) and opposing teeth present with at least one contact point. - Sufficient language skills Exclusion criteria: - Sufficient isolation not possible, dry working field cannot be guaranteed - Participants with a proven allergy to one of the ingredients of the materials used (methacrylates, HEMA, potassium iodide, mequinol) - Participants with proven allergy to local anaesthetics (Articain, sulfite) - High caries activity/ poor oral hygiene - Participants with severe systemic diseases - Pregnancy - Tooth with irreversible pulpitis - Indication for direct pulp capping - Part of the development project team of [redacted] - Staff of the study management team - Staff of the internal clinic - Bleaching of teeth within the last 14 days - Usage of peroxide-based disinfectants within the last 14 days
Measurements and procedures:	After information and written informed consent the participants will receive a dental treatment in relation to the restorative indication (caries, tooth/restoration fracture, insufficient restoration, etc), which means that the inlay/onlay cavity will be prepared and a digital impression with an intraoral scanner (Trios 3Shape) will be taken. Then, the cavities will be temporarily restored with provisional restorations. The scans will be sent to the lab where dental technicians will provide the final restorations made of lithium disilicate e.max CAD. In the following appointment the final restorations will be luted and final corrections as well as the finishing and polishing procedures will be done. The baseline recall will take place 6-12 days after the insertion of the restoration. At the baseline recall the study specific parameters will be evaluated according to the FDI criteria ranging from 1 excellent to 5 clinically not acceptable. Further recalls will be performed at 1, 6, 12, 24, 36 and 60 months after placement of the restoration.
Intervention:	After getting a tooth which is in a need of a restoration (inlay or onlay), the cavity will be prepared, and an optical impression is taken. Then provisional restoration is cemented during the time, which is necessary to produce the indirect restoration in the dental lab. This first treatment appointment takes around 2.5 h. In a second treatment appointment the indirect ceramic restoration is luted to the tooth surface by the investigational product [redacted] and the well-established luting composite Variolink Esthetic DC. This will take at maximum 2 hours. During the baseline appointment a repolish of the restoration can be done by the operator before the evaluator assesses the restoration and the tooth. This will take at maximum 30 minutes. All following recall visits will take no longer than 30 minutes.
Control intervention (if applicable):	n.a.
Number of subjects with rationale:	45 teeth, at maximum two teeth per participant according to the statistical considerations.
Duration of the investigation:	5 years

Investigation schedule:	October 2024 First- subject –In (planned) April 2031 of Last- subject –Out (planned)
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. Glebova Tatiana, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Lydia Eberhard, Benderstrasse 2, 9494 Schaan [redacted] - Dr. Ronny Watzke, Benderstrasse 2, 9494 Schaan [redacted]
Investigational Site(s):	This is a single center study. R&D Clinic Ivoclar Vivadent AG Benderstrasse 2 9494 Schaan Fürstentum Liechtenstein
Statistical considerations:	The trial is a continuation of the clinical trial "Clinical evaluation of a new dual cure universal adhesive (Adhese Universal DC) in the indirect restorative therapy: A randomised, controlled clinical trial (NCT04475679)". The methodology, the endpoints and the hypotheses are the same. The test product [redacted] is a further development of Adhese Universal DC. Therefore, the test group ([redacted]) will be compared to the control group (Adhese Universal) of the study mentioned above. In this clinical trial a dropout of 5 restorations is assumed. Therefore, the sample size is 45 instead of 40.
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
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

INVESTIGATION SCHEDULE

Study Periods	Screening	Treatment, Intervention Period			Follow-up						
Visit	1	2	3	4***	5	6	7	8	9	10	11
Time (hour, day, week)	-17- (-45) d	-14- (-5) d	0 d	Before visit 5	6-12 d	1 m	6 m	12 m	24 m	36 m	60 m
Patient Information	x										
Signed informed consent		x									
Medical History	x										
In- /Exclusion Criteria	(x)	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, impression and cementation of provisional restoration		x									
Try-in and cementation of final restoration			x								
Use of [redacted]			x								
Excess removal, polishing, occlusion check			x	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	x	x

* only for participants who suffer from any kind of postoperative hypersensitivity

** Not all variables will be assessed (only dental hard tissue defects at restoration margin, patient's view and fracture of material and retention)

*** optional visit

1. BACKGROUND AND RATIONALE

1.1 Background and Rationale for the clinical investigation

Caries is 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, Petersen et al. 2005). The evolution of carious lesions 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 and function of teeth by replacing the missing tooth substance with restorative materials. There are two ways of therapeutic approaches to restore the lost tooth substance: In the case of a direct restorative procedures the tooth structure is restored directly in the oral cavity by a dentist with materials such as dental composites, amalgams or glass ionomers. For indirect procedures the tooth is prepared in a particular manner, so that insertion axes and material thicknesses of the final restoration are guaranteed. An impression of the preparation is taken, and the indirect restoration is manufactured in the dental laboratory. Indirect restorations are inlays, onlays, overlays, crowns and bridges. Materials such as glass ceramics and oxide ceramics, metal alloys and resin polymers are used for the fabrication of indirect restorations. The indirect restoration is cemented to the tooth with a luting cement or a luting composite. A digital approach is possible that implies a digital impression by the aid of an intraoral scanner. Then, the indirect restoration is designed on the computer with the support of a specific software (CAD computer aided design) and finally milled from a block or a disc in a specific milling unit (CAM computer aided manufacturing). The tooth preparation and the cementation of CAD-CAM restorations are similar to the conventional type of indirect restorations that imply impressions, a gypsum model and the manual fabrication by a dental technician.

Dental adhesives provide the bond between direct restorative materials or luting composites and tooth structure. Dental adhesives are classified according to the historical evolution in generations from 1st to 8th generation, or according to the adhesion mechanism in etch and rinse adhesives, self-etch adhesives (Sofan et al. 2017). Universal adhesives belong to 1-step selfetching group. Regarding the polymerisation mechanism, dental adhesives can be grouped into light-, dual- or self-curing materials. When indirect restorations are adhesively cemented, the adhesive system is used in conjunction with a luting composite. The adhesive is applied on the tooth structure and afterwards it is either cured by a light curing unit before the restorations is inserted or it is cured together with the luting material. If the light curing option is chosen, the adhesive has to be applied in a very thin layer and has therefore to be thinned out very carefully with the air blast. Otherwise, the layer of adhesive could be too thick and could compromise the good fit of the restoration. The adhesive liquid has the tendency to accumulate in areas where it is difficult to control by air thinning, such as the transition from the cervical part of the proximal box to the axio-proximal part. If the adhesive is light cured in such a situation it will affect the fit of the final restoration. In this situation the restoration is too high and disturbs an adequate occlusion with the opposing teeth (hyperocclusion). A slight hyperocclusion can be corrected by grinding. However, a gross misfit affects not only the occlusion but also the marginal adaptation which sometimes makes the fabrication of a new restoration necessary. In order to avoid this shortcoming, dual-curing adhesive systems are available. They offer the benefit that no light curing of the adhesive layer is needed before the final restoration is seated. Another benefit of this type of adhesive system is that the polymerisation takes place and continues, even in areas that are not reached by the light of the light curing unit. The dual-curing adhesives possess initiators that guarantee a polymerization without any light activation. Therefore, a dual-cure universal adhesive combines the benefits of the universal adhesives with those of a dual-curing adhesive. Few data are available on the clinical performance of dual-cure universal adhesives. The primary aim of this clinical trial is to assess the rate of postoperative hypersensitivity and to compare it to the control group of an already performed study with a similar study design (NCT04475679). The secondary objectives are to assess the marginal adaptation and the retention/fracture rate of restorations, as well as the vitality and fracture rate of the restored teeth over a period of 5 years.

1.2 Identification and description of the Investigational Medical Device

[redacted] is a dual-curing single-component dental adhesive for enamel and dentin that is compatible with all etching techniques (self-etch, selective-enamel-etch and etch & rinse techniques). The areas of application include adhesive cementation of indirect restorations and direct restorative procedures. More detailed 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 study is to evaluate the clinical performance and safety of [redacted] for luting indirect ceramic restorations (inlays and onlays).

2.2 Primary Objective

The investigation seeks primarily to determine the rate of postoperative hypersensitivity occurrence after using [redacted] for the placement of indirect restorations. The results will be compared to the control group (Adhese Universal) of a previously conducted clinical investigation.

2.3 Secondary Objectives

The secondary objective of this study is to assess the long-term clinical performance of [redacted] in terms of marginal quality, retention/fracture rate of the ceramic restorations, and vitality/fracture rate of the restored teeth.

2.4 Safety Objectives

The safety objectives are already covered in the primary and secondary objectives. This study aims to assess the long-term safety of [redacted] in terms of tooth vitality and failure rate of the 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 before and after the treatment. A healthy dental pulp offers a positive response to the vitality test. Once the dental pulp is injured an irreversible inflammatory reaction starts with a possible necrosis of the dental pulp. Pulpa necrosis is followed by a negative response to the vitality test.

3. CLINICAL INVESTIGATION OUTCOMES

3.1 Primary Outcome

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 6-12days). The assessment of postoperative hypersensitivity includes questions about type and duration of pain, intensity of pain and on the stimulus inducing the pain (Hickel et al. 2007, Hickel et al. 2010, Hickel et al. 2022). 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

The secondary outcomes are the vitality, dental hard tissue defects at restoration margin and the retention/fracture rate of restorations. These parameters provide information about the clinical performance of the bond of the restoration to the tooth structure.

Another secondary outcome is the marginal quality of the restorations that also provides information about the quality of the bond between tooth structure and luting composite.

The secondary outcomes will be assessed at all recalls with the respective FDI criteria (Hickel et al. 2022, Hickel et al. 2007; Hickel et al. 2010).

3.3 Other Outcomes of Interest

Other outcome variables are translucency, colour match, surface gloss, form and contour, occlusion and wear of the ceramic restorations. These outcome variables provide information about the quality and stability of the lithium disilicate ceramic used for this type of restorations.

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. No laboratory parameters or other measurement or devices come to use in this clinical trial.

4.. CLINICAL INVESTIGATION DESIGN

4.1 General clinical investigation design and justification of design

[redacted] a new dental adhesive will be used to lute 45 inlays or onlays out of e.max CAD to teeth of at least 23 patients.

This prospective study has only one group ([redacted]) because the planed study is similar to a trial which has recently been executed in the internal clinic of Ivoclar Vivadent AG (NCT04475679). The only difference to the already performed study is the device under assessment. Therefore, the coded results of the control group of the previous clinical investigation (Adhese Universal) will be compared with the clinical performance of the new dental adhesive ([redacted]).

There are 5 operators and 2 evaluators. All operators are very experienced dentists in the field of restorative dentistry. The treatment of restoring teeth with ceramic inlays or onlays is a standard treatment in the internal clinic of Ivoclar Vivadent AG.

Postoperative sensitivities arise within days after the treatment. Therefore, the occurrence of postoperative sensitivities can be assessed already at baseline. Final assessment of postoperative hypersensitivities will be performed at the 1-month recall. If such an incident is still present after 1 month, it will be followed regularly.

The study duration of 5 years corresponds to the minimal duration recommended in restorative dentistry (Hickel et al., 2022). The patients will attend a recall after 6-12 days (baseline), 1, 6, 12, 24, 36, and 60 months.

4.2 Methods for minimising bias

4.2.1 Randomisation

This section is not applicable.

4.2.2 Blinding procedures

This section is not applicable.

4.2.3 Other methods for minimising bias

Confounding factors obscuring the 'real' effect of an exposure on outcome, will be controlled by inclusion and exclusion criteria. Attention is paid to equal gender distribution.

To minimize the bias of the evaluation of product performance, the evaluators who independently assess the restorations do not place any restorations and are also not informed about who the operator was. The restorations are all produced by the same PM 7 CAD/CAM system from experienced dental technicians. Therefore, an influence of different CAD/CAM systems on the quality of the restorations can be excluded. Five different operators will place the restorations. This is important in order to minimize the effect of the handling of one single operator on the quality of the restorations.

4.3 Unblinding Procedures (Code break)

None, as no blinding procedures are applied.

5. CLINICAL INVESTIGATION INTERVENTION

5.1 Identity of the medical device under investigation

5.1.1 Experimental Intervention (medical device)

The newly developed dental adhesive [redacted] will be used together with a cement for luting an indirect restoration on tooth structure.

[redacted] is a dual-curing single-component dental adhesive for enamel and dentin that is compatible with all etching techniques (self-etch, selective-enamel-etch, etch & rinse techniques). The product is indicated for both indirect restorations and direct restorations. In this clinical investigation, [redacted] in the VivaPen® (primary packaging) is used. VivaPen DC cannula (blue) is coated with the co-initiator required for the self-curing reaction. For hygienic reasons, a VivaPen protective sleeve is used by sliding the Pen with the cannula into the protective sleeve until the cannula punctures through the sleeve (Fig. 1). As described in the IFU, a new cannula and protective sleeve must be used for each patient. The [redacted] VivaPen can be re-used. By pressing the VivaPen push button (blue), the flocked cannula tip is saturated with adhesive liquid and mixes with the co-initiator. Following activation, the adhesive can be applied for approx. 120 seconds. Starting with the enamel the tooth surfaces to be treated need to be completely coated with [redacted]. The adhesive must be scrubbed onto the tooth surface for at least 20 seconds. Then [redacted] is dispersed with oil- and moisture-free compressed air until a glossy, immobile film layer result. Since [redacted] is a dual curing material, it does not need to be light cured after application. Most adhesives on the market must be light cured. The application without light curing is of interest for this trial. The application of the material is in accordance with the instruction for use.

A)

B)

Fig 1: A) [redacted] delivered in the VivaPen with the blue cannula for the dual curing adhesive and B) VivaPen with with protective sleeve.

5.1.2 Control Intervention (standard/routine/comparator)

This section is not applicable.

Data will be compared with coded results of the control group (Adhese Universal) of a previously conducted clinical investigation ("Clinical evaluation of a new dual cure universal adhesive (Adhese Universal DC) in the indirect restorative therapy: A randomised, controlled clinical trial", NCT04475679).

6. STATISTICAL METHODS

The trial is a continuation of the clinical trial "Clinical evaluation of a new dual cure universal adhesive (Adhese Universal DC) in the indirect restorative therapy: A randomised, controlled clinical trial (NCT04475679)". The methodology, the endpoints and the hypothesis are the same. The test product [redacted] is a further development of Adhese Universal DC. In the planned clinical investigation, the test group will be compared to the control group (Adhese Universal) of the study mentioned above. The statistical considerations of the already performed study are re-used and are therefore mentioned in the paragraphs below.

6.1 Hypothesis

The null hypothesis is that there is a statistically significant difference between control and test group with respect to postoperative hypersensitivity.

The alternative hypothesis is that there is no difference between control and test group with regard to postoperative hypersensitivity.

We do not expect in this equivalence study to find any statistical significance between control and test group with regard to postoperative hypersensitivity.

6.2 Determination of Sample Size

The number of samples estimated to be needed for each study arm is 40 to achieve the objective. The G*Power sample calculator software Version 3.1.9.2 was used to determine the sample size, at a power of 80% and a type I error of 0.1 (Faul et al., 2007; Faul et al., 2009).

Different to the previous study, this time a drop-out of 5 restorations is assumed. Therefore, the sample size aimed at is 45 instead of 40.

6.3 Statistical criteria of termination of the investigation

The study will be terminated if more than 20% of the restorations fail (FDI grade 5 on any of the criteria).

The study would be terminated prior to reaching baseline if more than 5 treated teeth were found to have post-operative hypersensitivity (FDI 11 >grade 3).

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 that received a final restoration 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 completion of the 1-month recall. The analysis will be done by the principal investigator within 3 months after the collection of the 1-month data.

A non-parametric test (Mann-Whitney) between two independent groups will be used to compare the level of postoperative hypersensitivity (FDI 11) between the control and the test group.

6.4.3 Secondary Analyses

Regarding the secondary outcomes, the analysis will be done after completion of the 1, 6, 12, 24, 36 and 60 months recall examinations, respectively. The analysis will be done by the principal investigator within 3 months after the collection of the baseline data. It will be a descriptive analysis.

6.4.4 Interim analyses

The interim analysis will be done after the collection of data of the 6, 12, 24, 36 and 60 months recall examinations of all restorations. The analysis will be done by the principal investigator within 3 months after the collection of the recall data. In case of any further therapy related to the restorative intervention the restoration maybe regarded either as failure or as drop-out. Stopping guidelines are not necessary since the restorations are final interventions.

No adjustment methods are needed for this clinical study since the interim analysis are for safety stopping reasons only.

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

If a participant withdraws before all baseline examinations are completed, he/she will be replaced by another participant. Once all baseline examinations are completed, drop-outs are no longer replaced. There have only been few drop-outs and no-shows in the internal clinic in previous clinical trials so far. However, a drop-out of 5 restorations was assumed. Therefore, 45 instead of 40 restorations will be placed.

7. REFERENCES

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