Study Title	Prospective, randomized, split-mouth study evaluating the clinical performance of a new dental adhesive, 3M™ Scotchbond™ Universal Plus Adhesive, compared to 3M™ Scotchbond™ Universal Adhesive when used with 3M™ Filtek™ Universal Restorative to restore Class V non-carious cervical lesions
Study Number	EM-11-050068 (ClinicalTrials.gov Identifier: NCT05361746)
CIP Version	Version 6
Date	12/09/2022 11:34:18 AM CST
Name of Device Under Investigation	Scotchbond™ Universal Plus Adhesive
Sponsor Address	3M Company 3M Healthcare Business Group 3M Center – 270-4N St. Paul, MN. 55144
Manufacturer Address	3M Deutschland GmbH 3M Oral Care ESPE Platz 82229 Seefeld, Germany 3M

ELECTRONIC SIGNATURES:

Signer	Role	Date Signed
ACVCMZZ:Okeefe Lauren	Clinical	December 08, 2022 12:24:30 PM CST
us267473:Myhre Paula E	Clinical	December 08, 2022 09:44:42 AM CST
GES10885:Wittig-Barger Ulrice	Regulatory and Compliance	December 09, 2022 09:38:12 AM CST
ge320710:Syrek Andreas	Medical Monitor	December 09, 2022 11:34:16 AM CST

INVESTIGATOR STATEMENT

Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

This clinical investigation shall be conducted in accordance with ISO-14155:2011 and future versions, US FDA 21 CFR parts 812, 50, 54, 56, and any regional or national regulations, as appropriate.

The clinical investigation shall not begin until the required approval/favorable opinion from the Institutional Review Board (IRB)/Ethics Committee (EC) and regulatory authority (if applicable) has been obtained and permission to proceed has been received from the study Sponsor. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed.

I have read the Clinical Investigation Plan (CIP), including all appendices, as well as supporting study related documents and I agree that it contains all necessary details for me and my staff to conduct this study as described. I agree to record all adverse events/ deviations and report those adverse events/ deviations to the Sponsor per this CIP and IRB/EC per local requirements. I always agree to maintain product accountability and ensure security of study materials. I agree to comply with financial disclosure requirements.

All Subjects will sign and date the approved Informed Consent before any study procedures are conducted, as applicable

I will ensure that all Subjects meet inclusion criteria before enrolling them in the study.

I agree to maintain and retain records as required by this Clinical Investigation Plan.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date of Signature:	

ABBREVIATIONS/ACRONYMS

AE	adverse event
ADE	adverse device effect
AFR	annual fail rate
BPA	bisphenol A
CFR	code of federal regulations
CIP	clinical investigation plan
CRF	case report form
d	days
DCA	dual-core activator
DD	device deficiency
EC	ethics committee
eCRF	electronic case report form
EDTA	ethylenediamine tetraacetic acid
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalized estimating equation
GI	glass ionomer
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IDE	investigational device exemption
IFU	instructions for use
IRB	Institutional Review Board
mos	months
MP	monitoring plan
NCCL	non-carious cervical lesion
NSAID	non-steroidal anti-inflammatory
PHI	Personal Health Information
PI	Principal Investigator
PPS	Per Protocol Set
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBU	Scotchbond Universal
SBU+	Scotchbond Universal Plus
SD	standard deviation
SE	self-etch

SOP	standard operation procedure
SS	Safety Set
TE	total-etch
USA	United States of America
USADE	unanticipated serious adverse device effect
wk	week
yr	year

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1. SUMMARY

Study Title	Prospective, randomized, split-mouth study evaluating the clinical performance of a new dental adhesive, 3M™ Scotchbond™ Universal Plus Adhesive, compared to 3M™ Scotchbond™ Universal Adhesive when used with 3M™ Filtek™ Universal Restorative to restore Class V non-carious cervical lesions
Study Type	Post-market, interventional
Principal Investigator (PI)	**Name**: John O. Burgess, DDS, MS, DMD **Title:** Clinical Professor of Research **Site:** Louisiana State University, School of Dentistry
Device under Investigation Summary	The investigational device in this study is Scotchbond™ Universal Plus (SBU+) Adhesive, which is manufactured by 3M. It is a light-curing, single-component dental adhesive that is compatible with light-, dual-, and self-cure composite filling materials, cements, and core build-up materials. The adhesive can be used for "self-etch" procedures, selective enamel etching procedures, or "total-etch/etch-and-rinse" procedures, and a separate dual-cure activator (DCA) is not necessary. The intended purpose of SBU+ Adhesive is to be used as a bonding-promoting substance between tooth substance and dental restorations. It may also be used for bonding methacrylate-based fissure sealants and as a bonding agent for repair of restorations. The intended users of Scotchbond™ Universal Plus Adhesive are educated dental professionals who have theoretical and practical knowledge on usage of dental products.
Sponsor	3M 3M Healthcare Business Group 3M Center – 270-4N St. Paul, MN. 55144
Purpose	The purpose of this study is to confirm the clinical effectiveness of Scotchbond™ Universal Plus Adhesive by comparing it with the predicate device.
Design	This is a prospective, controlled, within-subject, randomized, double-blind, single-center study that will enroll Subjects scheduled to undergo Class-V non-carious cervical lesion (NCCL) restorations on a minimum of two teeth. The study will enroll enough subjects to perform a minimum of 110 restorations.

Selection of Subjects	In order to be considered eligible for randomization, Subjects must meet all the inclusion criteria and none of the exclusion criteria. Subjects are to be assessed for eligibility no more than 21 days prior to the planned oral care procedures, and eligibility will be confirmed on the day of the restorations. If, for any reason, a Subject's restorative appointment is delayed beyond 21 days after screening, then the Subject will be reassessed to ensure that they still meet the eligibility criteria. Subjects who have provided informed consent but who do not meet all eligibility criteria at the time of the restorations will not be eligible for randomization, will not qualify for participation in the study, and will be considered a screen failure. Inclusion Criteria: Subjects may be included that meet the following criteria: 1. Subject is at least 18 years of age at the time of consent 2. Subject is able to provide their own informed consent 3. Subject has a minimum of two teeth that: • have non-carious Class V lesions that are at least 1.5 mm deep • are not devitalized • have not undergone root canal treatment 4. Subject has an Approximal Plaque Index score ≤ 40% as assessed via explorer and without the use of plaque-disclosing agents 5. Subject is able and willing to return for all scheduled study visits 6. Subject meets the Level-I or Level-II classification criteria of the American Society of Anesthesiologists (ASA) Physical Status Classification System For Dental Patient Care Exclusion Criteria: Subjects may not be included that meet any of the following criteria: 1. Subject has any of the following: • rampant caries • chronic periodontitis • salivary gland dysfunction 2. Subject is unable, for any reason, to tolerate the procedure time required to place the restorations 3. Subject has unacceptable oral hygiene (eg, chronic moderate to heavy plaque accumulation along the gumline) 4. Subject has known sensitivity to the study product components (ie, acrylate)

	5. Subject is planned to be enrolled in another investigational trial that requires additional interventions at any time during the study
Device Regulatory Classification	In accordance with regulation number 21CFR872.3200 from the United States Food & Drug Administration (FDA), Scotchbond™ Universal Plus Adhesive is a 510(k)–cleared, Class II device (K192961) with the following indication for use: **Direct Indications:** • Bonding for all methacrylate-based light-, dual-, and self-cure composite or compomer filling materials • Root surface desensitization • Bonding of methacrylate-based fissure sealants • Protective varnish for glass ionomer fillings • Repair of composite and compomer fillings • Sealing of cavities prior to placement of amalgam restorations **Indirect Indications:** • Cementation of indirect restorations in combination with RelyX Universal and other resin cements (follow applicable Instructions for Use) • Bonding for all methacrylate-based light-, self-, and dual-cure core build-up materials and cements • Cementation of veneers when combined with RelyX Veneer Cement • Intraoral repair of composite restorations, porcelain fused to metal, and all-ceramic restorations without extra primer • Sealing of cavities and preparation of tooth stumps prior to temporary cementation of indirect restorations
Primary Objective(s)	The primary objective of this study is to compare the clinical efficacy of Scotchbond™ Universal Plus Adhesive with Scotchbond™ Universal Adhesive when used in total-etch mode restoration of Class-V NCCLs using Filtek™ Universal Restorative material in adult patients.
Endpoint(s)	**Primary Endpoint(s)** The primary endpoints, which are based partly on the FDI World Dental Federation criteria, are the following criteria at the final assessment (24 months): • the proportion of teeth with partial or complete loss of the restoration materials • marginal adaptation score

	Secondary Endpoint(s) The secondary endpoints are the following modified FDI World Dental Federation criteria: • the proportion of teeth with partial or complete loss of the restoration materials at baseline, 6 months, and 12 months • marginal adaptation score at baseline, 6 months, and 12 months • fracture scores at baseline, 6 months, 12 months, and 24 months • incidence of secondary caries at baseline, 6 months, 12 months, and 24 months **Additional/Exploratory Endpoints** The exploratory endpoints are the following criteria: • surface staining score at baseline, 6 months, 12 months, and 24 months • marginal staining score at baseline, 6 months, 12 months, and 24 months • color match score at baseline, 6 months, 12 months, and 24 months • polish retention/luster score at baseline, 6 months, 12 months, and 24 months • hypersensitivity (subject self-assessed) at baseline • hypersensitivity and tooth vitality at 6 months, 12 months, and 24 months • time to restoration failure • patient satisfaction at baseline, 6 months, 12 months, and 24 months **Safety Endpoints** The safety endpoint is the incidence of AEs.
Randomization	Subjects who satisfy all inclusion criteria and none of the exclusion criteria and who have provided informed consent will be eligible for randomization, which will occur immediately after teeth preparation but before the initial application of any adhesive agent. Randomization of the teeth, which will be numbered using the Universal Numbering System, to study treatments will be centralized, electronic, and web-based. Either two or four teeth for each Subject will be randomized in a 1:1 ratio with at least half of the teeth (ie, 1 tooth for Subjects with 2 eligible teeth or 2 teeth for Subjects with 4 eligible teeth) randomized to undergo restoration(s) using SBU+ Adhesive (Treatment group) and the other half of the teeth undergoing restoration(s) using SBU Adhesive (Control group). Study teeth will be paired according to lesion depth and assigned randomization

	numbers starting with the lowest tooth number. For Subjects with randomization of 4 teeth, randomization numbers will be assigned in order, starting with the pair with the lowest tooth number based on the Universal Numbering System. The first material for assignment according to the randomization schedule will be assigned to the lower tooth number for each pair.

Duration of the Study	The entire duration of the study is expected to last approximately 3 years, with individual Subject participation expected to last up to 2 years (± 45 days). Subject participation will include the following:
	• Screening visit (no more than 21 days before the restoration procedure)
	• Restoration procedures & baseline assessments – Day 0
	• Subject-provided hypersensitivity self-assessment (by phone) – 7 days (± 3 days) post-restoration.
	• Follow-up visits after the restorations at:
	  ○ 6-months (± 14 days)
	  ○ 1-year (± 30 days)
	  ○ 2 years (± 45 days)
	Subjects may participate in additional unscheduled visits as needed during the study if evaluation of any study tooth is required outside of the scheduled study visits due to subject concern.

Sponsor Study Contact	**Name:** Paula Myhre **Address:** 3M Center, 270-4N-04, St. Paul, MN 55144 **Telephone:** [redacted] **Email:** [redacted]
Medical Monitor Contact	**Name:** Andreas Syrek, Dr. Med. Dent., PhD **Address:** 3M Deutschland GmbH, Espe Platz, 82229 Seefeld, Germany **Telephone:** [redacted] **Email:** [redacted]

2. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The investigational device in this study is Scotchbond™ Universal Plus (SBU+) Adhesive, which is manufactured by 3M (Table 2-1). SBU+ Adhesive is a light-curing, single-component dental adhesive that is compatible with light-, dual-, and self-cure composite filling materials, cements, and core build-up materials. The adhesive can be used for "self-etch" procedures, selective enamel etching procedures, or "total-etch/etch-and-rinse" procedures, and a separate dual-cure activator (DCA) is not necessary. SBU+ Adhesive is radiopaque (radiopacity similar to dentin) and does not contain any bisphenol A (BPA) derivative. The intended purpose of SBU+ Adhesive is to be used as a bond-promoting substance between the tooth and dental restorations. It may also be used for bonding methacrylate-based fissure sealants and as a bonding agent for repair of restorations. The intended users of SBU+ Adhesive are educated dental professionals who have theoretical and practical knowledge on usage of dental products.

The comparator product (ie, Control product) for the investigational device will be Scotchbond™ Universal (SBU) Adhesive, which is also manufactured by 3M (Table 2-1). SBU Adhesive bonds methacrylate-based restoratives, cement and sealant materials to dentin, enamel, glass ionomer and various indirect restorative substrates (metals, glass ceramics, alumina and zirconia) without an extra primer step. SBU Adhesive can be used reliably in total-etch, self-etch or selective-etch mode for both direct and indirect restorations. The primary use is with light-cured materials, however, when used in conjunction with a separate activation solution, Scotchbond™ Universal DCA Dual Cure Activator, it has the capability to also bond to self- or dual-cure composite and cement materials that rely on self-cure polymerization.

In this study, the investigative device and the comparator product will be applied and polymerized using a curing light before applying 3M™ Filtek™ Universal Restorative.

Table 2-1: Device Information

Investigational Device		**Comparator Device**	
Device Name	**Manufacturer**	**Device Name**	**Manufacturer**
Scotchbond™ Universal Plus Adhesive	3M	Scotchbond™ Universal Adhesive	3M

2.1. DEVICE REGULATORY CLASSIFICATION

In accordance with regulation number 21CFR872.3200 from the United States Food & Drug Administration (FDA), SBU+ Adhesive is a 510(k)–cleared, Class II device (K192961) with the following indication for use:

Direct Indications:

- Bonding for all methacrylate-based light-, dual-, and self-cure composite or compomer filling materials
- Root surface desensitization
- Bonding of methacrylate-based fissure sealants
- Protective varnish for glass ionomer fillings
- Repair of composite and compomer fillings
- Sealing of cavities prior to placement of amalgam restorations

Indirect Indications:

- Cementation of indirect restorations in combination with RelyX Universal and other resin cements (follow applicable Instructions for Use)
- Bonding for all methacrylate-based light-, self-, and dual-cure core build-up materials and cements
- Cementation of veneers when combined with RelyX Veneer Cement
- Intraoral repair of composite restorations, porcelain fused to metal, and all-ceramic restorations without extra primer
- Sealing of cavities and preparation of tooth stumps prior to temporary cementation of indirect restorations

2.2. INTENDED USE OF DEVICE

For the teeth of Subjects in this study that are randomized into the Treatment arm, SBU+ Adhesive will be applied and polymerized using a curing light before applying 3M™ Filtek™ Universal Restorative. For this study, SBU+ Adhesive will be used in accordance with its cleared labeling and indications for use and is, therefore, exempt from the investigational device exemptions (IDE) regulation because it meets the conditions for an exempt investigation as provided in paragraph C of 21CFR812.2 from the FDA. The indications, precautionary measures, and instructions can be found in the IFU document for SBU+ Adhesive.

3. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

3.1. BACKGROUND

Resin Composite Restorations

Resin composite restorations are a commonly used treatment option for dental caries and non-carious cervical lesions (NCCLs).[1] Upon application, these restorations undergo extreme challenges in the oral cavity, including mechanical degradation (eg, thermocycling from hot and cold food and beverage consumption), chemical and biochemical degradation, short-term elution of unreacted composite monomers, and long-term enzymatic breakdown due, in part, to hydrolase/esterase activity in the oral cavity.[1] For these reasons and others, composite restoration failure is a major concern and can lead to costly repair or replacement of the restoration, potentially more costly treatments (eg, root canal therapy), or eventual loss of the tooth.[1] The leading cause for restoration failure is secondary caries occurring at the margin between the restoration materials and the remaining tooth[2], and dental resin adhesives critically effect the performance of resin restorations.[1] Therefore, this study focuses on restoration retention and marginal integrity (ie, marginal adaptation) when using two different dental resin adhesives to bond a resin composite to the dentin and enamel of Class-V NCCLs.

Classification of Dental Resin Adhesives & Retention in Class-V NCCLs

Contemporary dental resin adhesives are generally classified by their mode of application, including the following: (i) self-etch (SE) adhesives, which use a non-rinse acidic monomer to simultaneously condition and prime the enamel/dentin; (ii) total etch (TE) adhesives, also known as etch-and-rinse adhesives, which involved the application of acid followed by rinsing; (iii) selective etch adhesives, whereby an etch/rinse application occurs only on the enamel surrounding a lesion; and (iv) glass ionomer (GI) adhesives, which micromechanically bond to the tooth structure following an acid pre-treatment.[1, 3] A systematic review by Peumans et al in 2014 compared the retention rates for different classes of adhesives when used in restorations of Class-V NCCLs – the review included 87 comparative clinical trials involving 78 different adhesive materials.[4] GI adhesives had the lowest annual fail rate (AFR) with a mean (± SD) of 2.0% (1.4%), followed by 3-step TE adhesives, which had a mean (± SD) AFR of 3.1% (2.0%).[4] SE adhesives had a mean (± SD) AFR ranging from 4.4% (4.6%) to 4.7% (5.7%) for 1-step and 2-step applications, respectively[4], and two-step TE adhesives had the lowest AFR of all the adhesive classes reviewed, with a mean (± SD) AFR of 5.8% (4.9%).[4]

Scotchbond™ Universal Adhesives

Scotchbond™ Universal Plus Adhesive (SBU+), which is based on the chemistry of a predicate device, Scotchbond™ Universal Adhesive (SBU), is a multimode dental resin adhesive that can be used in self-etching or total-etching (with or without selective enamel etching) procedures. While

there have been no publications regarding clinical studies of SBU+ Adhesive, there has been 1 publication reporting on the laboratory evaluation of SBU on extracted human teeth (ie, *ex vivo* study) and 15 publications reporting on clinical trials that included the use of SBU.[5-19] The *ex vivo* study assessed microtensile bond strength, nanoleakage, and *in situ* degree of conversion using extracted, caries-free, human third molars.[13] Two publications were related to the treatment of caries in primary teeth, with one of the publications being a trial design only[10, 14], and two other publications reported on Class I/Class II cavity restorations.[5, 7] The remaining 10 publications reported the use of SBU in restoration of NCCLs.[6, 8, 9, 11, 12, 15-19]

Three publications resulting from two independent studies compared application strategies in NCCLs, comparing restorations applied using SBU via an SE procedure (with or without selective enamel etching) to restorations applied using SBU via a TE procedure (with moist or dry dentin).[11, 12, 16] All three studies reported no significant differences between application strategies regarding the restoration retention rate or marginal adaptation scoring – marginal adaptation was reportedly satisfactory for all Subjects in the studies – when using SBU in SE mode or TE mode, regardless of selective enamel etching or dentin moisture at the time of application.[11, 12, 16] Also, the three studies reported that no secondary caries occurred in any of the treatment groups.[11, 12, 16] The retention rate for restorations that used SBU adhesive with an SE procedure ranged from 94%-100% at 6 months, 94%-98% at 18 months, and 88.9%-97.8% at 36 months, depending on the study and selective enamel etching. The retention rate for restorations that used SBU adhesive with a TE procedure ranged from 98%-100% at 6 months and at 18 months and was 97.8% at 36 months, depending on the study and moisture state of dentin.[11, 12, 16]

Three other studies have compared NCCL restorations using SBU with restorations using other types of adhesives (eg, other types of acrylate adhesives used via SE or TE procedures or GI adhesives).[9, 17, 19] In these three studies, there were no significant differences between restorations using SBU adhesive when used in either TE or SE mode with restorations using other adhesive types regarding the restoration retention rate, marginal adaptation scoring, or secondary caries.[9, 17, 19] Marginal adaptation scores for Subjects treated with SBU or any of the other adhesive types decreased during the course of the studies[9, 17, 19], and Lawson et al reported a significant decrease in marginal adaptation scoring from baseline to 24 months for SBU and two other acrylate adhesives.[9] The retention rate for restorations that used SBU adhesive with an SE procedure in these three studies was 95.9% at 12 months and ranged from 93.3%-94.7% at 24 months, depending on the study; the retention rate for restorations that used SBU adhesive with a TE procedure was 95.9% at 12 months and ranged from 94.7-100% at 24 months, depending on the study.[9, 17, 19]

Lastly, Perdigao et al compared NCCL restorations using SBU adhesive applied in TE mode or SE mode, with each type of adhesive being applied with or without the addition of a hydrophobic bonding agent.[15] In this study, the retention rate after 36 months for restorations applied using SBU

adhesive via SE mode were significantly lower (76% and 86.2% for applications with and without the hydrophobic agent, respectively) when compared to those applied using SBU via TE mode (100% retention for applications with or without the hydrophobic agent), regardless of whether the hydrophobic agent was used.[15] Marginal adaptation scores and the incidence of secondary caries after 36 months were not significantly different between any of the groups.[15]

Since there have been no publications regarding clinical studies of SBU+ Adhesive to date, this study aims to confirm the safety and efficacy of SBU+ Adhesive in comparison to the predicate device.

3.2. RATIONALE FOR STUDYING THE SPECIFIC POPULATION/CONDITION

Subjects with Class-V NCCLs were selected as the specific population/condition for this study since NCCLs are commonly used to test the clinical effectiveness of dental adhesives. In fact, a systematic review in 2014 yielded over 178 different comparative clinical trials analyzing various adhesives when used for Class-V NCCLs.[4] Class-V NCCLs are also recommended by the American Dental Association to test the clinical effectiveness of dental adhesives due to a number of reasons, including: (i) the cervical lesions do not provide any macromechanical retention and ineffective bonding will result in loss of the restoration; (ii) the restoration contains both enamel and dentin margins; (iii) the lesions are widely available and are generally seen in multiple teeth, thus facilitating patient selection and study design; and (iv) the mechanical properties of the composite resin is less important to the outcome than the actual performance of the adhesive.[20] Subjects with Class-V NCCLs that are at least 1.5 mm deep were selected for this study since the comparator device, SBU Adhesive, was previously assessed in a clinical trial enrolling Subjects with NCCLs of at least this depth.[9] Finally, Class-V NCCL restorations are one of the less durable restoration types and have a relatively higher loss of retention, marginal excess, and secondary caries.[20]

3.3. RATIONALE FOR STUDY DESIGN

To have a high level of evidence, a prospective, controlled, within-subject, randomized, double-blind, single-center trial was the design selected for this study. The within-subject design includes randomizing at least one tooth of a Subject to the Treatment arm and at least one other tooth to the Control arm, thereby allowing each Subject to be exposed to both treatment arms. SBU Adhesive was selected as the comparator (Control product) as it is the predicate device for SBU+ Adhesive and, as mention in Section 3.1, has been studied previously in self-etch and total-etch mode restorations of NCCLs.[5-19] Total-etch mode restorations have been selected for this study since previous studies have shown a slightly higher retention rate, albeit not a significant difference, for restorations using SBU in TE mode when compared to those that used SBU in SE mode, especially for longer post-restoration time-points.[15]

The primary purpose of this study is not to test any formal statistical hypothesis but to confirm the effectiveness of the investigative device; therefore, the sample size was not derived statistically. It is hypothesized that the SBU+ Adhesive will have a similar clinical performance as its predicate regarding its intended use as a bonding agent. The primary endpoints of this study are restoration retention and marginal adaptation scoring at the final assessment (24 months after restoration), which are based on the modified criteria of the FDI World Dental Federation.[21] The follow-up time period of 24 months was selected based on a previous 2-year study assessing the predicate device.[9]

4. BENEFITS AND RISKS OF THE INVESTIGATIONAL DEVICE, CLINICAL PROCEDURE, AND CLINICAL INVESTIGATION

4.1. BENEFITS OF THE DEVICE

The clinical benefit of the investigational device is that it holds direct restorations in place, holds indirect restorations in place when used in combination with a luting agent, and helps in sealing and desensitization.

4.2. RISKS OF THE DEVICE

Dental adhesives are commonly used medical devices throughout dental care settings that have resulted in few problems. A potential risk to the Subjects in this study includes an allergic reaction by skin contact. If an allergic reaction occurs, the Subject should seek medical attention as needed, the product should be removed if necessary, and future use of the device should not occur.

4.3. ANTICIPATED ADVERSE DEVICE EFFECTS

Due to substances in the investigative device and the comparator device used for this study, it is anticipated that the device may cause an allergic reaction by skin contact in certain individuals. Symptoms of allergic reactions (eg, erythema) are being captured as adverse events in this study.

4.4. RESIDUAL RISKS

The Subjects will undergo long-term exposure to polymerized material, including polymerized acrylate, which is more inert (ie, less sensitizing) than monomeric acrylate. Therefore, residual risks are expected to be minimal.

4.5. RISK OF INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

There is minimal risk of interaction between the investigative device or the comparator device and concomitant medical treatments. The manufacturer advises against the use of substances such as desensitizers, disinfectants other than chlorhexidine-containing agents, astringents, dentin sealants, and rinsing solutions before applying SBU+ Adhesive as residues of these substances can be

detrimental to the bonding strength of the device. Only chlorhexidine-containing solutions are permitted during tooth preparation prior to restoration in this study (see Section 6.4.6).

4.6. MITIGATION OF RISK

Risks related to the device may be mitigated or controlled through appropriate selection of study Subjects for inclusion into this study, adherence to this Clinical Investigation Plan (CIP), and reporting of Adverse Events (AEs), Device Deficiencies (DDs) and deviations to the Sponsor. For example, Subjects with known acrylate allergies are excluded from participating in this study (see Section 6.3.1.2).

4.7. RATIONALE FOR BENEFIT-RISK RATIO

Based upon the risks and benefits listed above and adherence to this Clinical Investigation Plan, the study Subjects are at no greater risk of harm than individuals being treated for similar lesions who are not participating in this study. The use of SBU+ Adhesive is being used in accordance with its intended use consistent with standard dental treatment plans for patients not participating in this study.

5. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

5.1. PURPOSE

The purpose of this study is to confirm the clinical effectiveness of Scotchbond™ Universal Plus Adhesive by comparing it with the predicate device.

5.2. PRIMARY OBJECTIVE(S)

The primary objective of this study is to compare the clinical efficacy of Scotchbond™ Universal Plus Adhesive with Scotchbond™ Universal Adhesive when used in total-etch mode restoration of Class-V NCCLs using Filtek™ Universal Restorative material in adult patients.

5.3. ENDPOINT(S)

5.3.1. Primary Endpoint(s)

The primary endpoints, which are based partly on the FDI World Dental Federation criteria[21], are the following criteria at the final assessment (24 months):

- the proportion of teeth with partial or complete loss of the restoration materials
- marginal adaptation score

5.3.2. Secondary Endpoint(s)

The secondary endpoints are the following modified FDI World Dental Federation criteria:

- the proportion of teeth with partial or complete loss of the restoration materials at baseline, 6 months, and 12 months
- marginal adaptation score at baseline, 6 months, and 12 months
- fracture scores at baseline, 6 months, 12 months, and 24 months
- incidence of secondary caries at baseline, 6 months, 12 months, and 24 months

5.3.3. Additional/Exploratory Endpoints

The exploratory endpoints are the following criteria:

- surface staining score at baseline, 6 months, 12 months, and 24 months
- marginal staining score at baseline, 6 months, 12 months, and 24 months
- color match score at baseline, 6 months, 12 months, and 24 months
- polish retention/luster score at baseline, 6 months, 12 months, and 24 months
- hypersensitivity (subject self-assessed) at baseline
- hypersensitivity and tooth vitality score at 6 months, 12 months, and 24 months
- time to restoration failure
- patient satisfaction at baseline, 6 months, 12 months, and 24 months

5.3.4. Safety Endpoints

The safety endpoint is the incidence of AEs.

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1. DESIGN

This is a prospective, controlled, within-subject, randomized, double-blind, single-center study that will enroll Subjects scheduled to undergo Class-V NCCL restorations on a minimum of two teeth. The study will enroll enough subjects to perform a minimum of 110 restorations from a single site located in New Orleans, LA, USA. A minimum of two restorations (two teeth) and a maximum of four restorations (four teeth) per eligible Subject may be included, with each tooth restoration using only one type of adhesive. For Subjects needing treatment of 3 teeth or more than 4 teeth, only a

pair of teeth (ie, 2 teeth) or two pairs of teeth (ie, 4 teeth), respectively, will be included in the study – study teeth will be paired according to lesion depth. All teeth needing treatment that are not included in the study will be treated by the dentist using the standard of care.

Subjects will be seen during Screening (no more than 21 days before the restoration procedure), on the day of the restoration procedure, 6 months (± 14 days) after the restorations, 1 year (± 30 days) after restorations, and 2 years after restorations (± 45 days). Subjects will be contacted by phone 1 week (± 3 days) after restorations for baseline assessment of tooth hypersensitivity. Subjects may participate in additional unscheduled visits as required during the study if evaluation of any study tooth is required outside of the scheduled study visits. Unscheduled visits may be initiated by either the Investigator or the Subject. The entire duration of the study is expected to last approximately 3 years, with individual Subject participation expected to last up to 2 years (± 45 days).

To help minimize or avoid bias in the study, randomization of study teeth will occur after teeth preparation (see Section 6.4.6.1) but before the initial application of any adhesive. All assessments will be performed by two dental examiners that are independent of the dentist that placed the restorations and are blinded to the treatment arms. Subjects will also be blinded to the treatment arms. All examiners will be trained and calibrated for the scoring criteria before any Subject assessment occurs (see Section 6.4.7), and examiners will be retrained and recalibrated if any new evaluator is added to the list of assessors. After the second examiner has completed their assessments, then the examiners will compare their evaluations and a consensus will be reached for each of the scoring criteria at each visit. A consensus will be reached before the Subject leaves the visit. The consensus assessments will be entered into the Case Report Form (CRF).

6.2. INVESTIGATIONAL DEVICE(S) AND COMPARATOR(S)

Restorations will include the use of 3M™ Filtek™ Universal Restorative to match and blend to the color of the surrounding dentition. On one tooth, the restorative material will be bonded with SBU+ Adhesive (Treatment arm), and restorative material on the other tooth will be bonded using SBU Adhesive (Control arm).

6.3. SUBJECT ENROLLMENT

Subject enrollment will remain open until enough subjects are enrolled and confirmed eligible to perform 110 restorations.

6.3.1. Enrollment Criteria

In order to be considered eligible for randomization, Subjects must meet all the inclusion criteria listed in Section 6.3.1.1 and none of the exclusion criteria listed in Section 6.3.1.2. Subjects should be assessed for eligibility no more than 21 days prior to the planned oral care procedures, and

eligibility will be confirmed on the day of the restorations. If, for any reason, a Subject's restorative appointment is delayed beyond 21 days after consent, then the Subject will be reassessed to ensure that they still meet the eligibility criteria. Subjects who have provided informed consent but who do not meet all eligibility criteria at the time of the restorations will not be eligible for randomization, will not qualify for participation in the study, and will be considered a screening failure.

6.3.1.1. Inclusion Criteria

Subjects may be included that meet the inclusion criteria in Table 6.3.1.1-1.

Table 6.3.1.1-1: Inclusion Criteria

Number	Inclusion Criteria
1	Subject is at least 18 years of age at the time of consent
2	Subject is able to provide their own informed consent
3	Subject has a minimum of two teeth that: • have non-carious Class V lesions that are at least 1.5 mm deep • are not devitalized • have not undergone root canal treatment
4	Subject has an Approximal Plaque Index score ≤ 40% as assessed via explorer and without the use of plaque-disclosing agents
5	Subject is able and willing to return for all scheduled study visits
6	Subject meets the Level-I or Level-II classification criteria of the American Society of Anesthesiologists (ASA) Physical Status Classification System For Dental Patient Care

6.3.1.2. Exclusion Criteria

Subjects must be excluded from participating in this study if they meet any of the criteria in Table 6.3.1.2-1.

Table 6.3.1.2-1: Exclusion Criteria

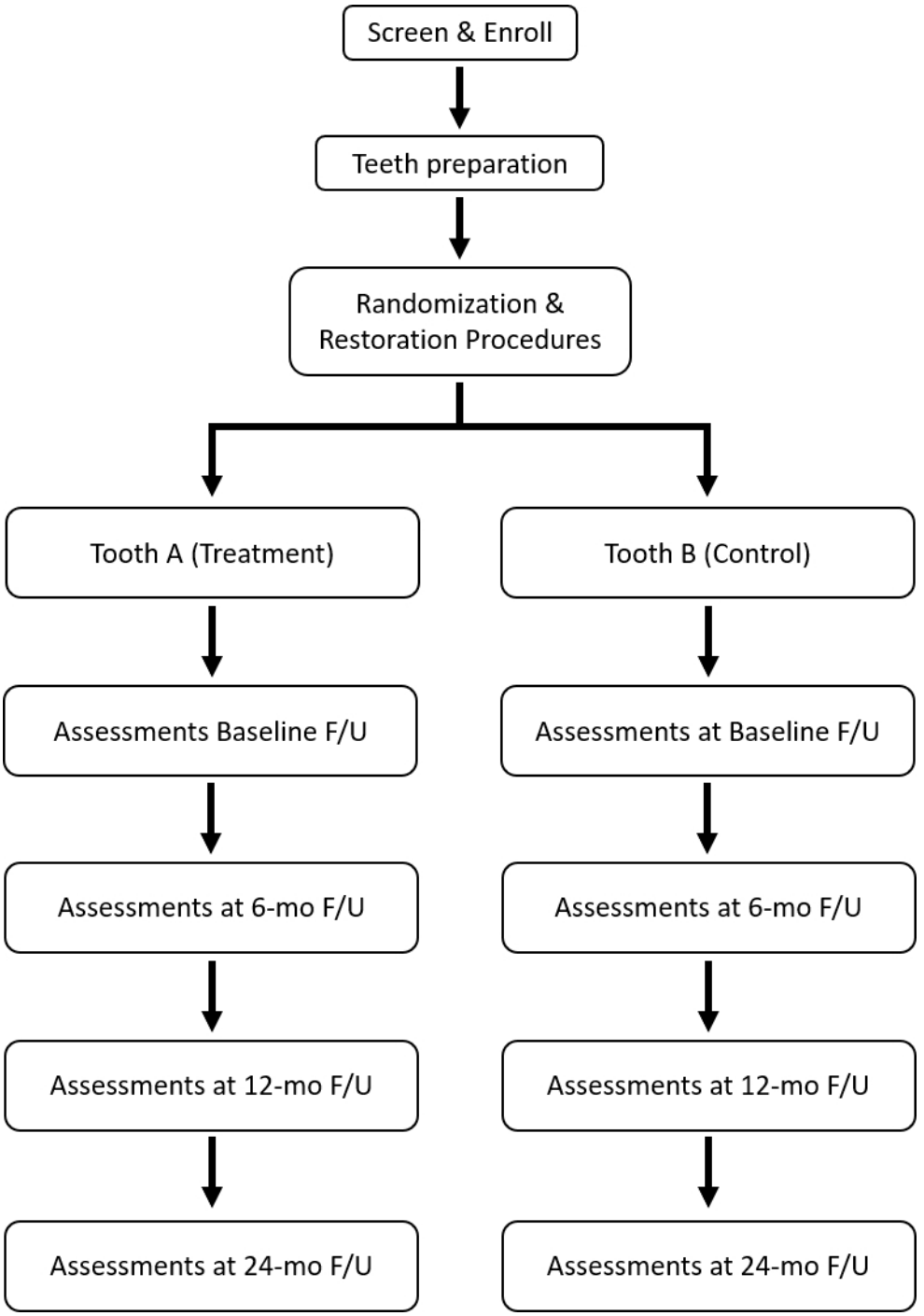
Number	Exclusion Criteria
1	Subject has any of the following: • rampant caries • chronic periodontitis • salivary gland dysfunction

Number	Exclusion Criteria
2	Subject is unable, for any reason, to tolerate the procedure time required to place the restorations
3	Subject has unacceptable oral hygiene (eg, chronic moderate to heavy plaque accumulation along the gumline)
4	Subject has known sensitivity to the study product components (ie, acrylate)
5	Subject is planned to be enrolled in another investigational trial that requires additional interventions at any time during the study

6.4. PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and data that will be collected at each visit for the duration of the study. The data listed below, and any relevant safety data will be collected during this study.

6.4.1. Procedures and Assessments Diagram



6.4.2. Demographics and Subject Characteristics

After a Subject signs the informed consent form (ICF; see Section 13) and before the initial tooth restoration, the following demographic data and Subject characteristics will be collected and documented:

- Age
- Sex
- Race
- Ethnicity
- Tooth numbers for treated teeth
- Estimated depth of each study NCCL
- Date of restoration

6.4.3. Vital Signs

No vital signs (eg, pulse, temperature, blood pressure, etc) or laboratory assessments will be captured as part of this study.

6.4.4. Randomization and Subject and Teeth Numbering

Subjects who sign an ICF will be assigned a unique Subject identification number, and study data will be reported according to this unique Subject identifier. The unique Subject identification number will not contain information that could identify the Subject.

Subjects who satisfy all inclusion criteria and none of the exclusion criteria and who have provided informed consent will be eligible for randomization, which will occur immediately after teeth preparation (see Section 6.4.6) but before the initial application of any adhesive agent. Randomization of the teeth, which will be numbered using the Universal Numbering System, to study treatments will be centralized, electronic, and web-based. Either two or four teeth for each Subject will be randomized in a 1:1 ratio with at least half of the teeth (ie, 1 tooth for Subjects with 2 eligible teeth or 2 teeth for Subjects with 4 eligible teeth) randomized to undergo restoration(s) using SBU+ Adhesive (Treatment) and the other half of the teeth undergoing restoration(s) using SBU Adhesive (Control). Study teeth will be paired according to lesion depth and assigned randomization numbers starting with the lowest tooth number. For Subjects with randomization of 4 teeth, randomization numbers will be assigned in order, starting with the pair with the lowest tooth number based on the Universal Numbering System. The first material for assignment according to the randomization schedule will be assigned to the lower tooth number for each pair.

If a screened Subject does not meet inclusion criteria or meets any exclusion criteria, the Subject will not undergo randomization and will be considered a screen failure. Screen failures or subjects who withdraw prior to randomization will be replaced.

6.4.5. Intra-oral photographs

Intra-oral photographs will be taken in accordance with the Investigator's standard practice. On the day of restorations, the mouth region(s) containing the study teeth will be photographed before teeth preparation, and immediately after the restoration is finished and polished. For the 6-month, 1-year, and 2-year follow-up visits, photographs will be taken before clinical performance assessments are initiated.

6.4.6. Restoration and Application of Study Treatments

The restoration procedure for each lesion will be performed in accordance with the Investigator's standard practice. If the restorations need to be completed over multiple visits, all restorations should be scheduled in a timely manner (preferably within a week of the first restoration) in order to maintain the study schedule.

6.4.6.1. Tooth Preparation

Each tooth will be isolated using a rubber dam and appropriate retainers, and the tooth/lesion will be cleaned with pumice (applied with a prophylaxis cup and slow speed electric handpiece) and rinsed with water. A short enamel bevel (~ 0.5 mm) will then be placed at the enamel margin on the facial or buccal surface of each preparation. After tooth preparation, restorations for each tooth will be performed as described in Sections 6.4.6.2 and 6.4.6.3.

6.4.6.2. Treatment Group – Scotchbond™ Universal Plus Adhesive

For teeth in the Treatment arm, the SBU+ Adhesive will be applied following manufacturer's (3M™) directions using a "Total Etch/Etch and Rinse Procedure". Teeth assigned to the treatment group should be treated with Scotchbond™ Universal Etchant (see Section 11). After application and polymerization of the adhesive using a calibrated Elipar™ DeepCure-S Curing Light (see Section 11), and after selection of an appropriate composite shade, 3M™ Filtek™ Universal Restorative will be placed in 2 mm increments and light-cured. The restoration will be finished and polished in accordance with the Investigator's standard practice using the Sof-Lex™ Disks and the Sof-Lex™ Diamond Polishing System (see Section 11). Finishing and polishing should be similar for teeth in both treatment arms and across Subjects.

6.4.6.3. Control Group – Scotchbond™ Universal Adhesive

Following preparation, teeth in the Control arm will have the SBU Adhesive applied following the manufacturer's (3M™) directions using a "Total Etch/Etch and Rinse Procedure". Teeth assigned to the control group should be treated with Scotchbond™ Universal Etchant (see Section 11). After application and polymerization of the adhesive using a calibrated Elipar™ DeepCure-S Curing Light (see Section 11), and after selection of an appropriate composite shade, 3M™ Filtek™ Universal Restorative will be placed in 2 mm increments and light-cured. The restoration will be finished and polished in accordance with the Investigator's standard practice using the Sof-Lex™ Disks and the Sof-Lex™ Diamond Polishing System (see Section 11). Finishing and polishing should be similar for teeth in both treatment arms and across Subjects.

6.4.7. Post-Restoration Assessments

The clinical performance of the investigative device and comparator device, when used with 3M™ Filtek™ Universal Restorative, will be assessed by post-operative physical inspection and exploration of the facial and buccal surface of teeth in each treatment arm of the study. Performance will be evaluated using criteria that include restorative material retention, fracture of restorative material, marginal adaptation, secondary caries, surface staining, marginal staining, color match, polish retention (ie, luster), and postoperative hypersensitivity. Scoring categories for each of these criteria is listed in Sections 6.4.7.1 to 6.4.7.10. In addition, a patient satisfaction survey will be performed at each *scheduled* visit (see Section 6.4.7.11).

Baseline performance assessments for marginal adaptation (Section 6.4.7.3), surface and marginal staining (Sections 6.4.7.5 and 6.4.7.6, respectively), and surface luster (Section 6.4.7.8) can be performed upon removal of restoration-related isolation devices (eg, rubber dams or dental isolation adapters); however, baseline color match and translucency scoring (Section 6.4.7.7) should be performed a minimum of 30 minutes after removal of restoration-related isolation devices to allow for rehydration. Baseline postoperative hypersensitivity will be based on subject self-assessment conducted by phone at 7 days (± 3 days) post restoration using the scoring in Section 6.4.7.10. For the subsequent follow-up visits, performance assessments (listed in Sections 6.4.7.1 to 6.4.7.10) should be performed after routine cleaning procedures, if applicable.

If a tooth is withdrawn from the study (Section 6.5.2) because the tooth was missing/extracted, coronally fractured, or root canal filled, or the filling was replaced by a non-study dentist, then no further assessments will be scored for the withdrawn tooth. If a tooth is withdrawn from the study (Section 6.5.2) because of root fracture, cracks not affecting the restoration, or rampant caries, then final performance assessments listed in Sections 6.4.7.1 to 6.4.7.10 should be performed for that tooth on the day of withdrawal, excluding the postoperative hypersensitivity and tooth vitality

assessment in the case of root fracture; no further assessments will be required for the withdrawn tooth after it is withdrawn.

6.4.7.1. Retention of Restorative Material

Categories for retention of restorative material will include:

1. No loss of restorative materials
2. Partial or complete loss of restorative materials

6.4.7.2. Fracture of Restorative Material

Scoring categories for the retention of restorative material are defined as follows:

1. Excellent/very good: No fractures/cracks
2. Good: Small hairline cracks
3. Sufficient/Satisfactory: Two or more or larger hairline cracks and/or material chip fracture not affecting the marginal integrity or approximal contact
4. Unsatisfactory: Material chip fractures which damage marginal quality or approximal contacts

6.4.7.3. Marginal Adaptation (ie, marginal integrity)

Scoring categories for marginal adaptation are defined as follows:

1. Excellent/very good: No clinically detectable gap. Margins represent a harmonious continuation of the outline at the tooth/restoration transition
2. Good: Marginal integrity deviates from the ideal but could be upgraded to ideal by polishing. Small marginal chip fracture of the restoration can be eliminated by polishing and/or a localized gap is just perceptible with a dental probe < 150 µm. Sub-grading of unsatisfactory marginal adaptation should be applied as follows:
    a. Marginal gap (<150 µm), white lines.
    b. Small marginal fracture removable by polishing.
    c. Slight ditching, slight step or small flashes, minor irregularities.
3. Sufficient/satisfactory: Leakage/discoloration is present but limited to the marginal area. Generalized marginal gap >150 µm but <250 µm, is easily perceptible on probing but cannot be modified without minor damage to the tooth or surrounding tissue and is not considered to result in long-term negative consequences for the tooth or surrounding tissue if left

untreated. Presence of several small marginal fractures that are unlikely to cause long-term effects. Sub-grading should be applied as follows:

a. Gap < 250 µm not removable.

b. Several small marginal fractures.

c. Major irregularities, ditching or flashes, steps.

4. Unsatisfactory: Localized gap larger than 250 µm, may result in exposure of dentine or base. Repair is necessary for prophylactic reasons. Sub-grading should be applied as follows:

   a. Gap > 250 µm or dentine/base exposed.

   b. Severe ditching or marginal fractures.

   c. Larger irregularities or steps (repair necessary).

5. Poor: Generalized gap larger than 250 µm or the restoration is loose but in situ, re-placement is necessary to prevent further damage or there are large fractures at the margins and loss of material is too extensive to be repaired.

6.4.7.4. Secondary Caries

Scoring categories for secondary caries are defined as follows:

1. Excellent/very good: No secondary or primary caries
2. Good: Small and localized areas of demineralization
3. Sufficient/satisfactory: Larger areas of demineralization
4. Unsatisfactory: Caries with cavitation and suspected undermining caries
5. Poor: Deep caries or exposed dentin that is not accessible for repair of restoration

6.4.7.5. Surface Staining

Scoring categories for surface staining are as follows:

1. Excellent/very good: No surface staining
2. Good: Minor surface staining (under dry conditions) is present but is evenly spread over all the teeth. It does not affect the aesthetic properties because it is generalized and acceptable
3. Sufficient/satisfactory: Moderate surface staining not noticeable from a speaking distance
4. Unsatisfactory: Surface staining is present on the restoration but not the tooth and is clearly recognizable from a speaking distance. The aesthetic properties of the dentition are affected. Restoration requires major correction and layering of new material

5. Poor: Surface staining is unacceptable/unsightly, and the restoration needs to be re-placed

6.4.7.6. Marginal staining

Scoring categories for marginal staining are as follows:

1. Excellent/very good: No marginal staining
2. Good: Minor marginal staining, easily removable.
3. Sufficient/satisfactory: Moderate marginal staining, not aesthetically unacceptable.
4. Unsatisfactory: Pronounced (mainly localized) marginal staining and not removable by polishing; major intervention necessary for improvement of aesthetics
5. Poor: Deep marginal staining (generalized and/or profound), not accessible for intervention.

6.4.7.7. Color Match and Translucency

Scoring categories for color matching are as follows:

1. Excellent/very good: Color and translucency of the restoration have a clinically excellent match with the surrounding enamel and adjacent teeth. There is no difference in shade, brightness or translucency between restoration and tooth.
2. Good: Color match is clinically acceptable but minor deviations in shade between tooth and restoration are apparent.
3. Sufficient/satisfactory: Color match is satisfactory; there is a clear deviation in color match that does not affect aesthetics. Sub-grading should be applied as follows:
    a. more opaque
    b. more translucent
    c. darker
    d. brighter
4. Unsatisfactory: Color and/or translucency are clinically unsatisfactory. There is a (localized) discoloration or opaqueness in the restoration making it immediately recognizable from a speaking distance and affecting the appearance of the dentition. Partial removal and repair (veneering) is possible. Sub-grading should be applied as follows:
    a. too opaque
    b. too translucent
    c. too dark

d. too bright

5. Poor: Color match and/or translucency are clinically unsatisfactory. The restoration displays an unacceptable alteration in color and/or translucency.

6.4.7.8. Polish Retention (surface gloss/luster and roughness)

Scoring categories for polish retention are as follows:

1. Excellent/very good: Surface gloss/luster is comparable to that of the surrounding tooth tissues (mainly enamel).
2. Good: Surface is slightly dull but not noticeable from a speaking distance of 60 – 100 cm.
3. Sufficient/satisfactory: Surface is dull but still acceptable if the surface of the restoration is covered with a film of saliva. Some isolated small pores.
4. Unsatisfactory: Surface is rough and not masked by salivary film. Major re-finishing or veneering is necessary and possible. Multiple pores on more than 1/3 of the surface or 1-2 big pores.
5. Poor: Surface is unacceptably rough which makes it ugly and/or it retains noticeable biofilm (plaque). Improvement by finishing or veneering is not feasible.

6.4.7.9. Postoperative hypersensitivity and tooth vitality

Postoperative hypersensitivity upon exposure of the study tooth to a cold cotton pellet will be scored according to the following categories:

1. Excellent/very good: No hypersensitivity, normal vitality
2. Good: Minor hypersensitivity for a limited period of time, normal vitality
3. Sufficient/satisfactory: Clinically satisfactory with either of the following:
    a. moderate hypersensitivity, or
    b. delayed/mild sensitivity; no subjective complaints, no treatment needed
4. Unsatisfactory: Clinically unsatisfactory due to:
    a. intense hypersensitivity, or
    b. delayed sensitivity with minor subjective symptoms, or
    c. no clinical detectable sensitivity
5. Poor: Intense, acute pulpitis or non-vital tooth

6.4.7.10. Baseline postoperative hypersensitivity (Subject Self-Assessment)

Baseline postoperative hypersensitivity will be self-assessed by the subjects based on the following categories:

1. No hypersensitivity noted by the subject, especially when eating or drinking cold foods or beverages.
2. Minor hypersensitivity noted by subject for a limited period of time, no treatment needed.
3. Intense hypersensitivity noted by subject, treatment required.

6.4.7.11. Patient satisfaction survey

Categories for patient satisfaction will include:

1. Highly satisfied with aesthetics and function
2. Satisfied with aesthetics and function (minor roughness):
3. Minor criticism but no unfavorable clinical effects such as:
    a. Aesthetic shortcomings
    b. Some lack of chewing comfort
    c. Unpleasant treatment procedure
4. Desire for improvement with:
    a. Aesthetics
    b. Function (eg, tongue irritation)
5. Completely dissatisfied

6.4.8. Adverse Events and Adverse Device Effects

AEs and Adverse Device Effects (ADEs) will be collected from the time of restoration through the 24-month follow-up visit. AEs and ADEs will be reported according to Section 14.

6.4.9. Prohibited Procedures and Treatments

Any dental procedure or treatment of the study teeth other than routine cleaning and the procedures described in Section 6.4.6 will be considered a protocol deviation. In addition, the use of peroxide-based tooth-bleaching agents applied to the study teeth is prohibited during the study and would be considered a protocol deviation.

6.4.10. End of Study Documentation

Subjects may withdraw or be discontinued from this study at any time (Section 6.5 and 6.6.3). The Investigator may discontinue a Subject's study participation if the Investigator feels it is in the best interest of the Subject.

The following information will be documented at the End of Study:

- Last day of study participation
- Completion status – Did the Subject complete the study (Yes/No)?
- Reason for study discontinuation

6.5. SUBJECT WITHDRAWAL

6.5.1. Reasons for Subject Withdrawal

Subjects may withdraw from participation in the study at any time upon request. In addition, the Investigator may choose to terminate the participation of a Subject from the study with or without their consent. The Investigator shall record the reason for withdrawal and discontinuation of the study in an applicable Case Report Form (CRF). These reasons include, but are not limited to:

- Study completion (all study related visit(s) are completed)
- Withdrawal by the Subject
- Withdrawal by Investigator
- Lost to follow-up
- Death
- Adverse events
- Noncompliance
- For any reason that may, in the opinion of the Investigator, negatively affect the safety or well-being of the Subject

6.5.2. Reasons for Tooth Withdrawal

An individual study tooth may be withdrawn from the study at any time at the discretion of the Investigator to maintain subject safety. The Investigator shall record the reason for tooth withdrawal in an applicable CRF. These reasons include, but are not limited to:

- Cracked tooth

- Fractured tooth
- Missing / extracted tooth
- Replaced filling
- Root canal
- Rampant caries
- Other

6.5.3. Handling of Withdrawal or Termination

Every effort should be made to complete assessments required for the primary endpoint and safety endpoints prior to a Subject withdrawal. In the event of withdrawal or discontinuation of a randomized Subject prior to study completion, study Subjects will not be replaced. Screen failures or Subjects who withdraw prior to randomization to treatment will be replaced.

For study Subjects lost to follow-up, the Investigator shall make 3 documented attempts before confirming the Subject is lost to follow-up. If the study Subject withdraws from the study for any reason and there is an ongoing safety event, additional safety event information may need to be collected by the Investigator and shared with Sponsor.

Once the Subject withdraws from the study, all study teeth will be considered withdrawn. Upon Subject withdrawal, no further study evaluations will be performed, and no additional data will be collected. The Investigator may retain and continue to use any data collected before withdrawal.

If for any reason the Subject is withdrawn by the Investigator from this study, the Investigator will inform the Subject and the Sponsor.

If an individual study tooth is withdrawn from the study (see Section 6.5.2), then the remaining tooth may remain in the study until study completion.

6.6. VISIT SCHEDULE AND DESCRIPTION OF STUDY VISITS

6.6.1. Point of Enrollment

Following recruitment and eligibility screening during Visit 1, a Subject will sign the ICF. A Subject is considered enrolled in this study at time the informed consent form is signed by the Subject.

6.6.2. Visits

After informed consent has been obtained, the following study procedures and assessments will be performed. All applicable data are to be recorded in the applicable CRF.

6.6.2.1. Schedule of Events

A schedule of events is in Table 6.6.2.1-1 below:

Table 6.6.2.1-1. Schedule of procedures and assessments by study visit

Procedure Description & Visit Windows	Visit 1 Screening & Enrollment Day -21 to 0	Visit 2 Teeth Restorations Day 0	Phone call Baseline Postoperative Hypersensitivity (7 days ± 3 d)	Visit 3 6-mo Follow-up (6 mos ± 14 d)	Visit 4 1-yr Follow-up (1 yr ± 30d)	Visit 5 2-yr Follow-up (2 yr ± 45d)	Unscheduled
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X[1]					
Demographics and Subject Characteristics	X						
Teeth preparation		X					
Randomization		X					
Intra-oral photographs		X[2]		X[3]	X[3]	X[3]	X[3]
Restoration Procedure Treatment Application		X[4]	X[5]				
Post-Restoration Assessments		X[6]		X	X	X	X
Adverse Events & Adverse Device Effects		X		X	X	X	X
End of Study						X	X[7]

[1] Confirm eligibility if screening visit and restoration occur on different days (re-screen if > 21 days).
[2] Before teeth preparation, and immediately after the restoration is finished and polished.
[3] Before clinical assessments are initiated.
[4] All assessments except Color Match and Translucency performed after removal of tooth isolation devices. Color Match and Translucency assessment performed at least 30 minutes after tooth isolation device removal.
[5] Baseline postoperative hypersensitivity self-assessed by subjects via phone at 7 days (± 3 days) post restoration.
[6] Excluding patient satisfaction survey.
[7] If the Subject is withdrawn early.

6.6.2.2. Visit 1 (Screening & Enrollment Visit – Study Day -21 to 0)

The following procedures and assessments will be completed at Visit 1:

1. Assessment of eligibility, as described in Section 6.3.1
2. Informed consent, as described in Section 13
3. Undergo screening and dental assessment to corroborate that the patient meets all eligibility criteria described in Sections 6.3.1
4. Document Subject demographic and characteristics, as described in Section 6.4.2

6.6.2.3. Visit 2 (Restoration Procedures and Baseline Assessments – Study Day 0)

The following procedures and assessments will be completed at Visit 2:

1. Confirmation that Subject meets eligibility criteria, if Visit 2 occurs on different day than Visit 1 (re-screen if >21 days)
2. Teeth preparation, as described in Section 6.4.6.1.
3. Randomization of teeth into treatment arms, as described in Section 6.4.4
4. Intra-oral photographs, as described in Section 6.4.5
5. Restoration procedure for each tooth, including application of the study treatments, as described in Section 6.4.6
6. All post-restoration assessments will be captured according to Section 6.4.7
7. Assessment and documentation of adverse events and adverse device effects, as described in Section 6.4.8

6.6.2.4. Baseline postoperative hypersensitivity follow-up – Study Day 7 (± 3 days)

The following subject self-assessment will be completed by phone call at Study Day 7 (± 3 days):

1. Assessment and documentation of baseline postoperative hypersensitivity, based on subject self-assessment using grading scale in Section 6.4.7.10. Any intense hypersensitivity noted by subject that requires treatment should be followed up with an in-person unscheduled visit.

6.6.2.5. Visit 3 (Study Day – 6 months ± 14 days)

The following procedures and assessments will be completed at Visit 4:

1. Intra-oral photographs, as described in Section 6.4.5
2. All post-restoration assessments will be captured according to Section 6.4.7.

3. Assessment and documentation of adverse events and adverse device effects, as described in Section 6.4.8

6.6.2.6. Visit 4 (Study Day – 1 year ± 30 days)

The following procedures and assessments will be completed at Visit 5:

1. Intra-oral photographs, as described in Section 6.4.5
2. All post-restoration assessments will be captured according to Section 6.4.7
3. Assessment and documentation of adverse events and adverse device effects, as described in Section 6.4.8

6.6.2.7. Visit 5/Final Visit (Study Day – 2 year ± 45 days)

The following procedures and assessments will be completed at Visit 6:

1. Intra-oral photographs, as described in Section 6.4.5
2. All post-restoration assessments will be captured according to Section 6.4.7
3. Assessment and documentation of adverse events and adverse device effects, as described in Section 6.4.8
4. Documentation of end of study, as described in Section 6.4.10

6.6.2.8. Unscheduled Visits

The following procedures and assessments will be completed at any unplanned visits involving symptoms related to the study teeth:

1. Intra-oral photographs, as described in Section 6.4.5
2. All post-restoration assessments will be captured according to Section 6.4.7.
3. Assessment and documentation of adverse events and adverse device effects, as described in Section 6.4.8
4. Documentation of end of study, as described in Section 6.4.10, if necessary

6.6.3. Point of Exit

For each Subject, the Investigator shall record the reason for withdrawal and discontinuation of the study in the applicable CRF, as described in Section 6.5.1. The Study Subject is considered to be exited from the study upon completion of the applicable CRF.

6.7. ROLE OF SPONSOR REPRESENTATION

6.7.1. Monitoring

Study monitoring is conducted to ensure that (i) the rights, safety, and well-being of study participants are protected, (ii) the reported study data are accurate, complete, and verifiable, and (iii) the conduct of the study is in compliance with the currently approved CIP, with good clinical practice (GCP) principles, and with applicable regulatory requirement(s). 3M, as Sponsor of this clinical investigation, is responsible for study oversight and for providing the PI and study staff with training regarding the proper conduct of the clinical investigation with regard to CIP adherence and validity of the data recorded on the CRFs. 3M, has therefore assigned study monitor(s) to this clinical investigation. The progress of the clinical investigation will be monitored by:

- Periodic in-person and/or remote review of study documents
- Telephone and electronic communications with the study staff and PI
- Review of CRFs and source documents (eg, Subject records)

The study monitor(s), other authorized representatives of the Sponsor, representatives of the IRB/EC, or regulatory authorities may inspect all documents and records required to be maintained by the Investigator, including but not limited to, Subject records (office, clinic, or hospital) for the participants in this study. The clinical study site personnel will permit access to such records. The Investigator will give 3M study monitor(s) direct access to source documents that support data on the CRFs, including any electronic records. If site policies restrict access to Subjects' dental files to site personnel, the PI will designate a staff member to work with the Sponsor's monitor to verify source documents on an as needed basis. This verification will be conducted in a way that will ensure that only study-related information is examined.

6.7.2. Other Sponsor Oversight

In addition to study monitoring, the Sponsor, or their representatives may conduct the following tasks during this study:

- Audits of the Investigator
- Provision of technical support/product specific training for the study device

Investigator non-compliance of required study responsibilities will require Sponsor sanctions to alleviate the non-compliance, including corrective and preventative actions up to and including disqualification.

Details of clinical site monitoring are documented in a Monitoring Plan (MP). The MP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

7. STATISTICAL DESIGN AND ANALYSIS

A separate Statistical Analysis Plan (SAP) will not be generated for this study.

7.1. STATISTICAL HYPOTHESES

The objective is to compare the clinical effectiveness and safety between SBU+ Adhesive and the control, SBU Adhesive. Although the study is not powered to assess the differences in any of the endpoints between the two adhesives, comparisons will be made for exploratory purposes.

7.2. SAMPLE SIZE DETERMINATION

The expected annual restoration failure rate is 3.3%[22]. With a sample size of 55 restorations per treatment, a one-sided 95% Wilson Score confidence interval for restoration failure will yield an upper confidence limit of 9.9% within treatment group and 7.4% overall. Since Subjects can have either 2 or 4 restorations, we will enroll and treat enough subjects to obtain 110 restorations (up to 55 subjects). Based on a previous study[23], each Subject had an average of 2.9 restorations, so we anticipate enrolling approximately 38 subjects to meet the recruitment goal. We determined that 110 restorations allocated to treatment is reasonable when considering American Dental Association Guidelines[24] and previously published literature[9, 11, 25]. Sample size calculations were conducted using nQuery v9.2.1.0 module POC6-1.

7.3. ANALYSIS POPULATIONS

The following analysis sets will be used:

- Full Analysis Set (FAS) – Full Analysis Set will consist of all randomized Subjects who have post-baseline data available.
- Safety Set (SS) – Safety Set includes all Subjects who receive either SBU+ Adhesive or SBU Adhesive for any length of time.

Prior to any interim or final analysis, the Subject(s) excluded from any statistical sensitivity analyses will be determined based on deviations deemed to impact the primary and/or secondary analyses. Critical deviations will include deviations related to restorations procedures (e.g., not using the total-etch mode), a missing assessment, and study visits outside the pre-defined windows. Subjects excluded from sensitivity analyses may differ for each time point and for each endpoint. Documentation of these decisions will occur prior to any interim analyses.

7.4. STATISTICAL ANALYSES

The analysis of all endpoints will be based on the FAS with and without imputation. Statistical sensitivity analyses will be performed on the primary and secondary endpoints excluding those subjects with critical deviations related to restoration procedures, missing endpoint of interest, or assessment occurring outside of scheduled follow-ups. The result of sensitivity analyses will be presented alongside the primary FAS findings. The analysis of the safety endpoint will be based on SS. There will not be any adjustment for multiplicity as the study is non-confirmatory. All analyses will be conducted using SAS software (release 9.4 or higher). Unless otherwise specified, statistical tests will be two-sided and performed at a significance level of 5%. The corresponding p-values and 95% confidence intervals will be reported for all analyses.

7.4.1. Demographics and Baseline Characteristics

Subject demographics, baseline characteristics, and other relevant clinical information and treatment history will be summarized for all Subjects, and if relevant, by each treatment arm using descriptive statistics (frequency and percentage for categorical variables; n, mean, standard deviation, median, minimum and maximum for continuous variables).

7.4.2. Analysis of Primary Endpoints

The primary endpoints are the rate of restoration retention and marginal adaptation score, based on the FDI World Dental Federation criteria, evaluated at 24 months. Descriptive statistics will be used to summarize the primary endpoints, for each of the two adhesive products and overall, using FAS with imputed endpoints. The Wilcoxon signed-rank test and McNemar (or Cochran-Mantel-Haenszel) test will be used to compare the retention rate and marginal adaptation, respectively.

7.4.3. Analysis of Secondary Endpoints

The secondary endpoints include restoration retention rate at 6 months and 12 months, marginal adaptation score at baseline, 6 months, and 12 months as well as fracture score and incidence of secondary caries evaluated at baseline, 6 months, 12 months, and 24 months. These endpoints will be summarized using descriptive statistics. The Wilcoxon signed-rank test will be used to compare the endpoints at each of the time points.

7.4.4. Analysis of Exploratory Endpoints

The exploratory endpoints include time to retention failure, surface staining score, marginal staining score, color match score, polish retention score, cold hypersensitivity/tooth vitality, and patient satisfaction measured at baseline, 6 months, 12 months, and 24 months. Descriptive statistics will be used to summarize the endpoints at each of the aforementioned time points. Restoration retention survival time is defined as the time between the restoration date and the first report of the presence

of restoration failure. Censored observations will include surviving restorations at the date of last follow-up or completely random drop-outs. A marginal Cox model[26, 27] utilizing a robust sandwich covariance matrix estimate will be fitted to compare restoration retention survival time between the two adhesives, assuming underlying statistical assumptions are met. Considering there were multiple observations measured from the same Subjects, to account for the intracluster dependence, a logistic or linear regression model using generalized estimating equations (GEEs) will be fitted to compare the treatment arms relative to the exploratory endpoints at the 12-month and 24-month time points. This analysis will use a robust estimator and assume a compound symmetry working correlation of restorations within Subjects.

7.4.5. Analysis of Safety Endpoint

The incidence of treatment-related adverse events throughout the study will be summarized using descriptive statistics per study arm.

7.5. Planned Interim Analyses and Criteria for Clinical Investigation

A full interim analysis will be conducted at 12 months follow-up. Only descriptive statistics will be provided for the baseline and 6 months assessments. The result from the interim analysis will be used for generating a formal interim report. Given there is one full interim analysis, the O'Brien Fleming adjusted type I error rate of $\alpha = 0.005, 0.048$ for statistical significance will be used in the analyses conducted at 12 months and 24 months respectively[28, 29].

7.6. Procedures for Missing, Unused or Spurious Data

Missing data will be displayed as missing, whereas Subjects whose data are not available (ie, “not reported”, “N/A” or “not available”) will be considered as a separate category and presented in the reports. Restoration failure will be information carried forward and will impact the calculation of retention rate at each subsequent visit, whereas all other endpoints under consideration that are missing will be imputed using the time-specific treatment mean for that endpoint.

7.7. Procedures for Reporting Deviations from Statistical Plan

Any deviations in the statistical plan from those described in the CIP will be documented in the final report.

7.8. Validation Plan

Validation of the statistical programs, output and result for interim and final analyses will be performed by an independent Biostatistician. The Biostatistician will also review the statistical section of the Clinical Study Report for completeness and correct interpretations of the analysis results and provide comments.

8. DATA MANAGEMENT

Data collected for this study will be analyzed and stored at 3M. Permission to transmit, store, and use data outside of the study will be included in the informed consent.

8.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will occur at the study site and is the responsibility of the clinical study staff under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents (ie, all information in original records, certified copies of original records, observations, or other activities necessary for the reconstruction and evaluation of the study) should be completed in a neat, legible, and permanent (ie, cannot be edited) manner to ensure accurate interpretation of data. Data derived from source documents of each Subject will be entered into the Subject's electronic case report form (eCRF) and must be consistent with the data recorded on the source documents. Guidance for eCRF completion will be provided and reviewed with the site staff before receiving study product.

All data, including AEs and expected adverse event data will be entered into a data capture system provided by 3M that is compliant with part 11 of Title 21 of the Code of Federal Regulations. The 21 CFR Part 11-compliant data system includes password protection and internal quality checks such as automatic range checks to identify data that appear inconsistent, incomplete, or inaccurate.

3M is responsible for compilation and verification of the clinical study data, retention of the clinical study database, performance of statistical analysis, and preparation of the clinical study report.

8.2. STUDY RECORDS RETENTION

The study participant's information will be securely stored at the respective clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for a period no longer than that dictated by the reviewing IRB/EC, Institutional policies, regulatory authorities, or Sponsor requirements, as outlined in the study contract.

The Investigator will contact the Sponsor prior to the destruction of any study records, and no records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

8.3. SPONSOR OVERSIGHT

The Investigator will allow access to clinical study records for periodic on-site or remote monitoring visits by a designated 3M representative, with the understanding that the representative is bound by professional secrecy and will not disclose the identity of any Subject or personal medical

information. The representative will review eCRFs for completeness during monitoring visits and after the eCRFs are submitted; any discrepancies will be resolved with the Investigator or designee, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

In addition to on-site or remote monitoring, routine review of submitted study information will be conducted by the Sponsor to ensure compliance with the CIP. Items reviewed include but are not limited to adverse events, deviations, number of withdrawn/terminated Subjects, which all may impact the completion of the study. Appropriate measures may be taken to ensure Investigator compliance with the CIP.

9. AMENDMENTS TO THE CIP

In the event that modifications to this CIP are necessary (eg, to protect the safety of the Subjects and/or the integrity of the data), the CIP will be amended and approved by the Sponsor. All changes will be evaluated for impact per the Sponsor's standard operating procedures (SOPs). In collaboration with the Investigator(s), the CIP modifications will then be documented and submitted for ethical and regulatory approval (as required) prior to implementation. Modifications will be considered implemented after all ethical and regulatory approvals (as required) are received and all key Sponsor personnel, Investigators, and Investigator designees, including key site staff, have been trained regarding the modified CIP.

10. DEVIATIONS FROM THE CIP

The Investigator is not allowed to deviate from the CIP except as specified in Section 5.6.4 of the International Standard, ISO/FDIS14155:2020(E). Briefly, deviations from the CIP to protect the rights, safety, and well-being of human subjects under emergency circumstances may proceed without prior approval of the Sponsor and the IRB; however, such deviations shall be documented and reported to the Sponsor and the IRB in accordance with IRB requirements. All deviations shall be documented on a deviation report form or appropriate CRF, and a deviation report form shall be completed for each event per individual Subject. The Investigator is responsible for reporting all deviations to the Sponsor and the reviewing IRB, per local requirements.

10.1. DEVIATION REPORTING TIMELINES

The timelines and methods for reporting the different types of deviations to the Sponsor are provided in Table 10.1-1.

Table 10.1-1. Timeline and methods for reporting deviations.

Type of Deviation	Report to Sponsor	Method
Subject safety, rights, or welfare; OR Data integrity; OR Compromise the statistical analysis of the study; OR Lack of Informed Consent; OR Inclusion/Exclusion	Within 24 hours of study staff becoming aware of event	• Initial Report: Phone/Email to Sponsor • Complete CRF
All other protocol deviations	Per protocol visits	• Complete CRF

11. DEVICE ACCOUNTABILITY

The device(s) under investigation and additional study-specific equipment to be used in both arms of the study (listed in Table 11-1) will not be distributed to the investigational site until all agreements between the site and 3M are finalized and IRB/EC approval has been obtained. 3M requires that Investigator maintains device accountability and security of the devices at all times. The Investigator or designee will keep records documenting the following:

- Maintain and account for devices at the Investigator site, including:
    - the name(s) of person(s) who received, used, returned, or disposed of the device;
    - the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code);
    - the expiration date of the device, if applicable.
- Keep devices in a secure storage area, accessible only to authorized individuals.
- Dispense devices only to Subjects properly enrolled in and eligible for the study, including the following:
    - Subject identification;
    - the date or dates of use;
    - the date on which the investigational device was returned/explanted from Subject, if applicable.
- Return all unused investigational materials to the Sponsor at the end of the study or dispose of as agreed upon, including:
    - the date of return of unused, expired, or malfunctioning investigational devices, if applicable;

- the date and documentation of disposal of the investigational devices as per instructions of the Sponsor, if applicable.

The Sponsor shall have instructions in place and make packaging materials available, if applicable, for the safe return or disposal of investigational devices.

Table 11-1: Additional Study-specific Device Information

Additional Study-Investigational Device	
Device Name	**Manufacturer**
Elipar™ DeepCure-S Curing Light	3M
Scotchbond™ Universal Etchant	3M
Filtek™ Universal Restorative	3M
Sof-Lex™ Disks	3M
Sof-Lex™ Diamond Polishing System	3M

11.1. DEVICE LABELING

The devices under investigation will be labeled according to applicable regulations. A sample label will be retained, along with other study-related documents, at the site (eg, in the Investigator Site File).

11.2. ADDITIONAL STUDY-SPECIFIC EQUIPMENT/DEVICE(S)

Additional study-specific equipment/devices used in this study shall be maintained, calibrated (if applicable) and ensured to be functioning correctly during the study, in accordance with this study CIP or applicable site policy and regulatory requirements. The Sponsor should be notified of any anticipated or known issues with the device functionality that may impact the study conduct or outcome.

12. STATEMENTS OF COMPLIANCE

12.1. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. In addition, this clinical investigation shall be conducted in accordance with ISO-14155:2011 and future versions, US FDA 21 CFR parts 812, 50, 54, 56, and any regional or national regulations, as appropriate.

Approving IRBs will be provided all relevant study documentation in order to safeguard the rights, safety, and well-being of Subjects as mandated. The participating Investigator will obtain IRB approval of the study prior to initiation of the study at the site. The protocol, Instructions for Use, informed consent, written information given to Subjects, safety updates, and any revisions to these documents will be provided to the IRB by the Investigator.

12.2. PERIODIC REVIEWS

Ongoing reviews by IRB are required for the duration of the clinical study. The Investigator will comply with IRB requirements for ongoing reviews, at a minimum annually.

12.3. PARTICIPANT CONFIDENTIALITY

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and their authorized representatives. Information collected about Subjects during the study will be kept confidential and managed according to the requirements of the IRB and Health Insurance Portability and Accountability Act of 1996 (HIPAA). This confidentiality is extended to cover all clinical information relating to participants. Therefore, the Clinical Investigation Plan, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

In the event that a Subject revokes authorization to collect or use Personal Health Information (PHI), the Investigator retains the ability to use all information collected prior to the revocation of Subject authorization.

Study data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at 3M or approved supplier. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number (see Section 6.4.4). The electronic data capture system used by clinical sites and by 3M research staff will be secured and password protected. At the end of the study, all study databases will be anonymized and archived at 3M.

12.4. CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

IRB/EC procedures should have provisions that the IRB/EC avoids any bias and conflict of interest, including proof of independent review of Sponsor-Investigator clinical investigations. The Sponsor can request that the IRB document that persons with conflict of interest or potential bias (eg, members of the investigation site team) were not part of the voting.

The Sponsor has established procedures for all Investigators to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. The Sponsor will receive disclosures of conflict of interest from the PI prior to commencing the clinical investigation.

12.5. INSURANCE

The Sponsor shall provide clinical study-related insurance covering the reasonable and necessary costs of diagnostic, therapeutic, and medical treatment including hospitalization costs (treatment costs) for such participant injuries following the administration or use of the study device(s) in accordance with this clinical investigational plan and in accordance with the national regulations. The Sponsor may reimburse the institution and/or study participants for treatment costs depending on who incurred such treatment costs. The Sponsor will not be responsible for paying for or reimbursing treatment costs if (i) the injury is attributable to the negligence or misconduct of any agent or employee of the institution or Investigator, or the failure of such persons to comply with a study protocol, (ii) the treatment costs are covered by the study participant's medical or hospital insurance coverage, or (iii) the treatment costs arose as a result of the treatment of normal progression of the study participant's disease or injuries resulting from interventions that the study participants would have incurred had they not participated in the study.

13. INFORMED CONSENT PROCESS

Informed Consent must be obtained for each Subject prior to any study activities being performed or data being collected. The Investigator or designee will review all relevant aspects of the study with the potential study Subject that may impact the Subject's decision to participate throughout the study. The Investigator or designee will provide ample time for the Subject to read and understand the IRB/EC-approved ICF and to consider participation in the study.

The study Subject and the Investigator (or qualified designee) must both sign and date the ICF before the Subject can undergo any study-related procedures. The Investigator or designee must file the original ICF and provide the Subject with a copy of the signed and dated ICF and any other written documentation per IRB/EC requirements. Subject privacy language (ie, HIPAA) per local regulations may be added to the local Informed Consent by the Investigator.

The Informed Consent Process must be documented by the Investigator or designee. The Informed Consent Process includes documentation of the discussion regarding study procedures, Subject concerns, that the Subject was provided ample time to consider participation, and that all questions were answered prior to participation in any research activity.

In order to minimize pressure and undue influence on vulnerable Subjects (see Section 15), the Investigator or designee who is obtaining Informed Consent should ensure appropriate communication techniques, such as visual aids and avoidance of jargon, in order to ensure minimal pressure and undue influence is avoided.

14. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

Investigators are responsible for ensuring that all safety events are recorded in the Subject record(s). Events defined in Section 14.1 will be reported to the Sponsor, as applicable, per the timelines in Section 14.3.

14.1. SAFETY AND ADVERSE EVENT REPORTING DEFINITIONS

This study utilizes the terms and definitions related to safety and event reporting listed in Table 14.1-1 below.

Table 14.1-1: Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in Subjects, users or other persons, whether or not related to the investigational medical device.

Term	Definition
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. This includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event that is a result of a user error or intentional misuse of the investigational device.
Serious Adverse Event (SAE)	Any adverse event that: • Led to death • Led to serious deterioration in the health of the Subject, that either resulted in: o a life-threatening illness or injury o a permanent impairment of a body structure or a body function o in-patient or prolonged hospitalization, o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death or a congenital anomaly or birth defect
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Serious Adverse Device Effect (USADE)	A serious adverse device effect, which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report
Device Deficiency (DD)	An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, such as malfunctions, use errors, and inadequate labelling
Complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a **device** after it is released for distribution

14.2. CLASSIFICATION OF EVENTS

14.2.1. Severity Ratings

The severity ratings for events are defined in Table 14.2.1-1. The Investigator shall ensure rating of reportable events on the applicable Case Report Form.

Table 14.2.1-1: Severity Ratings Definitions

Term	Definition
Mild	An event that is easily tolerated by the Subject, causing minimal discomfort and not interfering with everyday activities
Moderate	An event that is sufficiently discomforting to interfere with normal everyday activities
Severe	An event that prevents normal everyday activities

14.2.2. Relatedness to Study Treatment

Table 14.2.2-1 defines the relatedness definitions for events. The Investigator shall ensure rating of reportable events on the applicable Case Report Form.

Table 14.2.2-1: Relatedness Definitions

Term	Definition
Not Related	Relationship to the device or procedure can be excluded
Possible	Relationship with the use of the study device is weak but cannot be ruled out completely.

Causal	The event is associated with the study device or with the procedures beyond a reasonable doubt when:
	• The event is a known side effect of the device
	• The event has a temporal relationship with the study device/application procedures
	• The event involves a body/site or organ that
	  ○ The device or procedures are applied to;
	  ○ The device or procedures have an effect on
	• The event follows a known response pattern to the device

14.3. REPORTING TIMELINES

Table 14.3-1 below indicates the reporting timelines and methods for reporting different types of AEs to the Sponsor. The Investigator shall also report Events to IRB/EC and local regulatory authorities, per local requirements. Reporting to Sponsor begins when study staff are aware of the event. For any event listed in the Table 14.3-1 below, the study Sponsor may request additional information from the Investigator, including but not limited to, medical records, laboratory testing, radiological results, etc. regarding the event.

Table 14.3-1. Methods and Times for Reporting Safety Events.

Type of event	Report to Sponsor	Method
Adverse Events (AE) deemed by the Investigator to be related to participation in the study and considered to be due to the study intervention or comparator product.	Per protocol visits	Complete CRF
Unanticipated Adverse Device Effect (UADE)	Per protocol visits	Complete CRF
Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE)	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Sponsor Followed by: Complete CRF
Unanticipated Serious Adverse Device Effect (USADE)	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Sponsor Followed by: Complete CRF
Device Deficiency (DD)	Within 3 business days of becoming aware of event	Complete CRF
Product Complaints on 3M Marketed Product	Within 3 business days of becoming aware of event	Phone/Email to Sponsor

14.4. DETAILS CONCERNING SAFETY RECORDING AND REPORTING REQUIREMENTS

14.4.1. Investigator

It is the responsibility of each participating Investigator to ensure all safety events (eg, AEs, SAEs, device effects, or DDs) are recorded in the Subject's record. The collection/reporting period for safety events will begin after the teeth of the Subject have been randomized. Investigators should assess for AEs at each visit, and study Subjects should be instructed to report any AE that they experience to the Investigator.

All AEs, regardless of perceived relationship to study product, will be documented in a timely manner and reported according to the methods and timelines in Section 14.3. In addition, the worsening of an underlying medical condition should also be recorded as an AE.

The AE description will include the nature of the experience (AE term), the start date, the end date, the severity of each sign or symptom, the seriousness of the event or experience, relationship to

study treatment, the course of action taken, and the outcome of the experience. It will be indicated if the AE caused the Subject to be discontinued from the study.

Any AEs that are ongoing at the end of the study but are not safety-related should be marked as "*persistent'* per the study-specific CRF. Any Events which are related to safety OR are persistent and deemed related to the study device should be followed for up to an additional 30 calendar days or stabilization. Events reported by Subjects after the last study visit may be reported to the Sponsor up to 30 calendar days from the date of the last visit.

14.4.2. Sponsor

Safety oversight will be under the direction of the Dental Director(s) of 3M, which is composed of individuals with the appropriate expertise. The Dental Director(s) routinely review and assess the safety data of the study. Emergency contact information for reporting SAEs or SADEs will be provided to the Investigator or Investigator designee, as well as the IRB, before initiating the study.

The Sponsor will conduct an evaluation of the received AEs and if an event is confirmed to be a SAE/UADE, will report the results of the evaluation to all regulatory agencies overseeing the project and to participating Investigators. If the Sponsor determines that the event presents an unreasonable risk to the study Subjects, the Sponsor will terminate all clinical studies or parts of studies presenting risk as soon as possible.

14.5. ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Scotchbond™ Universal Plus Adhesive contains substances that may cause an allergic reaction by skin contact in certain individuals. To mitigate this potential adverse event, Subjects with a known allergy to acrylate will be excluded. In addition, the time of contact between the adhesive, especially uncured adhesive, and the Subject's oral soft tissue will be minimized. If prolonged contact with oral soft tissue occurs, the region will be flushed with large amounts of water.

15. VULNERABLE POPULATION

This study is intended to be conducted using a non-vulnerable population with no expectations of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. However, the study does not exclude pregnant Subjects or economically/educationally disadvantaged persons. The protection of rights, well-being, and safety of vulnerable populations is the most important consideration and should take precedent over the interests of the study. In addition, the protection of rights, well-being, and safety of vulnerable populations, and ascertaining appended safeguards, are the prerogative of the IRB, and the Investigator should comply with all institutional guidelines related to vulnerable populations.

In recruitment process, the Investigator will ensure that Subject recruitment is free from pressure and will respect the Subject's expectations of privacy. Participation will be presented as a voluntary option. In addition, the screening process will contain procedures to assess the pregnancy status of females of childbearing age as well as the decisional capacity of potential study Subjects. The study will be described to all potential Subjects by the Investigator in non-technical terms, and the ICF will be written in an essentially non-technical manner to suit the solicited community. The study will be presented in a manner that permits ample time for consideration of participation, with no undue pressure related to the timing of the request.

Lastly, it is not anticipated that any special dental/medical care will be needed for any Subject enrolled for the study.

16. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION PLAN

Both the Sponsor and the PI reserve the right to terminate the clinical investigation at any time. Should this be necessary, procedures will be arranged on an individual basis after review and consultation by both parties. If the study is terminated prematurely or suspended, study Subjects and the IRB will be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator. If applicable, regulatory authorities and the personal dentist of the Subjects will also be informed. In terminating the clinical investigation, the 3M study team personnel and the PI will assure that adequate consideration is given to the protection of the Subjects' interests.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to all study participants, participating Investigators, IRB and regulatory authorities, and the Sponsor. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to Clinical Investigation Plan requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Determination of futility

Suspended studies may resume once concerns about safety, Clinical Investigation Plan compliance, and data quality are addressed, and satisfy the Sponsor, IRB/EC and regulatory authorities.

16.1.1. By Sponsor

The Sponsor reserves the right to discontinue the clinical study for business or ethical reasons at any time, such as, but not limited to:

- Information regarding the study product causes doubt as to the benefit/risk ratio.
- Changes in medical practice limit utility of the data obtained from the study.
- Investigator(s) lack of compliance with the approved CIP, lack of oversight, and/or not following applicable regulatory or IRB/EC guidelines in conducting the study
- Incidence or severity of AEs indicates a potential health hazard or poses an unreasonable risk to the study participants
- Subject enrollment is unsatisfactory
- Fraud or misconduct

16.1.2. By IRB

The IRB/EC may choose to discontinue the study at the site for which they granted approval. If the IRB/EC discontinues the study, the Investigator will report a withdrawal of IRB/EC approval to the study Sponsor within five (5) working days.

17. REGISTRATION AND PUBLICATION POLICY

17.1. PUBLIC REGISTRATION

The Sponsor shall ensure that this study will comply with any required national registration requirements. This study will be conducted in accordance with the applicable publication and data sharing policies and regulations. A description of this study will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that identifies Subjects. At most, the website will include a summary of the results of the study and will be available for public review at any time.

17.2. PUBLICATIONS RESULTING FROM STUDY

When applicable, attempts will be made to publish the results of the study, and a publication policy for this study will be addressed in a separate agreement between the PI and the Sponsor.

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19. STUDY-SPECIFIC APPENDICES

List of Appendices:

Appendix A	Revision History

Appendix A

REVISION HISTORY

Overall summary of changes
Version 2. Changed Principal Investigator. Details provided in version 2.
Version 3. Corrected PI's title; changed to indicate 2nd tooth in a pair will not be withdrawn if 1 tooth is withdrawn; removed collection of concomitant meds; added restriction for H2O2 bleaching; updated photos. Details provided in version 3.
Version 4. Changed study site. Modified study design to make it a blinded study. Moved baseline assessments to be same day as restoration visit and added subject self-assessment of baseline hypersensitivity at Day 7. Clarified "sensitivity" assessment is for "hypersensitivity". Added instructions on tooth withdrawal. Added qualifiers to grading scales: excellent – poor. Modified polish grading scale from 7 pt to 5 pt scale. Modified list of photos at baseline. Clarified restrictions re: chlorhexidine solutions. Other minor grammatical and formatting changes. Details provided below.
Version 5. Added detail to the sample size determination, and modified the analysis of primary endpoints statement.

Version 6. Modify enrollment from minimum number of subjects to number of restorations. Correct surface of teeth is facial and buccal surface of teeth.

Section modified	Original text	Updated text
Summary & Section 5.3.1	Design The study will enroll a minimum of 46 Subjects.	Design The study will enroll enough subjects to perform a minimum of 110 restorations.
Summary & Section 5.3.1 and 5.3.2	Primary Endpoints • the proportion of Subjects with partial or complete loss of the restoration materials Secondary Endpoints • the proportion of Subjects with partial or complete loss of the restoration materials at baseline, 6 months, and 12 months	Primary Endpoints • the proportion of teeth with partial or complete loss of the restoration materials Secondary Endpoints • the proportion of teeth with partial or complete loss of the restoration materials at baseline, 6 months, and 12 months
6.1 Design	The study will enroll a minimum of 46 Subjects from a single site located in Baton Rouge, LA, USA.	The study will enroll enough subjects to perform a minimum of 110 restorations

Version 6. Modify enrollment from minimum number of subjects to number of restorations. Correct surface of teeth is facial and buccal surface of teeth.

Section modified	Original text	Updated text
		from a single site located in New Orleans, LA, USA.
6.3 Enrollment	Subject enrollment will remain open until 46 Subjects are confirmed eligible and enrolled.	Subject enrollment will remain open until enough subjects are enrolled and confirmed eligible to perform 110 restorations.
6.4.6.1 Tooth Preparation	A short enamel bevel (~ 0.5 mm) will then be placed at the enamel margin on the facial occlusal surface of each preparation.	A short enamel bevel (~ 0.5 mm) will then be placed at the enamel margin on the facial or buccal surface of each preparation.
6.4.7 Post-Restoration Assessments	… will be assessed by post-operative physical inspection and exploration of the occlusal surface of teeth in each treatment arm of the study.	… will be assessed by post-operative physical inspection and exploration of the facial and buccal surface of teeth in each treatment arm of the study.
7.2 Sample Size Determination	We estimate that 46 Subjects allocated to treatment are feasible in consideration of American Dental Association Guidelines[22] and previously published literature[9, 11, 23]. The estimated sample size will account for 10-15% drop-outs or attrition to allow a minimum of 40 subjects completing the study. Based on a previous study[24], each Subject had an average restoration of 2.9. Since Subjects can have either 2 or 4 restorations, it is anticipated that there will be 110-133 restorations for the 46 Subjects. The expected annual restoration failure rate is 3.3%[25]. With a sample size of 46 subjects contributing 110-133 restorations, a one-sided 95% Wilson score confidence interval for the restoration failure will yield upper confidence limits ranging from 6.9-7.4%.	The expected annual restoration failure rate is 3.3%[22]. With a sample size of 55 restorations per treatment, a one-sided 95% Wilson Score confidence interval for restoration failure will yield an upper confidence limit of 9.9% within treatment group and 7.4% overall. Since Subjects can have either 2 or 4 restorations, we will enroll and treat enough subjects to obtain 110 restorations (up to 55 subjects). Based on a previous study[23], each Subject had an average of 2.9 restorations, so we anticipate enrolling approximately 38 subjects to meet the recruitment goal. We determined that 110 restorations allocated to treatment is reasonable when considering American Dental Association Guidelines[24] and previously published literature[9, 11, 25]. Sample size calculations were conducted using nQuery v9.2.1.0 module POC6-1.