NCT05768373

Study Title	Clinical evaluation of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution in the treatment of dentin hypersensitivity
Study Number	EM-11-050084
Release Date	04/27/2023 10:23:21 AM CDT
Name of Device Under Investigation	Clinpro™ 2.1% Sodium Fluoride Aqueous Solution
Sponsor Address	3M Company 3M Center St. Paul, MN 55144
Manufacturer Address	3M Company 3M Center St. Paul, MN 55144

ELECTRONIC SIGNATURES:

Signer	Role	Date Signed
US113168:Morse Dan J	Clinical	April 27, 2023 06:16:33 AM CDT
ACQ6HZZ:Xu Xiaohui	Medical Monitor	April 27, 2023 10:23:19 AM CDT
A6T72ZZ:Han Helen	Clinical	April 26, 2023 01:37:28 PM CDT
A8R0XZZ:Parsram Cp	Regulatory and Compliance	April 26, 2023 01:39:54 PM CDT

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Investigator 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, 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/product deficiencies or complaints 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:	

Study Title	Clinical evaluation of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution in the treatment of dentin hypersensitivity
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ABBREVIATIONS/ACRONYMS

AE	adverse event
ADE	adverse device effect
CEJ	cementoenamel junction
CFR	code of federal regulations
CIP	Clinical Investigation Plan
cm	centimeter or centimeters
d	day(s)
DD	device deficiency
DHS	dentin hypersensitivity
ETAB	exposure time to air blast
F^-	fluoride
FDA	United States Food and Drug Administration
g	gram(s)
h	hour(s)
ICF	Informed Consent Form
IFU	instructions for use
IRB	Institutional Review Board
mm	millimeter or millimeters
OTC	over-the-counter
Q1	Quarter 1
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

SE	standard error
SR	Significant Risk
USADE	unanticipated serious adverse device effect
VAS	visual analog scale
VRS	verbal response scale

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1. SUMMARY

Study Title	Clinical evaluation of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution in the treatment of dentin hypersensitivity
Study Type	Pre-market
Principal Investigator (PI)	**Name**: Dr. Yiming Li, DDS, PhD, MSD **Title:** Distinguished Professor **Site:** Loma LindaUniversity Health
Device under Investigation Summary	The investigational device for this study is 3M™ Clinpro™ 2.1% Sodium Fluoride Aqueous Solution, which is a xylitol-sweetened aqueous fluoride coating that is applied topically to the tooth surfaces for the treatment of DHS. 3M™ Clinpro™ 2.1% Sodium Fluoride Aqueous Solution contains 9,500 ppm fluoride as well as added calcium and phosphate.
Sponsor	3M
Purpose	The purpose of this investigation is to generate data to support an indication for use of the Investigational product in treating dentin hypersensitivity (DHS) and to support global regulatory registration of the product.
Design	This is a prospective, randomized, single blinded, parallel, non-inferiority trial, that will enroll Subjects requiring treatment for DHS. Subjects will be randomized in a 1:1 ratio with half of the Subjects treated with Clinpro™ 2.1% Sodium Fluoride Aqueous Solution and the other half treated with Vanish™ 5% Sodium Fluoride White Varnish. The study will be conducted at a single investigational site in the following location: Loma Linda University Health.
Selection of Subjects	A minimum of 96 enrolled Subjects that complete the treatment is planned for this study. To achieve this minimum, the Investigator may enroll up to one hundred and twenty five (125) subjects. To be considered eligible for enrollment, Subjects must meet all the inclusion criteria and none of the exclusion criteria listed below.

	Inclusion Criteria: Subjects may be included that meet the following criteria: 1. Subject has at least one affected hypersensitive tooth upon air blast stimuli in the cervical area, and baseline pain score of 40 mm and above as assessed by the 100 mm VAS. 2. Subject is at least 18 years old and have a minimum of 20 natural teeth. 3. Subject is willing to withhold desensitizing treatment, including prescription, in-office or over the counter (OTC) desensitizing products, throughout the study period AND withhold during the washout period. 4. Subject agrees to only use the provided toothpaste, toothbrush, and follows all oral hygiene instructions throughout the study period AND follows all oral hygiene instructions during the washout period. 5. Subject is able to understand and willing to sign the Informed Consent, and is willing to return to the study facility for scheduled study visits and recalls Exclusion Criteria: Subjects may not be included that meet any of the following criteria: 1. Subject has medical (including psychiatric) and pharmacotherapeutic histories that may compromise the protocol – including the chronic use of anti-inflammatory, analgesic (pain), and mind-altering drugs; or analgesic (pain) medications within 48 hours prior to application of treatment. 2. Subject is pregnant (self-reported) or breast feeding. 3. Subject has allergies to product ingredients, eg, rosin, mint flavoring. 4. Subject has systemic conditions that are etiologic or predisposing to dentin hypersensitivity (eg, chronic acid regurgitation).

	5. Subject has excessive dietary or environmental exposure to acids at time of screening. 6. Subject had periodontal treatment, bleaching treatments, or orthodontic treatments within previous 3 months or plans to have any other dental treatments during the study period. 7. Subject is enrolled in another clinical trial at the time of screening that would interfere with this study. 8. Subject is, in the opinion of the investigator, unsuitable for enrollment in the study for reasons other than those specified in the above exclusion criteria. Individual teeth may not be included that meet any of the following criteria: 9. Study tooth has periodontal probing depth of ≥ 4 mm. 10. Study tooth or the surrounding supporting tissue has any other painful pathology or defects. 11. Study tooth has been restored in the preceding 3 months. 12. Study tooth is an abutment for fixed or removable prostheses or suffers traumatic malocclusion. 13. Study tooth is crowned or extensively restored and the restorations extending into the test area. 14. The tooth has dentin hypersensitivity due to cracked enamel.
Device Regulatory Classification	Clinpro™ 2.1% Sodium Fluoride Aqueous Solution is anticipated to be a class 2 medical device under FDA product code LBH (varnish, cavity per 21 CFR 872.3260) that will require FDA 510(k) ance. A 510(k) Pre-market Notification is planned for the first quarter (Q1) of 2023. Clinpro™ 2.1% Sodium Fluoride Aqueous Solution is not expected to have 510(k) ance when the study begins. For the purpose of this study, the product is not considered a Significant Risk(SR) investigational device under 21 CFR 812.3(m) because:

	• Is not intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is not purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; and • Does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject
Primary Objective(s)	The primary objective of this study is to evaluate the effect of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution (experimental) on DHS in comparison to 3M™ Vanish™ 5% Sodium Fluoride White Varnish (commercialized, control), a well-known product in the market used for this purpose.
Endpoint(s)	Co-primary endpoints include: 1. the change in pain, using a 100-mm VAS from baseline to immediately after application (within 15 minutes post treatment) of test product or comparator. 2. the change in pain score from baseline to 24 ± 4 h post-application, using VAS after exposure to air stimulus. The secondary endpoints include: 1. change in pain score, using VAS, from baseline to 7 ± 2 days post-treatment, after exposure to air stimulus. 2. change in pain score, using VAS, from baseline to 21 ± 2 days post-treatment, after exposure to air stimulus. 3. change in pain score, using VAS, from baseline to 30 ± 2 days post-treatment, after exposure to air stimulus. The exploratory endpoints will include the reduction in pain (using a VAS) upon tactile testing with a periodontal probe, including:

	1. change from baseline to immediately post-treatment (within 15 minutes post-treatment) 2. change from baseline to 24 ± 4 hours post-treatment 3. change from baseline to 7 ± 1 days post-treatment 4. change from baseline to 21 ± 2 days post-treatment 5. change from baseline to 30 ± 2 days post-treatment. The safety endpoint will be the incidence of all AEs.
Randomization and Blinding	Randomization should occur after obtaining informed consent and ensuring that the Subject meets all eligibility criteria; randomization should occur on the day of treatment before the initial application of the investigational device (Treatment arm) or control device (Control arm). Due to the nature of the investigative device, the duration of treatment application, and the study design, Investigator blinding is not feasible for the study. For Subjects with multiple eligible teeth, the PI will select the index tooth based on their experience and accessibility of the tooth for the stimuli; however, this selection must be made prior to randomization. Randomization of the Subjects will be performed using a permuted block technique and will be centralized and electronic.
Duration of the Study	The entire duration of the study is expected to last one year. Individual subject participation is expected to last 51 days, including a 3-week washout period before treatment.
Sponsor Study Contact	**Name:** Helen Han, PhD **Address:** 3M Center, Bldg 270 **Telephone:** 651-737-9234 **Email.:** mhan3@mmm.com
Dental Monitor Contact	**Name:** Xiaohui Xu, Dr. med. Dent. **Address:** Espe-Platz, 82229, Seefeld, Germany **Telephone:** +4915120906206 **Email:** xxu19@mmm.com

2. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

2.1. BACKGROUND

2.1.1. Dentin Hypersensitivity

Dentin hypersensitivity (DHS) is characterized as exposed dentin in which brief, sharp pain occurs in response to stimuli (eg, thermal and/or tactile stimulus) and cannot be ascribed to any other form of dentin defect.[1] DHS is a fairly common affliction for adults, with one study showing 21.3% of Subjects (163 of 767) with DHS in response to tactile stimulus and 38.6% of Subjects (296 of 767) with DHS in response to air-blast stimulus (ie, cold air exposure).[2] Not surprisingly, non-carious cervical lesions and gingival recession were significantly associated with DHS in response to both tactile and air stimulus ($P \leq 0.02$) in the aforementioned population, and female sex was significantly associated with DHS in response to air-blast stimulus ($P < 0.01$).[2]

There are currently two modes of action for agents used to manage DHS: (i) blocking pulpal nerve response or (ii) dentine tubule occlusion with resistance to removal by acidic challenges.[3] Fluoride (F^-)-containing products, including those that are self-administered (eg, pastes and rinses) and those that are professionally applied (eg, varnishes and gels), have been shown to relieve DHS via the second mode of action through the formation of precipitates (eg, calcium-phosphorous, calcium fluoride, and fluorapatite).[4-6] ***The focus of this study is to compare two professionally applied F-containing products, one of which contains a hexane-based solvent and the other a novel aqueous solution (Clinpro™ 2.1% Sodium Fluoride Aqueous Solution), on changes in DHS.***

2.1.2. Desensitizing F^- containing Agents in the Treatment of DHS

Previous publications reporting clinical trial results for the impact of professionally applied F^--containing products (with more than 1% F^- in the product) on DHS in at least one arm of the trial date back to the early 1990s,[7] with 22 clinical trials assessing DHS since that time.[7-28] One publication had an inconsistent description of methods and study results, which made a meaningful interpretation of the data impractical.[8] In addition, three other studies are not relevant for this trial since the F^--containing products were used along with an adjunctive therapy (eg, subsequent laser treatment or iontophoresis)[7,11] or citric acid was applied to teeth prior to assessing DHS.[19] Lastly, eight of the previous studies did not evaluate the immediate impact of the F^--containing product on DHS, which is the primary endpoint of this study, and fall outside of the main focus for this study.[10,15-18,20,24,27] However, there have been 10 clinical studies assessing the immediate impact of a professionally applied F^--containing product on

DHS.[9,12-14,21-23,25,26,28] Of these 10 studies assessing the immediate impact of professionally applied F^--containing products, half of the studies (5) examined 2% fluoride gels,[14,21,23,26,28] and the other half examined the impact of 5% fluoride varnishes.[9,12,13,22,25]

2.1.2.1. IMPACT OF 2% FLUORIDE GELS ON IMMEDIATE CHANGE IN DHS

Each of the 5 publications that assessed an immediate change in pain for study teeth with DHS used cold-air stimulus (ie, air blast stimulus) as part of the assessments. In one of the studies, a verbal response scale (VRS) was used to assess pain, whereby a "0" indicated the absence of pain and a "4" indicated unbearable pain.[23] Similar VRS scores were observed for 18 teeth before (2.5 ± 0.514) and immediately after (2.56 ± 0.511) application of the 2% F^- gel.[23] In the other four studies using 2% F^-gels in one of the study arms, a visual analog scale (VAS) ranging from 0 to 10 cm (or 100 mm) was used to measure pain levels, whereby a "0" indicated no pain and a "10" (ie, 10 cm or 100 mm on the scale) indicated unbearable pain.[14,21,26,28] In a study with a sample size of 27 teeth treated with 2% F^-gel, Soares et al observed a mean (± standard deviation, or SD) reduction in the VAS score of 2.5 cm (± 1.86 cm) points immediately after product application when compared with the baseline score ($P = 0.001$).[28] In a sample size of 65 teeth treated with 2% F^- gel, Femiano et al observed a change in the mean (range of single VAS values for the group) VAS score from 6.4 cm (±4 cm) at baseline to 3.2 cm (±5 cm) immediately after gel application ($P < 0.001$).[14] Similarly, Lund et al described a reduction in the mean VAS score from 6.1 cm (variance or range not provided) at baseline to 4.1 cm when assessed 5 minutes after application of a 2% sodium fluoride gel ($P < 0.05$).[21] In addition to VAS scores, Lund et al examined the exposure time to air blast (ETAB); for teeth treated with 2% F^- gel, there was an increased ETAB from 4.0 seconds at baseline to 9.3 seconds when measured 5 minutes after product application ($P < 0.05$).[21] Lastly, Pamir et al observed a change in the mean (± standard error, or SE) VAS score (n = 30 teeth) from 5.0 cm (± 0.3 cm) at baseline to 1.7 cm (± 0.3 cm) immediately after application of the 2% sodium fluoride gel ($P < 0.05$).[26] In this study, the change in VAS scores in response to tactile stimulus was also examined, and a change in the mean (± SE) VAS score from 4.1 cm (± 0.2 cm) at baseline to 1.1 cm (± 0.3 cm) immediately after application of the 2% sodium fluoride gel was observed ($P < 0.05$).[26]

2.1.2.2. IMPACT OF 5% FLUORIDE VARNISHES ON IMMEDIATE CHANGE IN DHS

Previous clinical trials reporting on the immediate impact of 5% F^- varnishes on DHS have assessed the response to cold-air stimulus and/or tactile stimulus. Pain assessments were made using a VAS scale (described in Section 2.1.2.1), a calibrated Yeaple probe (for tactile stimulus) that was used to measure the amount of pressure in grams (g) until the Subject felt discomfort, or the Schiff scale, depending on the trial. For the Schiff scale, scoring categories included:

"0", indicating no response to the stimulus, "1", indicating the Subject responded to the stimulus but did not request its discontinuation, "2", indicating the Subject responded to the stimulus and requested its discontinuation or moved away from the stimulus, and "3", indicating that the Subject considered the stimulus painful and requested its discontinuation.

In 2003, Corona et al reported the number of Subjects (n = 30) within each Schiff category in response to air blast stimulus both before and immediately after application of a 5% F^- varnish. Before treatment, there were no (0) Subjects with a score of "0", 11 Subjects with a score of "1", 13 Subjects with a score of "2", and 6 with a score of "3". Immediately after treatment, 11 Subjects had a score of "0", 6 had a score of "1", ten had a score of "2", and 3 had a score of "3".[12] In 2018, Anderson et al analyzed the immediate impact of a 5% F^- varnish on immediate changes in DHS by analyzing both the VAS and Schiff score upon air blast stimulus for 11 Subjects. The mean (± SD) VAS was reduced from 58.18 mm (± 15.16 mm) at pre-treatment to 30.5 mm (± 28.51 mm) after treatment, and the mean (± SD) Schiff score was reduced from 2.32 (± 0.72) at pre-treatment to 0.91 (± 1.0) after treatment ($P < 0.05$).[9] In a study of 36 teeth treated with a 5% F^- varnish, Eyüboğlu et al showed a significant reduction in VAS upon air blast stimulus ($P < 0.001$), changing from 56.39 mm (± 19.91) at baseline to 10 mm (± 15.11 mm) immediately after treatment.[13] Additionally, there was significant change in the amount of pressure (ie, tactile stimulus) before the Subject felt discomfort ($P < 0.01$), changing from 18.89 g (± 12.1 g) at baseline to 32.78 g (± 23.49 g) immediately after treatment.[13] Finally, Machado et al observed a significant reduction in VAS ($P < 0.05$) in response to air blast stimulus, with a mean (± SD) VAS of 5.9 cm (± 1.5 cm) at baseline versus 3.4 cm (± 2.4 cm) immediately after treatment.[22] In this study, a significant reduction in VAS ($p < 0.05$) was also seen for teeth (n = 38) treated with a F^--containing ionomeric sealant, with a mean (± SD) VAS of 6.7 cm (± 1.7 cm) at baseline and 3.4 cm (± 2.5 cm) immediately after treatment.[22]

2.2. RATIONALE FOR STUDYING THE SPECIFIC POPULATION/CONDITION

Subjects with at least one tooth with DHS, defined as having a baseline VAS score of at least 40 mm in response to air blast stimuli, were selected as the specific population/condition for this study since desensitizing agents are commonly used to treat DHS (see Section 2.1.1). Subjects with surrounding teeth or tissues with painful pathology or defects are being excluded in an effort to eliminate the potential for pain from an area other than the study tooth (ie, to not impact VAS scores from the study tooth itself). Similarly, teeth with previous restorations or periodontal treatments are being excluded to limit other potential causes of tooth pain.

2.3. SCIENTIFIC RATIONALE FOR DESIGN

To have a high level of evidence, a prospective, randomized, single-blinded, parallel, non-inferiority study was the design selected for this study. A within-subject (ie, split-mouth) design was not included since the product compositions allow spreading to adjacent areas of the mouth.

Vanish™ 5% Sodium Fluoride White Varnish was selected as the comparator product (ie, Control device) for this study since it is a well-known fluoride varnish used as a desensitizing agent, with three previous publications describing its impact on the reduction of DHS when used in a clinical trial.[13,20,22]

The primary endpoint for this study will focus on the immediate reduction in DHS in response to a air blast stimulus (ie, the change from before product application to immediately after application), as measured using a VAS (see Section 5.3.1). This timepoint was selected primarily due to the abundance of literature analyzing immediate changes in DHS in response to professionally applied F^--containing desensitizing agents (see Section 2.1.2). In addition, the baseline VAS and immediate post-application VAS will be assessed at the same visit, thereby limiting the number of Subjects that may be lost to follow-up prior to collection of data for the primary endpoint.

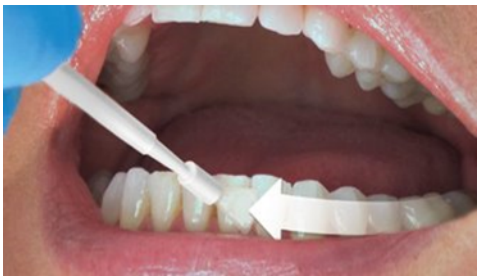
It is hypothesized that Clinpro™ 2.1% Sodium Fluoride Aqueous Solution will be non-inferior to Vanish™ 5% Sodium Fluoride White Varnish in immediately reducing DHS.

3. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

The investigational device for this study is Clinpro™ 2.1% Sodium Fluoride Aqueous Solution, which is a xylitol-sweetened aqueous fluoride coating that is applied topically to the tooth surfaces for the treatment of DHS. Clinpro™ 2.1% Sodium Fluoride Aqueous Solution contains 9,500 ppm fluoride as well as added calcium and phosphate.

This product is supplied in unit-dose packages containing 0.5 ml (0.5 grams) of the gel and is expected to be offered in a neutral, mint, and fruit (eg, melon) flavor. Clinpro™ 2.1% Sodium Fluoride Aqueous Solution will utilize the 3M L-Pop delivery system shown in Table 3-1, Figure A, along with a depiction of product application (Table 3-1, Figure B).

Table 3-1. Investigational Device

Name of Investigational Device	Depiction of the Investigational Device
A) Clinpro™ 2.1% Sodium Fluoride Aqueous Solution **B) Depiction of product application**	A  B 

3.1.1. Control Device

The control device used in this study is Vanish™ 5% Sodium Fluoride White Varnish, which is a 22,600-ppm fluoride-containing varnish for application to enamel and dentin for the treatment of hypersensitive teeth. This product is supplied in unit-dose packages containing 0.5 ml (0.5 grams) of varnish coating and exhibits an extended-release formula that releases fluoride, calcium, and phosphate for 24 hours after application.

3.2. DEVICE REGULATORY CLASSIFICATION

Clinpro™ 2.1% Sodium Fluoride Aqueous Solution is anticipated to be a class 2 medical device under FDA product code LBH (varnish, cavity per 21 CFR 872.3260) that will require

FDA 510(k) ance. A 510(k) Pre-market Notification is planned for submission during the first quarter (Q1) of 2023.

Clinpro™ 2.1% Sodium Fluoride Aqueous Solution is not expected to have 510(k) clearance when the study begins. For the purpose of this study, the product is not considered a Significant Risk(SR) investigational device under 21 CFR 812.3(m) because:

- Is not intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is not purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; and
- Does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject

3.3. Intended Use of the Device/Indications for Use

The intended use of the device is the following:

Clinpro™ 2.1% Sodium Fluoride Aqueous Solution is a fluoridated tooth coating.

Data generated from this study is to support the indication for use in treating dentin hypersensitivity as well as support that the product is safe to use for the intended purpose. Data from this study will also be used for global regulatory registration.

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

4.1. Benefits of the Device

Participants may benefit from a reduction in tooth hypersensitivity upon application of the investigational device or the comparator device.

4.2. Risks of the Device

Fluoride varnishes and gels are considered to be low risk medical devices that are commonly used throughout dentistry. Subjects participating in this clinical study may face the following potential risks, including but not limited to:

- Product contact with eye resulting in irritation
- Skin irritation with possible blistering
- Ingestion of excess product resulting in gastrointestinal upset, light headedness, dizziness, and/or presyncope
- Product aspiration.
- Allergic reaction (eg, atopic dermatitis)

4.3. ANTICIPATED ADVERSE DEVICE EFFECTS

The anticipated Adverse Device Effects (ADEs) for Clinpro™ 2.1% Sodium Fluoride Aqueous Solution include the following:

- Ingestion of excess product resulting in gastrointestinal upset, light headedness, dizziness, and/or presyncope
- Allergic reaction

In addition to the anticipated ADEs for the investigational product, desensitizing agents that use organic solvents such as Vanish™ 5% Sodium Fluoride White Varnish, also have the following anticipated ADEs:

- Soft tissue erythema (redness)
- Soft tissue edema (swelling)
- Pruritus (itching), burning or other local sensations (eg, tingling or numbness)

Subjects with known allergies to components of the study devices are being excluded from participation in the study (see Section 6.5.1.2). In addition, the anticipated ADEs listed above are being captured as safety data as part of this trial.

4.4. RESIDUAL RISKS

The Subjects will undergo a single application of study product and are not expected to have long-term exposure to the material. Therefore, residual risks are expected to be minimal for this study.

4.5. RISK OF INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

No specific risk of interaction with concomitant medical treatment is known for the tested devices.

4.6. MITIGATION OF RISK

Risk 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), product deficiencies/complaints and deviations to the Sponsor.

4.7. RISK TO BENEFIT RATIONALE

Based upon the risks and benefits listed above and adherence to this CIP, 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 investigational device and the comparator device are being used in accordance with their intended use consistent with standard dental treatment plans for patients not participating in this study. Participants may benefit from a reduction in tooth hypersensitivity upon application of the investigational device or the comparator device.

5. OBJECTIVES OF THE CLINICAL INVESTIGATION PLAN

5.1. PURPOSE OF THE CLINICAL INVESTIGATION

The purpose of this investigation is to generate data to support an indication for use of the Investigational product in treating dentin hypersensitivity (DHS) and to support global regulatory registration of the product.

5.2. PRIMARY OBJECTIVE(S)

The primary objective of this study is to evaluate the effect of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution (experimental) on DHS in comparison to Vanish™ 5% Sodium Fluoride White Varnish (commercialized, control), a well-known product in the market used for this purpose.

5.3. STUDY ENDPOINT(S)

5.3.1. Primary Endpoint(s)

Co-primary endpoints include:

- the change in pain, using a 100-mm VAS from baseline to immediately after application (within 15 minutes post treatment) of test product or comparator.
- the change in pain score from baseline to 24 ± 4 h post-application, using VAS after exposure to air stimulus.

Sensitivity will be assessed using VAS after exposure to air stimulus.

5.3.2. Secondary Endpoint(s)

The secondary endpoints include:

1. change in pain score, using VAS, from baseline to 7 ± 2 days post-treatment, after exposure to air stimulus.
2. change in pain score, using VAS, from baseline to 21 ± 2 days post-treatment, after exposure to air stimulus.
3. change in pain score, using VAS, from baseline to 30 ± 2 days post-treatment, after exposure to air stimulus.

5.3.3. Additional/Exploratory Endpoints

The exploratory endpoints will include the reduction in pain (using a VAS) upon tactile testing with a periodontal probe, including:

1. Change from baseline to immediately post-treatment (within 15 minutes post-treatment)
2. change from baseline to 24 ± 4 h post-treatment
3. change from baseline to 7 ± 2 days post-treatment
4. change from baseline to 21 ± 2 days post-treatment
5. change from baseline to 30 ± 2 days post-treatment.

5.3.4. Safety Endpoint(s)

The safety endpoint will be the incidence of all AEs.

6. DESIGN OF CLINICAL INVESTIGATION

6.1. DESIGN

This is a prospective, randomized, single-blinded, parallel, non-inferiority study, that will enroll Subjects requiring treatment for DHS. Subjects will be randomized in a 1:1 ratio with half of the Subjects treated with Clinpro™ 2.1% Sodium Fluoride Aqueous Solution and the other half treated with Vanish™ 5% Sodium Fluoride White Varnish. The study will be conducted at a single investigational site(s) in the following location(s): Loma Linda University Health.

6.2. STUDY DURATION

The entire duration of the study is expected to last one year. Individual subject participation is expected to last up to 82 days, including a 3- to 6-week washout period before treatment.

6.3. MINIMIZATION OF BIAS

Due to the nature of the investigative device, the duration of treatment application, and the study design, Investigator blinding is not feasible for the study. However, the following measures have been taken to minimize or avoid bias in this study:

- Randomization in a permuted-block manner
- Blinding of study Subject
- Management of confounding factors – eg, exclusion of Subjects with other potential causes of tooth sensitivity (eg, previous restorations or periodontal treatments)

6.4. INVESTIGATIONAL USE OF DEVICE AND COMPARATOR

Clinpro™ 2.1% Sodium Fluoride Aqueous Solution (Treatment arm) or Vanish™ 5% Sodium Fluoride White Varnish (Control arm) will be used to treat DHS. The investigational device is a new-to-market product, and at the time of this protocol, the product is not authorized for commercial sale or investigational use in any markets. This investigation is being conducted prior to receiving formal market authorization in the country where the investigational site(s) is located; however, this study is considered a non-significant risk study, and appropriate approval from an IRB/ethics committee is required prior to the initiation of the study. The control device is being used in a manner consistent with the ed indication and IFU.

6.5. SUBJECT ENROLLMENT

A minimum of ninety six (96) enrolled Subjects that complete the treatment is planned for this study. To achieve this minimum, the Investigator may enroll up to one hundred and twenty five (125) subjects.

6.5.1. Enrollment Criteria

To be considered eligible for enrollment, Subjects must meet all the inclusion listed in section 6.5.1.1 and none of the exclusion criteria listed in Section 6.5.1.2. Subjects are to be assessed for eligibility no more than 3-6 weeks prior (ie, at least 3 weeks but no more than 6 weeks) to the planned procedure and eligibility will be re-confirmed including the use of (IC4) on the day of the procedure. Subjects who do not meet all the inclusion or meet any of the exclusion

criteria will not be eligible for randomization and will discontinue from the study. They will be considered a screen failure.

6.5.1.1. INCLUSION CRITERIA

Subjects may be included that meet the inclusion criteria in Table 6.5.1-1:

Table 6.5.1-1: Inclusion Criteria

Number	Inclusion Criteria
1	Subject has at least one affected hypersensitive tooth upon air blast stimuli in the cervical area, and baseline pain score of 40 mm and above as assessed by the 100 mm VAS.
2	Subject is at least 18 years old and have a minimum of 20 natural teeth.
3	Subject is willing to withhold desensitizing treatment, including prescription, in-office or over the counter (OTC) desensitizing products, throughout the study period AND withhold during the washout period
4	Subject agrees to only use the provided toothpaste, toothbrush, and follows all oral hygiene instructions throughout the study period AND follows all oral hygiene instructions during the washout period.
5	Subject is able to understand and willing to sign the Informed Consent, and is willing to return to the study facility for scheduled study visits and recalls.

6.5.1.2. EXCLUSION CRITERIA

Subjects must be excluded from participating in this study if they meet any of the criteria in Table 6.5.1.2-1.

Table 6.5.1.2-1: Exclusion Criteria

Number	Exclusion Criteria
1	Subject has medical (including psychiatric) and pharmacotherapeutic histories that may compromise the protocol – including the chronic use of anti-inflammatory, analgesic (pain), and mind-altering drugs; or analgesic (pain) medications within 48 hours prior to application of treatment.
2	Subject is pregnant (self-reported) or breast feeding.

Number	Exclusion Criteria
3	Subject has allergies to product ingredients, eg, rosin, mint flavoring.
4	Subject has systemic conditions that are etiologic or predisposing to dentin hypersensitivity (eg, chronic acid regurgitation).
5	Subject has excessive dietary or environmental exposure to acids at time of screening.
6	Subject had periodontal treatment, bleaching treatments, or orthodontic treatments within previous 3 months or plans to have any other dental treatments during the study period.
7	Subject is enrolled in another clinical trial at the time of screening that would interfere with this study.
8	Subject is, in the opinion of the investigator, unsuitable for enrollment in the study for reasons other than those specified in the above exclusion criteria.
Number	**Tooth Exclusion Criteria**
9	Study tooth has periodontal probing depth of ≥ 4 mm.
10	Study tooth or the surrounding supporting tissue has any other painful pathology or defects.
11	Study tooth has been restored in the preceding 3 months
12	Study tooth is an abutment for fixed or removable prostheses or suffers traumatic malocclusion.
13	Study tooth is crowned or extensively restored and the restorations extending into the test area.
14	The tooth has dentin hypersensitivity due to cracked enamel.

6.6. PROCEDURES AND ASSESSMENTS

6.6.1. Obtaining Informed Consent

Informed consent must be obtained for all Subjects 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 are relevant to 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 Institutional Review Board (IRB)-approved Informed Consent Form (ICF) and to consider participation in the study.

The study subject or legal authorized representative must sign and date the ICF. The Investigator or designee must sign and date the ICF. The ICF 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.

The Investigator or designee must file the original ICF and provide the subject with a copy of the signed and dated Informed Consent and any other written documentation per local IRB requirements.

Subject privacy language, Health Insurance Portability and Accountability Act (HIPAA) or General Data Protection Regulation (GDPR), per local regulations may be added to the local Informed Consent by the Investigator.

6.6.2. Laboratory Assessments to Determine Eligibility

No laboratory assessments will be performed as part of this study.

6.6.3. Demographics and Subject Characteristics

After a Subject signs the ICF but before treatment, the following demographic data and Subject characteristics will be collected and documented:

- Age
- Sex
- Baseline VAS upon air blast and tactile stimuli immediately before treatment
- Race
- Ethnicity
- Study tooth number

6.6.4. Vital Signs

No vital signs will be captured as part of this study.

6.6.5. Randomization and Blinding

Randomization should occur after obtaining informed consent and ensuring that the Subject meets all eligibility criteria; randomization should occur on the day of treatment before the initial application of the investigational device (Treatment arm) or control device (Control arm). Due to the nature of the investigative device, the duration of treatment application, and the study design, Investigator blinding is not feasible for the study. For Subjects with multiple eligible teeth, the PI will select the index tooth based on their experience and accessibility of the tooth for the stimuli; however, this selection must be made prior to randomization. Randomization of the Subjects will be performed using a permuted block technique and will be centralized and electronic.

6.6.6. Treatments

6.6.6.1. WASHOUT PERIOD

All Subjects will undergo a pre-treatment washout period for 3- to 6-weeks (± 4 days) post-enrollment. During this time, the Subject is to only use the oral hygiene products (Colgate Cavity Protection Fluoride Toothpaste - Great Regular Flavor 0.15% w/v Fluoride Ion, Colgate Company and Oral-B® Indicator™ Toothbrush, Sensitive 35 Extra Soft, Procter & Gamble Company) provided for the study, except for floss; beginning immediately after the consent visit. The Subject should perform tooth brushing during this period with the sponsor-provided toothbrush and toothpaste as directed by the Investigator. In addition, the Subject should refrain from taking prescription or OTC analgesic medications for 48 hours prior to the treatment visit and all post-treatment visits. Any use of analgesics within 48 h prior to treatment visit should be documented on concomitant medications CRF.

6.6.6.2. BASELINE PAIN ASSESSMENTS AND TREATMENT APPLICATIONS

The study tooth for Subjects in both arms of the study will be isolated from neighboring teeth according to standard dental practices (eg, VPS putty or cotton rolls) and should remain isolated during pain assessment. Isolation materials may be removed during treatment application; however, the study tooth should remain clean and free of excess saliva for the application of the product. The method of isolation should be documented and should remain consistent for each study visit. After isolation of the study tooth, a pain assessment will be performed (ie, a baseline pain score) in response to both an air-blast stimulus and tactile stimulus. For the air-blast stimulus, a pressure-calibrated air syringe should be placed perpendicular to the center cementoenamel junction (CEJ) of the study tooth. With the tip of the syringe placed approximately 1 cm from the tooth, the syringe is to be fully activated for 1 second. For the

tactile test, a periodontal probe will be moved from distal to mesial along the CEJ, with a continuous unidirectional stroke of around 1 second duration. After each stimulus, the Subject should score their pain by indicating their pain level on a 100-mm VAS that represents a continuum between "no pain", indicated by 0 mm on the scale, and "worst pain", indicated by 100 mm on the scale. A VAS score should be recorded for both the air-blast stimulus and tactile stimulus, with the VAS score for the air-blast stimulus occurring prior to initiating the tactile test, with a minimum of 3 minutes between tests.

After recording baseline pain scores, isolation should be maintained and excess saliva should be removed. Immediately apply Clinpro™ 2.1% Sodium Fluoride Aqueous Solution (Treatment arm) or Vanish™ 5% Sodium Fluoride White Varnish (Control arm) as described in Sections 6.6.6.2.1 or 6.6.6.2.2, respectively.

6.6.6.2.1. TREATMENT GROUP

After ensuring that the study tooth is clean and free of excess saliva, Clinpro™ 2.1% Sodium Fluoride Aqueous Solution should be applied to the tooth using the applicator brush, according to the manufacturer's IFU. The product should be applied to the tooth in a thin layer, reloading the applicator brush as needed. Only enough product should be used to form a thin coating on the desired treatment area, and it is not necessary to use all the product provided. After the application, any excess material or saliva may be suctioned from the mouth or the Subject may spit. To achieve the maximum benefit, the Subject should avoid food, beverages, and oral rinses for 15 minutes after application.

6.6.6.2.2. CONTROL GROUP

After ensuring that the study tooth of Subjects randomized to the Control group is clean and free of excess saliva, 3M™ Vanish™ 5% Sodium Fluoride White Solution should be applied to the tooth using the applicator brush, according to the IFU. Before application, use the brush to thoroughly mix the varnish since components of all sodium fluoride varnishes can separate during storage. The product should be applied to the study tooth in a thin layer, applying the varnish in sweeping horizontal brush strokes and avoiding excessive contact with soft tissue. Only enough varnish to form a thin coating should be used on the desired application area. After application, the Subject should close their mouth to allow the varnish to set and rinsing or suctioning immediately after application is not recommended. To achieve the maximum benefit after application, the Subject should not brush or floss the teeth for at least 4 hours and preferably up to 24 hours after the application. The Subject should also eat soft foods and should not consume hot drinks or alcohol (mouth rinses) during the 24-hour period after application.

6.6.7. Post-Treatment Pain Assessments

Post-treatment pain assessments will be performed for all Subjects in response to both an air-blast stimulus and tactile stimulus with the VAS score for the air-blast stimulus occurring prior to initiating the tactile test, and waiting a minimum of 3 minutes between tests, as described in Section 6.6.6.2.

For post-treatment tactile (probe) testing, the same type of instrument that was used for the pre-treatment test (ie, periodontal probe) should be used for the post-treatment test, taking care to use the similar force as before and not remove the coating on the tooth during the test performed immediately after treatment (whithin 15 minutes post-treatment). All post-treatment VAS scores should be documented in the appropriate CRF.

6.6.8. Concomitant Medications

Concomitant medications will be collected from the time of informed consent through the final study visit. The medical name, start date, end date; end time or ongoing and indication reason will be reported.

6.6.9. Adverse Events and Adverse Device Effects

AEs and ADEs will be collected from the time of initial application of control or investigational treatment until end of study visit (30 days post-application). AEs and ADEs will be reported according to Section 13.

6.6.10. Prohibited Procedures and On-Study Restrictions

No other treatments for the study tooth other than those described in Section 6.6.6 are permitted during the course of this study. Any divergence from these treatment conditions will be captured as a protocol deviation (see Section 10) and the reason for selecting alternative treatments in the absence of an AE or device defect should be documented. Study visits that occur outside of the study visit windows will also be documented as protocol deviations. In addition, Subjects should avoid the following from the time of tooth treatment until completion of the study to ensure the oral hygiene activities and products used are controlled prior to and throughout the study:

- Refrain from additional desensitizing treatments after application of the study product.
- Refrain from activities that would impair the function of the products, including:
    - acidic beverages
    - use of any tooth whitening/bleaching products for the entire study period.

- Refrain from any non-emergency treatment for the entire study period.

Any deviation(s) from the CIP that diminishes the integrity of the data, results in non-adherence to the eligibility criteria, or impacts the Subject's rights, safety, or welfare will be documented as major protocol deviation(s) (see Section 10).[29]

6.6.11. End of Study Documentation

Subjects may withdraw or be discontinued from this study at any time. 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 ending participation in the study

6.7. VISIT SCHEDULE AND DESCRIPTION OF STUDY VISITS

6.7.1. Point of Enrollment

A Subject is considered enrolled in this study at time the Informed Consent process has been completed. Since the subject will have signed the informed consent, if post-consent screening procedures or eligibility re-confirmation on the initial day of study procedures reveal that the subject does not meet eligibility criteria, the subject will be considered a Screen Fail and will not be assigned a treatment allocation number.

6.7.2. Visits

After Informed Consent has been obtained, each Subjects will be given Sponsor-supplied oral hygiene products (eg, toothbrush and toothpaste) to be used immediately after the consent visit and throughout the entire duration of the study. All Subjects will return for a treatment visit (Day 0) and post-treatment follow-up visits at 24 hours (± 4 hours), 7 days (± 2 days), 21 days (± 2 days), and 30 days (± 2 days) after the treatment visit. All applicable data are to be recorded in the applicable Case Report Form (CRF).

6.7.2.1. SCHEDULE OF EVENTS

A schedule of events is in Tables 6.7.2.1-1 below:

Table 6.7.2.1-1: Schedule

	Consenting Visit & pre-treatment washout	Treatment Visit	24-hour follow up	Day 7 follow-up	Day 21 follow-up	30 Day follow-up	Unscheduled Visit
Visit Number	1	2	3	4	5	6	
Visit Window	3-6 weeks	Day 0	24 ± 4 h	7 d ± 2 d	21 d ± 2 d	30 d ± 2 d	
Screening	X						
Informed Consent signed	X						
Concomitant meds	X	X	X	X	X	X	X
Eligibility confirmation	X	X*					
Enrollment	X						
Randomization		X					
DHS Treatment		X					
Pain assessments to air-blast stimulus and tactile stimulus	X	X**	X	X	X	X	X
AEs / SAEs / ADEs / DDs		X	X	X	X	X	X
End-of-Study						X	X***

* Before treatment
**Before treatment (baseline) and after treatment
***if applicable

6.7.2.2. STUDY VISIT 1 (CONSENTING AND QUALIFICATION VISIT)

1. The following procedures and assessments will be completed at Visit 1: Assessment of eligibility, including assessment of self-reported pregnancy/breastfeeding status for female Subjects, as described in Section 6.5.1.
2. Obtain informed consent, as described in Section 6.6.1.
3. Document Subject demographics and characteristics, as described in Section 6.6.3.
4. Document concomitant medications, as described in Section 6.6.8.
5. Provide Subjects with Sponsor-supplied study products for oral hygiene (eg, toothbrush, toothpaste).

6.7.2.3. STUDY VISIT 2 (DAY 0 – TREATMENT VISIT)

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

1. Confirmation that Subject meets eligibility criteria (see Section 6.5.1) and update concomitant medications (see Section 6.6.8) as Visit 2 occurs on a different day than Visit 1. If Visit 1 and Visit 2 are > 6 weeks apart, Subject should be re-screened.
2. Baseline pain assessments and DHS treatment, as described in Section 6.6.6.
3. Post-treatment pain assessments after application (within 15 minutes post-treatment), as described in Section 6.6.7.
4. Assessment and documentation of AEs, ADEs, and DDs, as described in Section 6.6.9.

6.7.2.4. STUDY VISIT 3 (24 ±4 H POST-TREATMENT)

The following procedures and assessments will be completed at Visit 3:

1. Pain assessments, as described in Section 6.6.7
2. Document concomitant medications, as described in Section 6.6.8.
3. Assessment and documentation of AEs, ADEs, and DDs, as described in Section 6.6. 9.

6.7.2.5. STUDY VISIT 4 (DAY 7 ± 1 D POST-TREATMENT)

1. Pain assessments, as described in Section 6.6.7
2. Document concomitant medications, as described in Section 6.6.8.
3. Assessment and documentation of AEs, ADEs, and DDs, as described in section 6.6.9.

6.7.2.6. STUDY VISIT 5 (DAY 21 ± 2 D POST-TREATMENT)

1. Pain assessments, as described in Section 6.6.7
2. Document concomitant medications, as described in Section 6.6.8.
3. Assessment and documentation of AEs, ADEs, and DDs, as described in section 6.6.9.

6.7.2.7. STUDY VISIT 6 (END OF STUDY – DAY 30 ± 2 D POST-TREATMENT)

1. Pain assessments, as described in Section 6.6.7
2. Document concomitant medications, as described in Section 6.6.8.
3. Assessment and documentation of AEs, ADEs, and DDs, as described in section 6.6.9.
4. Documentation of end of study (see Section 6.6.11).

6.7.2.8. UNSCHEDULED VISIT

1. Pain assessments, as described in Section 6.6.7
2. Document concomitant medications, as described in Section 6.6.8.
3. Assessment and documentation of AEs, ADEs, and DDs, as described in section 6.6.9.
4. Documentation of end of study, as described in Section 6.6.11, if applicable.

6.7.3. Point of Exit

Study Subjects may exit the study for a variety of reasons. The Investigator shall record the reason for ending participation in the study in the applicable Case Report Form. 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
- Study Termination

In the event of subject withdrawal or discontinuation prior to treatment visit (screen fail), study Subjects will be replaced until the desired enrollment is reached. In the event of subject withdrawal or discontinuation post treatment visit, Subject will not be replaced.

Data collected until the last known contact of study subject may be used in the analysis of study data. 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.

6.8. ROLE OF SPONSOR REPRESENTATIVE

6.8.1. 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 Principal Investigators (PIs) 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 and/or remote review
- Telephone communications
- Review of CRFs and source documents (eg subject records)

The study monitor(s), other authorized representatives of the Sponsor, representatives of the IRB, 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' 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.

Details of clinical site monitoring are documented in a Monitoring Plan (MP). The MP describes who will conduct the monitoring, the planned frequency of monitoring visits, records to be reviewed, and the distribution of monitoring reports.

Independent audits may be conducted by 3M personnel or an independent party to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

6.8.2. 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

7. DATA MANAGEMENT

Data collected for this study will be analyzed and stored at 3M or an approved supplier for use by researchers including those outside of the study. Permission to transmit, store and use data outside of the study will be included in the informed consent. Details of data management for this investigation are documented in a Data Management Plan (DMP). The DMP describes the procedures used for CRF tracking, data review, database cleaning, query management, coding and data reconciliation.

7.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site 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 should be completed in a neat, legible, permanent and un-editable manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) derived from source documents must be consistent with the data recorded on the source documents.

All data, including AEs and expected AE data, will be entered into a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks (eg, automatic range checks) to identify data that appear inconsistent, incomplete, or inaccurate.

The Sponsor 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.

7.2. STUDY RECORDS RETENTION

Information for each study participant will be securely stored at each 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 in accordance with policies from the reviewing IRBs, Institutions, regulatory authorities, and Sponsor requirements.

No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when study documents no longer need to be retained.

7.3. 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 AEs, 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.

8. STATISTICAL CONSIDERATIONS

8.1. PASS/FAIL CRITERIA

The null hypotheses that we seek to reject are that Vanish™ 5% Sodium Fluoride White Varnish has a 15.0 mm higher change from baseline VAS than Clinpro™ 2% Sodium Fluoride Aqueous Solution when measured immediately after application (within 15 minutes post-treatment) or at 24-hours after treatment (±4 hours). The null and alternate hypotheses are described below.

H_0: Vanish™ Varnish changed from baseline – Clinpro™ 2.1% Sodium Fluoride Aqueous Solution change from baseline >15 mm.

H_a: Vanish™ Varnish changed from baseline – Clinpro™ 2.1% Sodium Fluoride Aqueous Solution change from baseline ≤15 mm.

8.2. SAMPLE SIZE DETERMINATION

Twenty-eight hypersensitivity studies were reviewed for difference in treatment effect (change from baseline) of actives and several reported differences between actives in VAS change from baseline of greater than 20 mm. Even with these notable differences, the authors routinely declare all actives effective in treatment of hypersensitivity. This study will use a more conservative non-inferiority margin of 15 mm. A standard deviation for change from baseline at immediately after treatment (within 15 minutes post-treatment) and 24-hours of 20 mm will be used. There is uncertainty in the efficacy difference between treatments as well as the error term. An interim analysis will be conducted at approximately 50% of subject treatment to reassess sample size with no alpha spending required. Ninety-six (96; 48 per arm) total subjects will provide 80% power allowing for a 2 mm difference in efficacy difference between treatments and 2 co-primary endpoints tested. No subjects will be lost to follow-up for the primary time point of immediate hypersensitivity relief, but there may be loss to follow-up for co-primary endpoint of hypersensitivity relief at 24-hours after treatment.

8.3. ANALYSIS POPULATIONS

All dosed subjects without a major protocol deviation will be included in the analysis dataset for the co-primary endpoints of change in hypersensitivity immediately after product application and change in hypersensitivity 24-hours after application. For the secondary and exploratory endpoints, all dosed subjects without a major protocol deviation occurring up to the evaluation time for each endpoint will be included in the analysis dataset for that endpoint. All treated subjects will be included in the safety analysis dataset. Major protocol deviation(s) for exclusion from the analysis dataset will be defined and documented in a blinded fashion prior to interim and final analyses (eg, inadequate washout).

8.4. STATISTICAL ANALYSES

8.4.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics for the study will be generated and displayed by treatment arm and overall. Key baseline characteristics variables may include but are not limited to general health status, baseline pain, and any specific factors that may affect the change in pain after treatment.

8.4.2. Analysis of Primary Endpoints

At the final analysis, multiplicity will be controlled through a Hochberg procedure. Ninety-five- percent (95%) confidence intervals will be generated for the difference between treatments

in change from baseline immediately after application and separately for the difference between treatments in change from baseline 24-hours after application using Student's t distribution.

Scenario 1: Neither of the 95% confidence intervals contain 15 mm.

Result: Non-inferiority for both co-primary endpoints will be declared

Scenario 2: Both of the 95% confidence intervals contain 15 mm.

Result: No non-inferiority for either co-primary endpoints will be declared, and all analyses will be informational only.

Scenario 3: One confidence interval contains 15 mm, and the other confidence interval does not contain 15 mm.

The endpoint that does not contain 15 mm has the potential to be declared non-inferior. For this endpoint, as part of the Hochberg procedure, a 97.5% confidence interval will be generated. Non-inferiority for this endpoint will be declared if the new confidence interval does not contain 15 mm.

8.4.3. Analysis of Secondary Endpoints

If the null hypotheses are rejected for both co-primary endpoints, the alpha will be passed to test for non-inferiority of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution to Vanish™ Varnish for the various secondary endpoints. Ninety five percent (95%) confidence intervals will be generated for the difference between treatments in change from baseline using the Student's t distribution at each evaluation time. Non-inferiority will be declared if Vanish™ Varnish changed from baseline minus Clinpro™ 2.1% Sodium Fluoride Aqueous Solution change from baseline is less than or equal to 15 mm for each secondary endpoint. There are 3 secondary endpoints. The alpha will be passed sequentially in the order listed in section 5.3.2.

8.4.4. Analysis of Additional/Exploratory Endpoints

Ninety five percent (95%) confidence intervals will be generated for the difference between treatments in change from baseline using a Student's distribution at each evaluation time. No non-inferiority will be declared.

8.4.5. Analysis of Safety Endpoints

Adverse events will be summarized by treatment.

8.5. Planned Interim Analyses and Criteria for Clinical Investigation

An interim analysis will be conducted after treating approximately 50% of the planned sample size for the purpose of sample size re-estimation. No alpha will need to be spent because of this sample size re-estimation. The parameter estimates from the interim data will be used and the sample size necessary for 80% power will be calculated.

8.6. Procedures for Reporting Deviations From Statistical Plan

Any deviations from the original plan will be described and justified in the final report.

8.7. Procedures for Missing, Unused, or Spurious Data

If a subject withdraws, only the data up to withdrawal will be used. There will be no imputation of missing outcome data. Any non-use of data will be explained and justified in the final report.

8.8. Validation Plan

The results of this study will be used for registration, therefore level 2 validation of the statistical programs and output will be performed. Level 2 validation entails independent review of logs, output, program code, and report results.

9. AMENDMENTS TO THE CIP

If 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 standard operating procedures of the Sponsor. In collaboration with the Investigator(s), the CIP modifications will then be documented and submitted for ethical and regulatory approval (as required) before 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/FDIS 14155. 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 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. Deviation reporting timelines and methods

Type of Deviation	Report to Sponsor	Method
Major Subject safety, rights or welfare; OR Compromise the data integrity or statistical analysis of the study; OR Non-adherence to Inclusion/Exclusion criteria	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Sponsor Complete CRF
All other protocol deviations	Per CIP-designated 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 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.
- 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

Device Name	Manufacturer
Vanish™ 5% Sodium Fluoride White Varnish	3M™ Company
Colgate Cavity Protection Fluoride Toothpaste - Great Regular Flavor 0.15% w/v Fluoride Ion	Colgate
Oral-B® Indicator™ Toothbrush, Sensitive 35 Extra Soft	Procter & Gamble Company

11.1. Labeling for Device(s) Under Investigation

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, 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 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, IFU, ICF, 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 local IRB requirements for ongoing reviews, at a minimum annually. The Sponsor may provide an annual study report to participating Investigators.

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 HIPAA of 1996. This confidentiality is extended to cover the testing of biological samples and other clinical information relating to participants (eg, images related to the study wound). Therefore, the CIP, 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 the 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 an approved supplier. This data 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 6.6.5). 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 archived at 3M or an approved supplier.

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. 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.

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 CIP 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.

12.6. Future Use of Stored Collected Specimens

No biological specimens are being collected as part of this study.

13. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

Subject safety and event reporting are important in this study. Investigators are responsible for ensuring that all safety events are recorded in the subject record(s). Events defined in Section 13.1 will be reported to the Sponsor, as applicable, per the timelines in Section 13.3.

13.1. SAFETY AND EVENT REPORTING DEFINITIONS

This study utilizes the following definitions, as listed in Table 13.1-1 below.

Table 13.1-1: 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. This includes, but is not limited to, events related to the investigational device or the comparator and to procedures involved in this study.
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, users, or other persons as defined by one of more of the following:
	  ○ a life-threatening illness or injury, or
	  ○ a permanent impairment of a body structure or a body function including chronic diseases, or
	  ○ in-patient or prolonged hospitalization, or

Term	Definition
	○ 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 including physical or mental impairment. NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP without serious deterioration in health, is not considered a SAE
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. ***Note:*** *Device-related adverse events would meet this definition.*

13.2. CLASSIFICATION OF EVENTS

13.2.1. Severity Ratings

The severity ratings for events are defined in Table 13.2.1-1. The Investigator shall ensure rating of reportable events on the applicable Case Report Form.

Table 13.2.1-1: 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

13.2.2. Relatedness to Study Device or Study Treatment

Table 13.2.2-1 defines the relatedness definitions for events. The Investigator shall ensure rating of reportable events on the applicable Case Report Form.

Table 13.2.2-1: 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

13.3. Details Concerning Safety Recording and Reporting Requirements

13.3.1. Investigator Responsibilities

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 from the time of randomization through the end of the study. Investigators should assess for AEs at each visit after randomization, 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 13.4. 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, the 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.

USADEs must be reported by the Investigator to the Sponsor and the reviewing IRB according to their reporting requirements within 24 hours of becoming aware of the event (see Table 13.4-1). In addition to submitting UADEs to the IRB, the Investigators will, along with the Sponsor, decide to continue, suspend, or terminate the study.

13.3.2. Sponsor Responsibilities

Safety oversight will be under the direction of the Medical Monitor and Safety Monitor of 3M, which both have appropriate expertise. The Clinical Trial Safety Officer and Senior Medical Director will routinely review and assesses 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 evaluate the received AEs/SAEs and if an event is confirmed to be an SAE/USADE, will then immediately conduct an evaluation of a USADE and report the results of the evaluation to the FDA and participating Investigators within 5 working days after the Sponsor first receives notice of the event (21 CFR 812.46(b), 812.150). 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.

13.4. Reporting Timelines

Table 13.4-1 below indicates the reporting timelines for events to the Sponsor. The Investigator shall report to local IRB 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 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 13.4-1. Reporting Timelines for 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
Adverse Device Effects (ADE)/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 Dental Monitor Followed by: Complete CRF and complete 3M SAE Report Form. This form should be completed by the Investigator, or designee, and submitted (e-mail) to saereport@mmm.com
Unanticipated Serious Adverse Device Effect (USADE)	Within 24 hours of study staff becoming aware of event	Initial: Phone/Email to Dental Monitor Followed by: Complete CRF

Type of event	Report to Sponsor	Method
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	Complete CRF

13.5. Follow-up Period for Ongoing AEs

Any AEs that are not device-related and are ongoing at the end of the study should be marked as "persistent" per the eCRF. Any AEs that are device-related and ongoing at the end of the study may be followed for an additional 30 calendar days, as medically necessary. Any Events ongoing at the end of this 30-day period should be marked as "persistent" per the eCRF. 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. All unrelated AEs will be considered closed at the time the Subject completes participation in the study.

14. VULNERABLE POPULATION

This study is intended to be conducted using a non-vulnerable adult population (ie, 18 years of age or older) with no expectations of benefits associated with participation or of a retaliatory response from senior hierarchical members in case of refusal to participate. In addition, the study includes only Subjects that are capable of and can provide informed consent. However, the study does not exclude economically or 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 the 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 (self-reported) 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.

15. SUSPENSION OR PREMATURE STUDY TERMINATION

Both the Sponsor and the Principal Investigator (PI) reserve the right to terminate the clinical investigation at any time. Should this be necessary, the 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 study participants, participating Investigators, IRB and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRBs, 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
- Determination of early efficacy that would warrant stoppage – defined in section 8.5
- Determination of futility – defined in section 8.5
- Insufficient compliance to CIP requirements
- Data that are not sufficiently complete and/or evaluable

Suspended studies may resume once concerns about safety, CIP compliance, and data quality are addressed, and satisfy the Sponsor, IRB, and regulatory authorities.

15.1. 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

15.2. BY IRB

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

16. REGISTRATION AND PUBLICATION POLICY

16.1. PUBLIC REGISTRATION

The Sponsor shall ensure that the study is conducted in accordance with applicable publication and data sharing policies and complies with any national registration requirements. A description of this study will be publicly available at the website, http://www.ClinicalTrials.gov, as required by U.S. law. The online study description will include a summary of the study results but will not include information that identifies Subjects.

16.2. PUBLICATIONS RESULTING FROM STUDY/

When applicable, attempts will be made to publish the results of the study. Details regarding publication policies, including publication rights and timing, will be addressed in the study contracts between the Sponsor and the study sites if applicable.

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18. STUDY-SPECIFIC APPENDICES

18.1. APPENDIX A

REVISION HISTORY

The purpose of this appendix is to describe modifications made to this document, in detail, when moving from Version 1.0 to Version 2.0.

Overall summary of changes		
Version 2 Added a Co-primary endpoint by moving the first secondary endpoint (24-hour time point) to the primary endpoint. This change resulted in the following changes: 1. Sample size: the minimum number of the subjects changed from 80 to 96. The maximum number of the subjects was also changed from 90 to 125. 2. Statistical Considerations (Sections 8.1-8.5) were modified to reflect the changes of primary endpoints.		
Section modified	**Original text**	**Updated text**
Summary Endpoints Section 5.3.1 Primary Endpoint(s)	The primary endpoint for this study is the change in pain, using a 100-mm VAS from baseline to immediately after application (within 15 minutes post-treatment) of test product or comparator. Sensitivity will be assessed using VAS after exposure to air stimulus.	Co-primary endpoints include: • the change in pain, using a 100-mm VAS from baseline to immediately after application (within 15 minutes post treatment) of test product or comparator. • the change in pain score from baseline to 24 ± 4 h post-application, using VAS after exposure to air stimulus.

Summary Endpoint Section 5.3.2 Secodary Endpoint(s)	The secondary endpoints include: 1. the change in pain score from baseline to 24 ± 4 h post-application, using VAS after exposure to air stimulus. 2. change in pain score, using VAS, from baseline to 7 ± 2 days post-treatment, after exposure to air stimulus. 3. change in pain score, using VAS, from baseline to 21 ± 2 days post-treatment, after exposure to air stimulus. 4. change in pain score, using VAS, from baseline to 30 ± 2 days post-treatment, after exposure to air stimulus.	The secondary endpoints include: 1. change in pain score, using VAS, from baseline to 7 ± 2 days post-treatment, after exposure to air stimulus. 2. change in pain score, using VAS, from baseline to 21 ± 2 days post-treatment, after exposure to air stimulus. 3. change in pain score, using VAS, from baseline to 30 ± 2 days post-treatment, after exposure to air stimulus.
Summary Selection of Subjects Section 6.5 Subject Enrollment	A minimum of 80 enrolled Subjects that complete the study period is planned for this study. To achieve this minimum, the Investigator may enroll up to ninety (90) subjects.	A minimum of 96 enrolled Subjects that complete the treatment is planned for this study. To achieve this minimum, the Investigator may enroll up to one hundred and twenty five (125) subjects.
Section 8.1	The null hypothesis that we seek to reject is that Clinpro™ 2% Sodium Fluoride Aqueous	The null hypotheses that we seek to reject are that Vanish™ 5% Sodium

	Solution has a 15.0 mm lower change from baseline VAS than Vanish™ 5% Sodium Fluoride White Varnish measured immediately after application (within 15 minutes post-treatment). The null and alternate hypotheses are described below.	Fluoride White Varnish has a 15.0 mm higher change from baseline VAS than Clinpro™ 2% Sodium Fluoride Aqueous Solution when measured immediately after application (within 15 minutes post-treatment) or at 24-hours after treatment (±4 hours). The null and alternate hypotheses are described below.
Section 8.2 Sample Size Determination	A standard deviation of 20.0 mm for the change between baseline and immediately after treatment (within 15 minutes post-treatment) will be used. There is uncertainty in the efficacy difference between treatments as well as the error term. An interim analysis will be conducted at approximately 50% of enrollment. Based on the O'Brien-Fleming alpha spending function for group sequential design, the interim analysis will use an alpha of 0.002 (1-sided) and the final analysis will use an alpha of 0.023 (1-sided). Eighty (80; 40 per arm) total subjects will provide 92% power if there is no efficacy difference between treatments and 83% power if Clinpro™ 2% Sodium Fluoride Aqueous Solution has a 0.2 cm lower change from baseline then	A standard deviation for change from baseline at immediately after treatment (within 15 minutes post-treatment) and 24-hours of 20 mm will be used. There is uncertainty in the efficacy difference between treatments as well as the error term. An interim analysis will be conducted at approximately 50% of subject treatment to reassess sample size with no alpha spending required. Ninety-six (96; 48 per arm) total subjects will provide 80% power allowing for a 2 mm difference in efficacy difference between treatments and 2 co-primary endpoints tested. No subjects will be lost to follow-up for the primary

	the control. No subjects will be lost to follow-up for the primary time point of immediate hypersensitivity relief, but there may be loss to follow-up for the secondary time points	time point of immediate hypersensitivity relief, but there may be loss to follow-up for co-primary endpoint of hypersensitivity relief at 24-hours after treatment.
Section 8.3 Analysis Populations	All dosed subjects without a major protocol deviation will be included in the analysis dataset for the primary endpoint of change in pain immediately after product application.	All dosed subjects without a major protocol deviation will be included in the analysis dataset for the co-primary endpoints of change in hypersensitivity immediately after product application and change in hypersensitivity 24-hours after application. Major protocol deviation(s) for exclusion from the analysis dataset will be defined and documented in a blinded fashion prior to interim and final analyses (eg, inadequate washout).
Section 8.4.2 Analysis of Primary Endpoints	A ninety five percent (95%) confidence interval will be generated for the difference between treatments in change from baseline immediately after application using a Student's t-test. Non-inferiority will be declared if Vanish™ Varnish changed from baseline minus Clinpro™ 2.1% Sodium Fluoride Aqueous Solution	At the final analysis, multiplicity will be controlled through a Hochberg procedure. Ninety-five- percent (95%) confidence intervals will be generated for the difference between treatments in change from baseline immediately after application and separately

	change from baseline is less than or equal to 15.0 mm.	for the difference between treatments in change from baseline 24-hours after application using Student's t distribution. Scenario 1: Neither of the 95% confidence intervals contain 15 mm. Result: Non-inferiority for both co-primary endpoints will be declared Scenario 2: Both of the 95% confidence intervals contain 15 mm. Result: No non-inferiority for either co-primary endpoints will be declared, and all analyses will be informational only. Scenario 3: One confidence interval contains 15 mm, and the other confidence interval does not contain 15 mm. The endpoint that does not contain 15 mm has the potential to be declared non-inferior. For this endpoint, as part of the Hochberg procedure, a 97.5% confidence interval will be generated. Non-inferiority for this endpoint will be declared if the new

		confidence interval does not contain 15 mm.
Section 8.4.3 Analysis of Secondary Endpoints	If the null hypothesis is rejected for the primary endpoint, the alpha will be passed to test for non-inferiority of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution to Vanish™ Varnish for the various secondary endpoints. Ninety five percent (95%) confidence intervals will be generated for the difference between treatments in change from baseline using a Student's t-test at each evaluation time. Non-inferiority will be declared if Vanish™ Varnish changed from baseline minus Clinpro™ 2.1% Sodium Fluoride Aqueous Solution change from baseline is less than or equal to 15.0 mm for each secondary endpoint. There are 4 secondary endpoints. The alpha will be passed sequentially in the order listed in section 5.3.2.	If the null hypotheses are rejected for both co-primary endpoints, the alpha will be passed to test for non-inferiority of Clinpro™ 2.1% Sodium Fluoride Aqueous Solution to Vanish™ Varnish for the various secondary endpoints. Ninety five percent (95%) confidence intervals will be generated for the difference between treatments in change from baseline using the Student's t distribution at each evaluation time. Non-inferiority will be declared if Vanish™ Varnish changed from baseline minus Clinpro™ 2.1% Sodium Fluoride Aqueous Solution change from baseline is less than or equal to 15 mm for each secondary endpoint. There are 3 secondary endpoints. The alpha will be passed sequentially in the order listed in section 5.3.2.
Section 8.5 Planned Interim Analysis and Criteria for Clinical Investigation	An interim analysis will be conducted at approximately 50% of enrollment. Based on the O'Brien-Fleming alpha spending	An interim analysis will be conducted after treating approximately 50% of the planned sample size for the

	function for group sequential design, the interim analysis will use an alpha of 0.002 (1-sided) and the final analysis will use an alpha of 0.023 (1-sided). The study may be stopped if the conditional power is <50%, but the study will not be required to be stopped. In addition, sample size re-estimation will be carried out if condition power falls between 50 and 80%.	purpose of sample size re-estimation. No alpha will need to be spent because of this sample size re-estimation. The parameter estimates from the interim data will be used and the sample size necessary for 80% power will be calculated.

18.2. APPENDIX B

LISTING OF SITES AND INVESTIGATORS

Site No.	Name of Site	Name of Principal Investigator	Professional Title	Contact information
01	Loma Linda University Health	Dr. Yiming Li	Distinguished Professor	yli@llu.edu

18.3. APPENDIX C

Example of Visual Analogue Scale (VAS)

Subject Pain Assessment during Air Blast

Subject # _____

Instructions: Using a pen, draw a vertical mark on the colorful line that best represents the level of pain experienced during the sensitivity tesing. Pain score is calculated by measuring the distance or length of the mark from the left edge of the bar (0 mm). Scale will be printed to ensure the line maintains a length of 100mm for the study.

Very painful

Pain scoring: ☐☐☐ mm

Baseline

Very painful

Pain scoring: ☐☐☐mm

Immediately Post-treatment

Very painful

Pain scoring: ☐☐☐ mm

24 h post-treatment

Very painful

Pain scoring: ☐☐☐ mm

7 d post-treatment

Very painful

Pain scoring: ☐☐☐ mm

21 d post-treatment

Very painful

Pain scoring: ☐☐☐ mm

30 d post-treatment

Subject Pain Assessment during Tactile Test

Subject # _____

Instructions: Using a pen, draw a vertical mark on the colorful line that best represents the level of pain experienced during the sensitiity testing. Pain score is calculated by measuring the distance or length of the mark from the left edge of the bar (0 mm). Scale will be printed to ensure the line maintains a length of 100mm for the study.

Very painful

Pain scoring: ☐☐☐ mm

Baseline

Very painful

Pain scoring: ☐☐☐mm

Immediately Post-treatment

Very painful

Pain scoring: ☐☐☐ mm

24 h post-treatment

Very painful

Pain scoring: ☐☐☐ mm

7 d post-treatment

Very painful

Pain scoring: ☐☐☐ mm

21 d post-treatment

Very painful

Pain scoring: ☐☐☐ mm

30 d post-treatment