Study Title: **3M Oral Rinse incidence and patient acceptance of sloughing when used with Sodium Lauryl Sulfate (SLS) toothpastes**

NCT Number: **NCT04601103**

Issue Date: **01/07/2020**

1.0 3M Sponsored [redacted] Clinical Study [redacted] Summary

Study #	IRB Number	Project #	Request Date	Date Samples Available	Date Results Needed
[redacted]	[redacted]	[redacted]	15-Oct-2019	11-Oct-2019	15-Apr-2020

Study Title:	**3M Oral Rinse incidence and patient acceptance of sloughing when used with Sodium Lauryl Sulfate (SLS) toothpastes**
Objective:	The primary objective of this study is to evaluate the incidence of oral tissue sloughing through self-report by study subjects and by professional dental examinations. Adverse events will be tracked through study dental examinations and subject diaries with twice daily use of the 3M Oral Rinse used in combination with toothpaste containing one of three levels (no, medium, high) of Sodium Lauryl Sulfate (SLS). Determine the subjects' acceptance of sloughing and/or other side effects.

	Name	Title	Address	Phone #
Requestor:	[redacted]	Commercialization Manager	[redacted]	
Principal Investigator:		Clinical Affairs Manager		
Primary Study Contact:		Clinical Project Manager		
Staff Dentist:		3M Oral Care Staff Dentist		

Study Will be Used For:		
	X	Safety
		Screening

Statistical Analysis Requested:		
	X	Yes
		No

Test Assessments		Additional Description
X	Adverse Event (AE) incidence rate(s)	Subject reported incidence of adverse events (AEs) on subject diaries and observed during study dental exams.
X	Oral Mucosal Sloughing Index	Sloughing severity and location will be captured on study case report forms (CRFs).
X	Subject acceptability of sloughing	Subjects will be given a questionnaire on the acceptability of the sloughing and/or other side effects and the use of the 3M Oral Rinse in combination with the assigned toothpaste.

[redacted]

Time Points for Study Procedures		Additional Details
X	T=1 Period 1 Baseline	• Subjects will report to the 3M [redacted] facility for study baseline procedures • Study Coordinator will complete the consenting process with the subject • Study Coordinator and Dental Examiner will review inclusion and exclusion criteria • Dental Examiner will complete a dental examination • Study Coordinator will randomize the subject to their treatment group and dispense the assigned toothpaste, 3M Oral Rinse, and subject diary • Study Coordinator will provide verbal and written product use and subject diary instructions and collect demographic information • Subjects will initiate their treatment in the evening of baseline visit • Study Coordinator will provide subject payment for the visit(s); additional study payments will be made at the discretion of the Study Coordinator • Study Coordinator will schedule follow-up visit(s)
X	T=2 Period 1 Mid-Treatment Evaluation	• Subjects will report to the 3M [redacted] facility for study procedures • Dental Examiner will complete a dental examination and record any AEs, as required • Dental photographs may be taken by study staff if oral tissue sloughing or other abnormalities are found at the dental exam of the affected areas • Study Coordinator will schedule follow-up visit(s)
X	T=3 Period 1 End of Treatment	• Subjects will report to the 3M [redacted] facility for study procedures • Subjects will return completed subject diaries, study toothpaste tubes, and 3M Oral Rinse bottles. • Dental Examiner will complete a dental examination, review subject's diary, and record any AEs, as required • Dental photographs may be taken by study staff if oral tissue sloughing or other abnormalities are found at the dental exam of the affected areas • Subjects will complete the questionnaire • Study Coordinator will dispense the assigned toothpaste for at least a 1-week washout prior to Period 2 start • Study Coordinator will schedule follow-up visit(s)
X	T= 4 Period 2 Baseline	• Subjects will report to the 3M [redacted] facility for study procedures • Subjects will return study toothpaste tubes used in wash-out

[redacted]

		• Dental Examiner complete a dental examination and record any AEs, as required • Dental photographs may be taken by study staff if oral tissue sloughing or irritation are found at the dental exam of the affected areas • Study Coordinator will dispense the assigned toothpaste, 3M Oral Rinse, and subject diary • Study Coordinator verifies and records that washout lasted at least 1 week and what toothpaste was dispensed for Period 2 • Study Coordinator will provide verbal and written product use and subject diary instructions, as needed • Subjects will initiate their treatment in the evening of baseline visit • Study Coordinator will schedule follow-up visit(s)
X	T = 5 Period 2 Mid-Treatment Evaluation	• Subjects will report to the 3M [redacted] facility for study procedures • Dental Examiner will complete a dental examination and record any AEs, as required • Dental photographs may be taken by study staff if oral tissue sloughing or other abnormalities are found at the dental exam of the affected areas • Study Coordinator will schedule follow-up visit(s)
X	T= 6 Period 2 End of Treatment / End of Study	• Subjects will report to the 3M [redacted] facility for study procedures • Subjects will return completed subject diary, used assigned toothpaste, and used 3M Oral Rinse. • Dental Examiner will complete a dental examination, review diary and record any AEs, as required • Dental photographs may be taken by study staff if oral tissue sloughing or other abnormalities are found at the dental exam of the affected areas • Subjects will complete the questionnaire

Suggested Subject Payment:	[redacted]

Number of Subjects:	72
Other characteristics to consider for subject recruitment:	Healthy 3M employees ≥ 18 years of age

Restrictions on Subject's Activities **during study** participation:	
X	No use of other oral hygiene products (non-study toothpaste, toothbrush, mouth rinse, chewing gum)

[redacted]

Calculation of the number of samples needed:			
# of Subjects	x	# of Times each sample will be applied*	Total # needed
24	x	Twice daily brushing with treatment A toothpaste (no SLS) followed by 15mL swishing of 3M Oral Rinse and expectoration for three weeks	= 24 tubes of toothpaste A = 48, 500mL bottles of 3M Oral Rinse
48	x	Twice daily brushing with treatment B toothpaste (medium SLS) followed by 15mL swishing of 3M Oral Rinse and expectoration for three weeks	= 48 tubes of toothpaste B = 96, 500mL bottles of 3M Oral Rinse
72	x	Twice daily brushing with treatment C toothpaste (high SLS) followed by 15mL swishing of 3M Oral Rinse and expectoration for three weeks	= 72 tubes of toothpaste C = 144, 500mL bottles of 3M Oral Rinse
72	x	Twice daily brushing with treatment A toothpaste (no SLS) for wash-out between Period 1 and Period 2 NOTE: 3M Oral Rinse will not be used during washout	= 72 tubes of toothpaste A

Additional information needed by the coordinator to conduct this study:	Washout between Period 1 and Period 2 is at least one week

Identification of Test and Control Samples:

Characteristics common to all samples:	All subjects will receive the 3M Oral Rinse for both test periods of the study.

#	Sample Name	Description	Composition Number	Lot	Source
1	3M Oral Rinse	[redacted]	[redacted]	[redacted]	[redacted]

2.0 Introduction

3M Oral Care Solutions Division (OCSD) has developed an oral rinse containing [redacted] 3M Oral Rinse is also known as [redacted] oral rinse reduces the surface tension on tooth surfaces; this allows the rinse to better adhere to the teeth, which creates a physical barrier between the tooth surfaces and oral bacteria in the mouth. Preventing the adherence of oral bacterial to the teeth prevents the growth of dental plaque

[redacted]

and reduces the development of the gingivitis associated with dental plaque. Because the rinse acts as a physical barrier, the FDA classifies the rinse as a Class II Medical Device that requires clinical data for approval to sell the product.

A past study, [redacted] evaluated the efficacy of 3M Oral Rinse on plaque and gingivitis in 200 healthy dental patients that were randomized into 1 of 4 treatment arms. Each treatment arm contained 50 subjects, randomized to 3M Oral Rinse, 3M vehicle control, predicate device, or water control. Participants were asked to use an assigned toothpaste and randomly assigned oral rinse for a period of 6 months. The study found that 3M Oral Rinse reduced plaque and gingivitis and that the 3M Oral Rinse was not statistically different than the predicate device. There were, however, statistical differences for adverse events observed, namely sloughing.

The current study will evaluate the incidence of sloughing, and other adverse events, over time with three levels (high, medium, no) of Sodium Lauryl Sulfate (SLS) containing toothpaste in combination with the 3M Oral Rinse and to determine the subject acceptance of sloughing and/or other side effects.

3.0 Study Plan

3.1 Design

This will be a single-blind, randomized, internal, two-period crossover 3M sponsored study evaluating the incidence of sloughing over time with 3 levels (high, medium, no) of sodium lauryl sulfate (SLS) toothpaste in combination with the 3M Oral Rinse. In addition, this study is designed to determine the acceptance of sloughing and other side effects of using the 3M Oral Rinse in combination with the assigned toothpaste.

Each subject will be assigned to use the 3M Oral Rinse and randomized to one of three toothpaste sequences. Each sequence will consist of using two different fluoride toothpastes (Toothpaste A, B or C), as shown in the table below. The cumulative duration of dosing with 3M Oral Rinse will be six (6) weeks (two 3-week periods). There will be a wash-out period of at least one week between each period.

[redacted]

Sequence: Period 1 → Washout → Period 2

	Period 1 (3 weeks)	**Period 2 (3 weeks)**
Sequence 1	No SLS (Toothpaste A)	High SLS (Toothpaste C)
Sequence 2	Medium SLS (Toothpaste B)	High SLS (Toothpaste C)
Sequence 3	High SLS (Toothpaste C)	Medium SLS (Toothpaste B)

3.2 Duration

The overall time to conduct the study should be at least 14 weeks, including scheduling time for recruitment and conduct of the study. Each subject will be required to go through the study consenting and enrollment process. Individuals who qualify for the study will be scheduled for future dental examinations and participate in the study for at least 7 weeks.

3.3 Investigator/Facility

[redacted] 3M Clinical Research [redacted]

4.0 Subjects

4.1 Subject Selection

Subjects may only participate if they meet all study-specific selection criteria and sign a study-specific informed consent form. Exclusion criteria numbers 21 through 27 must be confirmed by the Screening Dental Exam by the Dental Examiner.

4.2 Inclusion Criteria:

1. Able to understand and willing to sign the informed consent;
2. Willing to agree to maintain confidentiality of the study and study materials;
3. 3M employee aged 18 years and older;
4. Willing to return to the study facility for scheduled study visits and recalls;
5. Agree not to use other oral hygiene products (non-study toothpaste, non-study toothbrush, mouth rinse, chewing gum);
6. Agree to the study instruction and schedule.

4.3 Exclusion Criteria:

7. A member of the [redacted] staff or [redacted] product team for the device under investigation;
8. Have a dental appointment scheduled during study duration for professional cleaning;
9. Is pregnant, nursing, or planning to become pregnant within the study duration;

[redacted]

10. History of antibiotic therapy within the previous 30 days or have a condition that is likely to need antibiotic treatment over the course of the study (e.g., cardiac conditions requiring antibiotic prophylaxis such as heart murmurs, pacemakers, or prosthetic heart valves and prosthetic implants);
11. History of using a prescription antimicrobial mouth rinse during the past 3 months;
12. Currently taking medications which may alter gingival appearance/bleeding;
13. Currently using anticonvulsants, calcium channel blockers, or other medications with side effects known to impact oral health;
14. Participation in any other clinical study within the last 30 days;
15. Resides in the same household with a subject already enrolled in the study;
16. Known history of sensitivity to oral hygiene products;
17. Currently using tobacco products (cigarettes, chewing tobacco) or vaping products (e-cigarettes);
18. History of diabetes;
19. Have removable partial/full dentures;
20. Have orthodontic appliances;
21. Have medical or oral conditions that may compromise the subject's safety or interfere with the conduct and outcome of the study;
22. Have known sloughing within the last 3 weeks;
23. Have dry mouth;
24. Have widespread caries or chronic neglect;
25. Have gross pathological changes of oral soft tissues;
26. Have advanced periodontal disease (purulent exudate, tooth mobility, and/or extensive alveolar bone loss);
27. Unsuitable for enrollment in this study based on the professional opinion of the dental examiner based on the oral exam or other reasons not specified in the protocol.

4.4 Subject Recruitment, Screening, Consent

The [redacted] staff will recruit subjects using a confidential database [redacted] containing names of [redacted] o be listed in the database. Potential subjects will be contacted once via e-mail to explain the purpose of the study, study requirements, including inclusion/exclusion criteria, restrictions on activities, information regarding who to contact for more information and the dates the study will run. The e-mail will include a copy

[redacted]

of the informed consent form for the subjects to review. See Appendix I for example recruitment letter. If the subject agrees to participate, an appointment is scheduled. If any additional measures, such as advertising, become necessary, they will be submitted to the IRB prior to their initial use.

4.5 Subject Restrictions

Emergency treatment for a broken tooth, lost filling, or crown is permitted during the study, at the discretion of the Investigator.

Subjects that need to be withdrawn from treatment during Period 1 are allowed to enter washout early and complete a longer washout until Period 2.

4.6 Subject Withdrawal

Subjects may voluntarily withdraw from the study at any time without prejudice.
Any subject may be withdrawn by the Investigator from further participation in the study if the subject:

- Fails to adhere adequately to the protocol requirements within or outside the clinical environment
- Fails to cooperate adequately with the Investigator or staff during clinical visits
- Presents with an illness or disease condition that is not allowed in the study
- Experiences a serious AE that requires discontinuation or withdrawal from the study
- Experiences an intolerable AE
- Found not to meet the original entry requirements
- Fails to return for an appointment(s)
- Is pregnant

If a subject discontinues due to an AE (reported by the subject or the Investigator), the causative condition will be followed until resolution or stabilization to the Investigator's satisfaction.

Withdrawn subjects will not be replaced.

4.7 Confidentiality

All proprietary information relating to 3M investigations and any information obtained during the study will be regarded as confidential. All study subjects will agree to maintain confidentiality of proprietary information relating to the investigation and information

[redacted]

obtained during the study. In addition, the right of each subject to privacy (confidential treatment of person data) will be respected at all time. The following safeguards will be taken to protect that privacy as noted below:

- All research activities will be conducted in as private a setting as possible.
- All clinical employees who have access to identifying information are trained in Good Clinical Practice (GCP) and data privacy.
- Data, reports, and communications relating to subjects enrolled in the study will identify each subject only by an assigned subject number. The link between subject name and subject number is accessible only to study coordinators and other study staff (investigator, study monitor, clinical manager) as needed for monitoring, subject payments, etc.
- The only documents with personal information (informed consent forms and enrollment log/pay information) are stored in a restricted access documentation center. Accessible only to a clinical manager and designated clinical employees. Retention of the documents is subject to applicable state and federal laws and regulations.
- The data from this study (and any non-identifying images, including dental photographs) may be shared within 3M and outside of 3M for future research, education, publications, presentation, marketing materials, and regulatory submissions. Subject name or identifying information will not be revealed in any of these activities or documents.
- Authorized representative of 3M (study staff, clinical managers, clinical auditors) or regulatory agencies, such as the US Food and Drug Administration (FDA) and/or other competent authorities, may examine and copy all study files and therefore may have access to subject names and identifying information.

5.0 Study Materials

5.1 Description

- 3M Oral Rinse: The principle components of the 3M Oral Rinse being used in this study are described in Section 1.0 of this document and are the same for all treatment arms being used in this study. 15mL of 3M Oral Rinse will be swished for about 30 seconds twice a day (morning and evening), after brushing teeth with assigned toothpaste, for each 3-week treatment arm.

- Treatment A consists of a no SLS containing toothpaste. For the study, subjects randomized to Treatment A will receive 1 tube of Sensodyne ProNamel Fresh Breath toothpaste. The information on the components of Sensodyne toothpaste are listed on the packaging and safety data sheet.
- Treatment B consists of a medium SLS containing toothpaste. For the study, subjects randomized to Treatment B will receive 1 tube of 3M ESPE Clinpro Tooth Creme toothpaste. The information on the components of 3M Clinpro toothpaste are listed on the packaging and safety data sheet.
- Treatment C consists of a high SLS containing toothpaste. For the study, subjects randomized to Treatment C will receive 1 tube of Colgate Cavity Protection toothpaste. The information on the components of Colgate toothpaste are listed on the packaging and safety data sheet.

Subjects will be randomized to take two treatment products in sequence: either A followed by C, B followed by C, or C followed by B. Each of the treatments will be used in combination with the 3M Oral Rinse.

5.2 Safety

A biocompatibility statement for this study prepared on December 1, 2017 documents that it is safe to use the 3M Oral Rinse product in this limited exposure taste-testing evaluation. In this statement, the 3M Oral Rinse was determined to be safe for the intended use. [redacted]

Subjects participating in this [redacted] clinical study may face the following risks:

- Temporary, mild, mouth or tongue sensations such as:
  - Numbness,
  - Mild taste alteration,
- Mild dry mouth,
- Mild superficial tissue sloughing.

These risks to the subjects are transient and should resolve over time after stopping usage of the study device.

[redacted]

Risks to the subjects are minimized through appropriate selection of subjects by adherence to the inclusion/exclusion criteria, adherence to the protocol, and through frequent study dental examinations by the Dental Examiner. Risks are in the consent form and will be communicated to the subject.

5.3 Regulatory Status

The 3M Oral Rinse formulation is reflective of formulations described in the FDA's Guidance for Industry and FDA Staff - Class II Special Controls Document: Oral Rinse to Reduce the Adhesion of Dental Plaque. According to this FDA Guidance, these experimental oral rinse formulations are subject to premarket notification procedures per 21 CFR 872.5580. As indicated in this guidance, the key risks associated with this oral rinse include the following:

- ineffective plaque reduction,
- alteration of oral flora,
- adverse tissue reaction (hard and soft tissue), primarily tissue sloughing,
- toxicity, and
- improper use

This study is conducted in compliance with the FDA requirements of 21 CFR 812: Investigational Device Exemptions.

5.4 Labeling

The clinical study batch of 3M Oral Rinse will be manufactured by 3M. It will have a unique lot number and be supplied in 500mL bottles, labeled with the following information:

- Product Name
- [redacted]
- [redacted]
- Lot Number
- Expiration date
- Instructions for use
- Investigational use statement
- Storage conditions
- Manufacturer name and location

[redacted]

5.5 Non-Investigational Material

Material ID	Description	Source
Sensodyne ProNamel Fresh Breath Toothpaste	Treatment A toothpaste	Commercially available
3M ESPE Clinpro	Treatment B toothpaste	Commercially available
Colgate Cavity Protection Toothpaste	Treatment C toothpaste	Commercially available
Toothbrush	Soft toothbrushes dispensed to each subject for each period to ensure no cross contamination	3M
Gloves	Latex-free gloves for study dental examiner to complete dental exams	3M [redacted]
Disposable mirrors	For dental exams	3M
Gauze	For dental exams	3M
Suction tips	For dental exams	3M
Air water syringes	For dental exams	3M
Camera	Digital camera used to capture photos of the subjects' mouths at baseline and end of study visits	3M [redacted]
Paper towels	For clean up	3M [redacted]
Paper bags	For subjects to hold their toothpaste, 3M Oral Rinse, and toothbrush	3M [redacted]
Garbage can	With liner to dispose of any used dental materials	3M [redacted]
Clip boards	For study staff to use to record study information	3M [redacted]
Pens	For subjects to record questionnaire responses	3M [redacted]
Case Report Forms	Study evaluation forms	3M

5.6 Computerized Systems

The computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit data include:

- [redacted] approve study documents)
- [redacted] ectronic database)
- [redacted] ta analysis)

[redacted]

- 3M email system (communication with IRB personnel, study subjects, Study Coordinator(s)/Study Monitor, data management personnel, and, possibly, [redacted] team members.)

6.0 Procedures

6.1 Subject Preparation

Once the subjects have enrolled in the study, subjects will be scheduled for future visits at the [redacted]. In order to minimize bias, study subjects will be asked to refrain from discussing any details about the 3M Oral Rinse study with any other subjects.

6.2 Schedule of evaluations

Procedure	Visit 1 Period 1 Baseline	Visit 2 Period 1 Mid-Treatment Evaluation	Visit 3[a] Period 1 End of Treatment	Visit 4 Period 2 Baseline	Visit 5 Period 2 Mid-Treatment Evaluation	Visit 6 Period 2 End of Treatment/ End of Study
	Day 0	Day 10 (±2 day)	Day 21 (±2 day)	Day 28+ (±2 day)	Day 38+ (±2 day)	Day 49+ (±2 day)
Informed Consent	X					
Eligibility	X					
Demographics	X					
Dental Exam	X	X	X	X	X	X
Dental Photographs		X[b]	X[b]	X[b]	X[b]	X[b]
Randomization	X					
Dispense 3M Oral Rinse	X			X		
Dispense Toothpaste	X			X		
Dispense Diary	X			X		
Questionnaire			X			X
Assess AEs		X	X	X	X	X
Diary collection			X			X
3M Oral Rinse collection			X			X

[a] All subjects will complete a minimum of 1-week wash out with Treatment A between Visits 3 and 4.
[b] Dental photographs are taken at the discretion of the Dental Examiner to capture sloughing and/or other abnormalities.

6.3 Test Procedures

6.3.1 Visit 1: Period 1 Baseline (Day 0)

- Subjects will report to the [redacted] facility for study baseline procedures
- Study Coordinator will complete the consenting process

[redacted]

- Study Coordinator and Dental Examiner will review inclusion and exclusion criteria
- The Dental Examiner will complete a dental examination
- Study Coordinator will randomize the subject to their treatment group and dispense the assigned toothpaste, 3M Oral Rinse, and subject diary
- Study Coordinator will collect demographic information
- Study Coordinator will provide verbal and written product use and subject diary instructions
- Subjects will initiate their treatment in the evening of baseline visit
- Study Coordinator will provide subject payment for the visit(s) and all follow-up visits at the Study Coordinator's discretion
- Study Coordinator will schedule follow-up visit(s)

6.3.2 Visit 2: Period 1 Mid-Treatment Evaluation (Day 10)

- Subjects will report to the [redacted] facility for study procedures
- Dental Examiner will complete a dental examination and record any AEs, as required
- Dental photographs may be taken by study staff if oral tissue sloughing or irritation are found at the dental exam of the affected areas
- Study Coordinator will schedule follow-up visit(s)

6.3.3 Visit 3: Period 1 End of Treatment (Day 21)

- Subjects will report to the [redacted] facility for study procedures
- Subjects will return completed subject diaries, study toothpaste tubes, and 3M Oral Rinse bottles.
- Dental Examiner will complete a dental examination, review subject diary, and record any AEs, as required
- Dental photographs may be taken by study staff if oral tissue sloughing or irritation are found at the dental exam of the affected areas
- Subjects will complete the questionnaire
- Study Coordinator will dispense the assigned toothpaste for at least a 1-week washout
- Study Coordinator will schedule follow-up visit(s)

[redacted]

6.3.4 Visit 4: Period 2 Baseline (Day 28+)

- Subjects will report to the [redacted] for study procedures
- Subjects will return study toothpaste tubes used in washout
- Dental Examiner will complete a dental examination and record any AEs, as required
- Dental photographs may be taken by study staff if oral tissue sloughing or irritation are found at the dental exam of the affected areas
- Study Coordinator will dispense the assigned toothpaste, 3M Oral Rinse, and subject diary
- Study Coordinator will provide verbal and written product use and subject diary instructions, as needed
- Subjects will initiate their treatment in the evening of baseline visit
- Study Coordinator will schedule follow-up visit(s)

6.3.5 Visit 5: Period 2 Mid-Treatment (Day 38+)

- Subjects will report to the [redacted] for study procedures
- Dental Examiner will complete a dental examination, review subject diary and record any AEs, as required
- Dental photographs may be taken by study staff if oral tissue sloughing or irritation are found at the dental exam of the affected areas
- Study Coordinator will schedule follow-up visit(s)

6.3.6 Visit 6: Period 2 End of Treatment / End of Study (Day 49+)

- Subjects will report to the [redacted] for study procedures
- Subjects will return completed subject diaries, study toothpaste tubes and 3M Oral Rinse bottles.
- Dental Examiner will complete a dental examination, review subject diary and record any AEs, as required
- Dental photographs may be taken by study staff if oral tissue sloughing or irritation are found at the dental exam of the affected areas
- Subjects will complete the questionnaire

[redacted]

6.4 Assessments

6.4.1 Dental Exam

All dental examinations will be completed by the Dental Examiner. The dental examinations will be documented on study CRFs. The dental examination will include a visual sloughing evaluation divided into 12 assessment areas: dorsal surface of the tongue, ventral surface of the tongue, floor of the mouth, roof of the mouth, right buccal mucosa, gingival tissue (upper right, upper anterior, upper left), left buccal mucosa, gingival tissue (lower left, lower anterior, lower right). The Dental Examiner will evaluate the severity of sloughing in these individual locations using the

the Oral Mucosal Sloughing Index[1].

6.4.2 Subject Diary

All subjects will record compliance to study toothpaste and 3M Oral Rinse and any adverse events experienced on the subject diary, as provided on study CRFs.

6.4.3 Subject Questionnaire

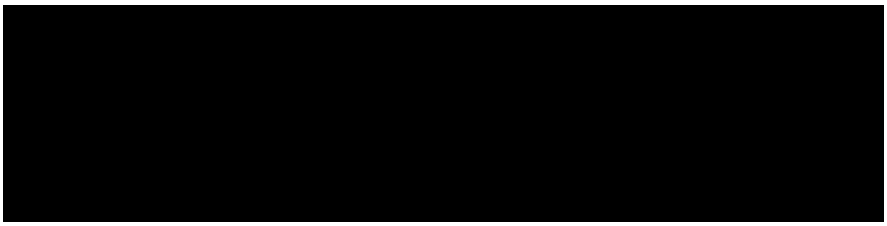
All subjects will complete an acceptability questionnaire at the required timepoints, as provided on study CRFs.

7.0 Adverse Events

According to the FDA Guidance (Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs-Improving Human Subject Protection-2009), an Adverse Event (AE) can be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not it's related to the investigational product.

AEs can range from anticipated to unanticipated and from mild to serious in nature. Any AE observed during the conduct of a study should be tracked on the AE CRFs, even if they are anticipated and mild. However, while we track these events/side effects, most of these occurrences do not meet the criteria for IRB notification.

Of greater concern are those AEs considered to be unexpected and/or serious in nature and could have implications for human safety. A serious adverse event is defined as any untoward medical or dental occurrence that, at any dose: 1) results in death, 2) is life-threatening, 3) requires inpatient



hospitalization, 4) results in persistent or significant disability/incapacity, or, 5) in a congenital anomaly/birth defect. AEs of this nature are required to be reported.

For this study, an adverse event record will be completed and reported to the 3M IRB within 48 hours for any observation of:

- Any occurrence of an unanticipated adverse event,
- Anticipated AEs that occur at a higher frequency or severity that is inconsistent with prior observations,
- Any occurrence that results in a medical or dental consultation, or,
- Any occurrence of a serious adverse event

In addition, an adverse record will be completed and will be included in the final report for the following anticipated observations of:

- Temporary, mild, mouth or tongue sensations such as:
    - Numbness,
    - Mild taste alteration,
- Mild dry mouth,
- Mild superficial tissue sloughing.

The study Principal Investigator (PI) will monitor all adverse incidents and will triage any subject who experiences either an unintended and/or serious AE and determine the course of action (i.e. if they need to be seen by a dental or medical professional). If a dental consultation is necessary the PI/Study Coordinator will contact the 3M Staff [redacted] If medical care is necessary, the subject will be directed to the [redacted] At the subject's request, they may be referred to another health care professional. In the event of a research-related injury, compensation will be determined on a case-by-case basis.

A written report of all unanticipated and/or serious AEs will be submitted to the 3M IRB office within 48 hours of the Investigator's knowledge of the event. The 3M IRB may require additional reports until the event is resolved. Reports for all Serious Adverse Events (SAEs) and Adverse Device Reaction (ADRs) will also be forwarded to the [redacted] department for FDA

[redacted]

notification as appropriate. The final study report will include a comprehensive listing of all AEs; anticipated, unanticipated, and from mild to serious in nature.

8.0 Randomization

8.1 Randomization

Subjects will be numbered from 01 through 72. This number will be used to identify the subject on the case report forms. Subjects will be randomized in a 1:1:1 ratio into three different two-treatment sequences: (1) A-> C (2) B->C and (3) C->B. All seventy-two (72) subjects will be exposed to the high SLS toothpaste (C), 48 subjects will be exposed to the medium SLS toothpaste (B), and 24 subjects will be exposed to the no SLS toothpaste (A). See Appendix II for the randomization schedule.

8.2 Blinding

The Dental Examiner(s) completing the dental examinations will be blinded to the subject sequence of treatments assigned. The subject, sponsor, and all other study staff will not be blinded to the treatment sequenced assigned.

9.0 Data Analysis

9.1 Statistical Hypothesis

The main hypothesis under investigation is that the incidence of sloughing over a 3-week period will be positively correlated with the level of SLS in the toothpaste assigned.

9.2 Sample Size Determination

A sample size of 72 represents a convenient sample size that should yield incidence rate estimates of adequate precisions to detect gross trends.

A sample size of 24 will give a precision (1/2 confidence interval width) of 4% if the observed incidence rate is 1%. Likewise, sample size of 48 will give precisions of 8.5-13% for incidence rates 10-30%, and a sample size of 72 will give precisions of 11.3-11.5% of incidence rates of 40-50%.

In addition, sample sizes of 72 and 48 will give 74% power to detect differences in proportions of 50% and 25%, respectively. Furthermore, sample sizes of 48 and 24 will give 77% power to detect differences in 25% and 1%, respectively using a two-sided Fisher's exact test with alpha of 0.05.

9.3 Populations for Analysis

The datasets that will be used for the primary and secondary analyses including the adverse event analysis will include all subjects randomized into the study (intent-to-treat population). There will be no additional subset datasets defined for other analyses or sensitivity analyses.

9.4 Statistical Analyses

9.4.1 Primary Analyses

The primary endpoint is the incidence rate of sloughing. All sloughing clinically observed or subject-reported over the three-week treatment period will be recorded as an adverse event and coded using the MedDRA dictionary (with a preferred term sf oral mucosal exfoliation). Differences in incidence rates will be tested for significance using a generalized logistic regression model that takes into account the crossover design with subject as a random effect and treatment, period, sequence and treatment-by-period interaction as fixed effects, non-significant treatment-by-period interaction effect will be dropped from the final model. In the event of failing convergence of the model or finding a significant treatment-by-period interaction (carry-over effect), the Fisher's Exact test maybe used to test for significant differences in sloughing rates among the treatment arms using all data or Period I data only, respectively.

9.4.2 Secondary Analyses

The 95% confidence intervals will be computed for the sloughing rates for each treatment group using the Wilson score method. Significant trends in incidence rates across the treatment groups (from high to medium to no SLS toothpaste) will be tested using the Cochran Armitage test.

The oral mucosal sloughing index score will be used to compute the following two outcomes: (a) Overall subject-level incidence based on any non-zero score among the 12 oral areas examined, and (b) an average subject-level score based on the mean of 12 severity scores over all oral areas for each subject. These outcome scores will be summarized for each treatment group and if appropriate, will be analyzed using a generalized linear regression model such as a Poisson model to test for significant treatment, period and sequence effects.

The diary data will used to compute treatment compliance with expected number of doses, and this will be summarized per period and treatment group.

Exploratory analysis may occur to examine the onset time and duration of adverse events.

The data collected on the subject acceptance questionnaire will be summarized by treatment group. If appropriate, these data will be analyzed for treatment differences using a generalized linear regression model such as an ordinal logistical model that takes into account the cross over design and the ordinal nature of the data.

9.4.3 Adverse Event Analyses

Adverse event data will be coded using the MedDRA dictionary and the incidence rates will be summarized by preferred term and treatment group. Differences in incidence rates among the three groups will be tested using an overall Fisher's exact test and further pairwise testing (A vs B, A vs C and B vs C) will be carried out if the overall p-value is significant (<0.05).

9.5 Planned Interim Analysis

There will be no interim analyses for this study.

9.6 Procedures for Missing, Unused, or Spurious Data

Missing data due to subject withdrawals or subjects lost to follow-up will not be imputed. All data collected from each subject will be used in the statistical analyses.

9.7 Procedures for Reporting Deviations from Statistical Analysis Plan

Any deviations from the statistical analyses outlined in this protocol will be described and justified in the final study report.

10.0 Personnel Responsibilities

10.1 All Study Staff

Investigator, dental examiners, and staff are required to be current int their [redacted] required CITI training and to comply as stated in [redacted] (Preclinical and Clinical Study Overview), [redacted] Clinical Studies), [redacted] (Biocompatibility Assessment and Testing), and [redacted] (Preclinical and Clinical Documentation Requirements).

[redacted]

The Investigator or staff, including the Study Coordinator(s), will review all data entries for completeness and correctness, and then sign each individual form. All completed CRFs and copies of subject sign consent forms are to be retained. When changes or corrects are made on any form, study staff must draw a single line through the error, initial, and date.

10.2 Principal Investigator

The Principal Investigator (PI) has overall responsibility for the welfare of the trial subjects, design and conduct of the study, ensuring that IRB requirements and applicable regulatory requirements are met, and that the study site staff has knowledge of their responsibilities as required for their role in the study. It is the overall responsibility of the PI to ensure that all study data are complete and accurate and that all study records are placed in the study file. The PI is responsible for the maintenance of the investigator file and IRB reporting, including writing the final report.

The PI or designee should maintain a list of appropriately qualified persons to whom significant study-related duties have been delegated and a signature sheet to document signatures and initials of all persons authorized to make entries or correction on study CRFs.

10.3 Dental Examiner

The Dental Examiner will be a qualified dental professional, such as a Dentist or Dental Hygienist. The Dental examiner will complete all dental examination activities, including dental photographs.

10.4 3M Staff Dentist

[redacted] Staff Dentist and will have clinical oversight for this study and complete all dental exam activities, including assessing adverse events.

10.5 Study Staff

The Study Coordinator(s) in the [redacted] Clinical Operations Division, are Laboratory/Technical Specialists who have extensive experience in all aspects of recruiting, screening, and consenting study subjects.

The Study Coordinator(s) assigned to this project will complete the recruitment of participants for this project, perform the screening procedures, the consenting process, and scheduling of all study-related visits/appointments. The Study Coordinator(s) will be

[redacted]

responsible for dispensing the study products assigned to each study subject, for providing and training subjects on subject diaries, and for completing CRFs that will be used at the assessment visits.

Study Coordinator(s) may be trained to assist the Dental Examiner during dental exams for activities that do not require a dental professional, such as uploading dental photographs, cleaning the exam room equipment, and scribing study CRFs.

Study Coordinator(s) will also share responsibilities with the Study Monitor in quality assurance procedures to ensure the integrity of the study data by assisting with checking the participants' responses on the study questionnaires, dental examination forms, study CRFs, and subject diaries for accuracy and legibility. The Study Coordinator(s) will assist in generating the final report for this project.

10.6 Study Monitor

The Study Monitor is responsible for ensuring the proper conduct of the study as regards protocol adherence and validity of the data recorded on the study CRFs. The Study Monitor will assist the PI and 3M in the maintenance of complete, legible, well-organized, and easily retrievable data. The Study Monitor will complete all monitoring activities in line with 3M Standard Operating Procedures (SOPs).

11.0 IRB

Using criteria set forth in Clinical Research Standard Operating Procedure ([redacted] Preclinical and Clinical Documentation Requirements), this study is considered to be the type of study requiring IRB approval before it can be conducted. Information concerning requirements for Investigational Review Board approval is addressed in Clinical Research Department Standard Operating Procedures ([redacted]).

12.0 Product Disposition

No special inventory is necessary because all materials remain in the control of 3M employees. All used and unused materials are to be returned to the Investigator.

13.0 Amendment / Deviations

13.1 Amendments

A protocol amendment is defined as a change in procedures that is identified and documented at any time while conducting the study. All protocol amendments must be documented and

[redacted]

approved by the Investigator, [redacted] Clinical Study Coordinator, and by the reviewing IRB prior to being implemented.

13.2 Deviations

A protocol deviation is defined as a change in procedure that has not been documented before initiation and therefore has not been reviewed and approved with the study sponsor prior to initiation. All deviations from the study protocol are to be documented and reported to the investigator and reviewing IRB.

14.0 Monitoring

Monitoring will be completed by the Study Monitor consistent with departmental SOPs and the study specific Monitoring Plan.

15.0 References

[1]Green, A., Crichard, S., Ling-Mountford, N., Milward, M., Hubber, N., Gupta, A. K., and Chapple, I. L. C. (2019). A randomized clinical study comparing the effect of Steareth 30 and SLS containing toothpastes on oral epithelial integrity (desquamation). *Journal of Dentistry*, 80(2019), S33-S39.

16.0 Investigator / Sponsor's Representative Signature

Approval of this document by the IRB representative indicates that the IRB has reviewed and approved the study submission.

Signer	Role	Date Signed
[redacted]		

[redacted]

APPENDIX I – Recruitment Letter

3M Oral Rinse incidence and patient acceptance of sloughing when used with Sodium Lauryl Sulfate (SLS) toothpastes

I am writing to tell you about a research project being conducted here at [redacted] The purpose of this study is to determine the incidence rate of adverse events and acceptance of sloughing and/or other side effects for an investigative 3M oral care rinse.

The study will involve 6 visits over at least 7 weeks of study participation, including dental exams. Participation will involve the following:

- A screening visit to see if you qualify for the study, including providing written consent for participation.
- The study procedures will be explained to you and your questions regarding the study will be answered.
- If you consent to participate, you will be scheduled for follow-up visits.
- During study participation, you will be asked to use a 3M Oral Rinse along with provided toothpaste and to avoid other dental products, such as other rinses, toothpastes, toothbrush, and chewing gum.
- You will be asked to use the provided oral rinse, tooth paste, and toothbrush for a total of 3 weeks.
- There will be a follow-up visit with a dental exam in the middle of the 3-week treatment. After 3 weeks, another dental exam will be performed.
- You will complete a washout with a toothpaste and toothbrush for at least one week. At end of the washout, you will have a dental exam and be provided with additional oral rinse and a different toothpaste to use for an additional 3 weeks with similar visits to the first 3-week regimen.
- You will be asked to complete a questionnaire on your experience using these combined products.
- You will be asked to complete a daily diary on your experience using these combined products.

You will not receive any personal health benefits as a result of your participation in this research study.

[redacted]

Primarily, you will be assisting the [redacted] members in understanding people's acceptance of this new oral rinse product in conjunction with toothpastes with varying levels of Sodium Lauryl Sulfate (SLS).

The attached consent form contains more specific information. If you are interested in participating in this study, please respond to this notice with a time that will work from the list below. If you are unable to participate, please use the voting button at the top of this email message to vote "No Thank You". If you do not respond to this email it will be understood that you are not interested in the study and you will not be contacted again for this study.

[redacted]

APPENDIX II – Randomization Schedule

Subject Number	Period 1	Period 2
01	B	C
02	A	C
03	C	B
04	B	C
05	C	B
06	A	C
07	C	B
08	A	C
09	B	C
10	B	C
11	A	C
12	C	B
13	C	B
14	A	C
15	C	B
16	B	C
17	A	C
18	B	C
19	A	C
20	A	C
21	B	C
22	C	B
23	B	C
24	C	B
25	A	C
26	C	B
27	A	C
28	C	B
29	B	C
30	B	C
31	A	C
32	C	B
33	B	C
34	B	C
35	A	C
36	C	B
37	A	C
38	A	C
39	B	C
40	C	B
41	C	B
42	B	C

Subject Number	Period 1	Period 2
43	B	C
44	A	C
45	B	C
46	A	C
47	C	B
48	C	B
49	C	B
50	A	C
51	B	C
52	B	C
53	A	C
54	C	B
55	B	C
56	C	B
57	A	C
58	B	C
59	A	C
60	C	B
61	C	B
62	A	C
63	B	C
64	B	C
65	C	B
66	A	C
67	A	C
68	B	C
69	C	B
70	C	B
71	B	C
72	A	C