CLINICAL PROTOCOL

A REAL-WORLD EVIDENCE STUDY EVALUATING ORAL HEALTH RELATED QUALITY OF LIFE FOLLOWING THE USE OF ANTI-SENSITIVITY TOOTHPASTE FOR DENTINE HYPERSENSITIVITY MANAGEMENT

Protocol Number:	216953
Compound/Product Name:	Potassium nitrate (5% w/w), sodium fluoride (0.15% w/v fluoride ion) dentifrice / Sensodyne Fresh Mint
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
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This document contains confidentiality statements that are not relevant for this publicly available version

Sponsor Information

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	The following administrative changes have been made: 1) clarifications in the administrative change letter dated 15 June 2021 have been added 2) typo correction on the DHEQ score section 2: "Effect of life" was changed to "Effect on life" throughout the protocol

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	PPD
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

1.1 Synopsis

Background and Rationale:

This study is designed to generate real-world data on dentin hypersensitivity (DH) sufferers among a general population. This study will aim to evaluate the impact of the use of a desensitizing toothpaste on oral health related quality of life. Data generated will provide real world information on the DH experience and how DH management treatment could impact oral health related quality of life.

Objectives and Endpoints:

Objective(s)	Endpoint(s)
Primary	
To describe subjects' oral health related quality of life over a 24 week period following the use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48) in a population of DH sufferers.	Plot over time in DHEQ mean scores (0, 4, 8, 12, 16, 20 and 24 weeks): Section 1 – Impact on everyday life (Q1-3) Section 2 – Total Score (Q1-34) – Individual Domain scores o Restrictions (Q1-4), o Adaptation (Q5-16), o Social Impact (Q17-21), o Emotional Impact (Q22-29) o Identity (Q30-34) – Global oral health score (Q35) – Effect on life overall score (Q36-39)
Exploratory	
To explore subjects' oral health related quality of life over a 24 week period following the use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the DHEQ-48 in further characterisation of DH sufferers by subgroups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	Plot over time in DHEQ mean scores (0, 4, 8, 12, 16, 20 and 24 weeks) for each sub-group: Section 1 – Impact on everyday life (Q1-3) Section 2 – Total Score (Q1-34) – Individual Domain scores o Restrictions (Q1-4), o Adaptation (Q5-16), o Social Impact (Q17-21), o Emotional Impact (Q22-29)

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To characterise subjects' change in oral health related quality of life over 24 weeks compared to baseline, following use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the DHEQ-48, in the overall population of DH sufferers and in 4 subgroups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	DHEQ Mean score over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall population of DH sufferers and each sub-group: Section 1 – Impact on everyday life (Q1-3) Section 2 – Total Score (Q1-34, section 2) – Individual Domain scores (section 2) ○ Restrictions (Q1-4), ○ Adaptation (Q5-16), ○ Social Impact (Q17-21), ○ Emotional Impact (Q22-29) ○ Identity (Q30-34) – Global oral health score (Q35) – Effect on life overall score (Q36-39)
To identify the DHEQ domain items important to the overall population of DH sufferers following 24 weeks use of the sensitivity toothpaste	Percentage of DH sufferers who agree (score 5-7) to items in each respective domain at baseline and week 24
To explore the potential impact a sensitivity toothpaste containing 5% potassium nitrate has on subjects' reported pain in relation to DH in the overall population of DH sufferers and in 4 sub-groups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	For overall population of DH sufferers and each sub-group: • Numeric Pain Rating Scale (NPRS) mean score over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) • Plot over time in NPRS mean scores (0, 4, 8, 12, 16, 20 and 24 weeks) • Percentage of DH sufferers who achieve pain reduction identified as clinically important (pain reduction NPRS > 30%)
To explore subjects' overall satisfaction with DH treatment in the overall population of DH sufferers and in 4 sub-groups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	At week 24, Satisfaction Numerical rating scale (NRS) mean scores for overall population of DH sufferers and each sub-group

To describe oral hygiene habits of DH sufferers according to oral hygiene questionnaire	At baseline, summary of oral hygiene habits

Study Design:

This will be a virtual, prospective, twenty-four weeks, open label study in subjects with DH (self-reported symptoms).

This study will aim to evaluate changes in oral health-related quality of life (OHrQoL) in subjects suffering from DH following the use of anti-sensitivity toothpaste for 24 weeks. Subjects' self-perception of DH will be evaluated by completion of a validated OHrQoL questionnaire (DHEQ-48) at baseline, 4, 8, 12, 16, 20 and 24 weeks.

Sufficient number of subjects (estimated 50% screen failure) aged between 18-65 years, who suffer from tooth sensitivity, will be screened to enroll approximately 650 to ensure 400 consumers complete the entire study (estimated 40%drop-out).

Subjects will be recruited through social media and other digital platforms. Subjects interested in the study will be sent to a landing page after clicking on an "Ad" or study link where they fill-out an initial pre-screening questionnaire and, if they are eligible, they will be sent an email with provided unique participant ID and the link to download the PPD app. After downloading the PPD app and logging in using a unique participant ID provided, they will review the electronic Inform Consent (eIC), they will be able to communicate with the PPD virtual site team via the PPD app's chat, via phone (study number linked to the study chat) or email. Subjects can use any or all of these methods as often as they need to until they are comfortable with their decision and may then accept or decline the eIC. No study-specific data collection will occur prior to subject consent. Subjects who do not actively access the study-specific website/app and provide consent will not have the possibility to contribute study data.

Once the subjects sign the eIC, they will complete a screening questionnaire which will aim to identify and exclude individuals whose sensitivity could be caused by other factors/clinical pathology for which dental healthcare professional advice should be sought. Subjects who qualify based on inclusion/exclusion criteria and the screening questionnaire will be enrolled and will be sent a desensitizing toothpaste (5% potassium nitrate). They will be asked to use it for 24 weeks, following the commercial tube instructions, recommended daily use and their normal oral healthcare habits, and to fill in the DHEQ form on 7 different occasions (Baseline (prior to any product use), 4, 8, 12, 16, 20 and 24 weeks).

At each DHEQ timepoint, subjects will receive reminders according to the schedule of activities.

Safety will be assessed by evaluation of AEs and will be collected remotely via an online, subject portal.

Study Products:

Sensodyne Fresh Mint Toothpaste (potassium nitrate 5%, sodium fluoride 0.15% w/v fluoride ion – CCI USA marketplace toothpaste)

Type and Planned Number of Subjects:

Sufficient number of subjects will be screened (estimated 50% screen failure) to enroll approximately 650 to ensure 400 evaluable subjects complete the entire study (estimated 40% drop out).

Statistical Analyses

For the primary objective, plots of the mean values for questions Q1-3 (section1) and for questions in section 2 total DHEQ score (sum Q1-34), each of the domain's mean values: Restrictions (sum Q1-4), Adaptation (sum Q5-16), Social Impact (sum Q17-21), Emotional Impact (sum Q22-29), Identity (sum Q30-34), Global oral health (Q35) and Effect on life overall (sum Q36-39) will be presented for the overall population of DH sufferers over 24 weeks to assess QoL over time, graphically.

The analyses for exploratory objectives are defined in the statistical section 12.4.3.

1.2 Schedule of Activities

The schedule of activities table provides an overview of the study.

Table 1-1 Schedule of Activities

Procedures	Screening	Baseline* Week 0 (Day 0)	Week 4 Day 28 (± 7 days)	Week 8 Day 56 (±7 days)	Week 12 Day 84 (±7 days)	Week 16 Day 112 (±7 days)	Week 20 Day 140 (±7 days)	Week 24 Day 168 (± 7 days)
Electronic Informed Consent	X							
Demographics	X							
Inclusion/exclusion criteria	X							
Screening questionnaire	X							
Subject eligibility	X							
Medical History[1]	X	X						
Concomitant Medications		X	X	X	X	X	X	X
DHEQ-48 completion		X	X	X	X	X	X	X
NPRS scale		X	X	X	X	X	X	X
Oral Hygiene questionnaire		X						
Study product shipped [dentifrice][2]		X						
Patients' satisfaction with treatment (NRS)								X
AEs [3]	X	X	X	X	X	X	X	X
Study Conclusion								X

Abbreviations:

AEs: Adverse Events
DHEQ: Dentin Hypersensitivity Experience Questionnaire
NRS: Numerical Rating Scale
NPRS: Numeric Pain Rating Scale

Footnotes:

[1] Medical occurrences and AEs which subjects experience from the time of consent signature, but prior the use of the study product, will be recorded in the Medical History

[2] Product will be shipped only after baseline assessments have been completed

[3] Any events experienced from the first use of the product until last administration of the study product will be recorded as AEs. All serious AEs (SAEs) will be collected immediately after a subject provides consent signature until last administration of the study product.

* Baseline activities must be conducted within 14 days from subject eligibility

2 INTRODUCTION

2.1 Study Rationale

GSKCH has conducted many clinical studies, showing robust and positive results on the relief and management of DH in clinical measurements and OHrQoL. However, these results have been obtained from randomized controlled trials which include a very well-defined DH sufferers' population and strict study procedures. These studies do not necessarily fully reflect the general dental population's behavior.

Real-world evidence (RWE) studies offer an opportunity to gather information of a marketed product working in real-world heterogeneous populations that can complement clinical evidence, consumer insight data and post-marketing surveillance. Real world data (RWD) generation ranges from observational studies (prospective/retrospective) to interventional studies, with or without randomization, and will help to overcome the well-known limitations of randomized controlled studies which make it difficult to generalize findings to larger, more inclusive populations of patients (Sherman *et al*, 2016).

There are limited number of published RWE studies focusing on DH and most of them are part of a large observational dental practice-based studies which focused on the diversity of methods available for diagnosing and treating DH (Cunha-Cruz *et al*, 2010; Heft *et al*, 2018; Kopycka-Kedzierawski *et al*, 2017a; Kopycka-Kedzierawski *et al*, 2017b; Litaker *et al*, 2019). DH is usually diagnosed by patient's self-report of pain, the evaluation of the patient's response to various stimuli, and the exclusion of other dental and periodontal conditions. However, studies from Joana Cunha-Cruz (Cunha-Cruz *et al*, 2010) and Kopycka-Kedzierawski (Kopycka-Kedzierawski *et al*, 2017a) showed that in a routine clinical practice setting, methods chosen to diagnose DH were diverse and inconsistent among practitioners. In addition, majority of practitioners reported to use one or multiple products to manage DH, with OTC potassium nitrate toothpaste and fluoride formulations/treatments to be the most widely used (Heft *et al*, 2018; Kopycka-Kedzierawski *et al*, 2017a; Kopycka-Kedzierawski *et al*, 2017b; Litaker *et al*, 2019). The effectiveness of DH treatments (VAS scale, Labelled Magnitude scale, patients' satisfaction) was also assessed from a patient perspective and derived from the use of a therapy independently of the accuracy of diagnosis (Heft *et al*, 2018), as per nature of the real-world study setting.

The aim of this study is to evaluate the impact of a commercially available toothpaste containing 5% potassium nitrate on oral health related quality of life in a real-world setting.

GSKCH studies have demonstrated clinical efficacy of 5% potassium nitrate, it is therefore relevant (and permitted) to explore its effectiveness in a real-world setting; to obtain data that is reflective of sufferers in their environment for a full DH experience and impact on oral health related QoL.

2.2 Background

Dentin hypersensitivity (DH) has been defined as 'pain derived from exposed dentine in response to chemical, thermal, tactile, or osmotic stimuli which can't be explained as arising from any other dental defect or disease' (Addy *et al*, 1985; Canadian Advisory Board on Dentin Hypersensitivity, 2003). The hydrodynamic theory of DH hypothesizes that a stimulus external to the tooth (for example, a temperature/osmotic differential, pressure) causes movement of the fluid resident within exposed dentinal tubules (Brännström, 1963). This movement may

stimulate nerve processes in the dental pulp (Addy, 2002; Hall *et al*, 2000), resulting in the characteristic short, sharp pain of DH.

Currently there are two approaches for the management of DH: nerve desensitization and the occlusion of exposed dentin tubules. Nerve depolarising agents, typically potassium salts, generally require a period of use (14 to 28 days) before their benefit is established. The delivery of potassium ions to the dentine-pulp junction (odontoblastic layer) via dentinal tubules is believed to result in depolarisation of the afferent nerve membrane thereby blocking the pain response. The second approach uses tubule occluding agents which physically block the exposed end of the dentinal tubules, thus reducing dentinal fluid movement and pulpal irritation. Tubule occluding agents such as strontium and stannous salts, bioglasses, silicas or oxalates serve to seal or block the dentine tubules and thereby reduce the effect of external stimuli. Such agents are believed to function by precipitating insoluble materials onto the dentine surface and/or within the dentinal tubules to reduce dentinal fluid transport.

Recently, there have been a wider consideration to the psychosocial impacts of DH on everyday life (Gibson *et al*, 2015). One qualitative study showed that DH can be triggered by several stimuli and responses, not always described as pain, can affect everyday activities such as eating, drinking, tooth brushing, talking and social interactions (Gibson *et al*, 2015).

Oral health-related quality of life (OHrQoL) questionnaires are tools increasingly used in dentistry to capture the impact of clinical interventions on OHrQoL, however these measures cover a number of oral health conditions which lead to limitations of these tools and may not detect the nuances of a specific condition (Bekes *et al*, 2009). The Dentine Hypersensitivity Experience Questionnaire (DHEQ) is a validated, condition specific measure of OHrQoL in relation to DH (Baker *et al*, 2014) (Boiko *et al*, 2010). It was developed by GSKCH in collaboration with Sheffield University through a robust theoretical framework, specific for DH (Boiko *et al*, 2010), and has shown reliability and validity in both a general population (Porritt *et al,* 2016) and in clinical studies (Boiko 2010, Gibson *et al,* 2015). The conception, development, validation and initial usage of the DHEQ has been published (Robinson, 2014). The measure has been validated with both long- and short-form versions, comprising 48 (Baker *et al*, 2014; Boiko *et al*, 2010) and 15 (Machuca *et al*, 2014) questions respectively, and has been translated into multiple languages (e.g., Chinese, Turkish, Portuguese) confirming its global relevance (Başaran and Celik, 2018) (Douglas-De-Oliveira *et al*, 2018) (He and Wang, 2015a) (He and Wang, 2015b).

Data generated as part of GSKCH efficacy clinical studies, showed robust and positive results on the relief and management of DH in clinical measurements and OHrQoL. However, these results have been obtained from randomized controlled trials which include strict study procedures and controlled, but contrived DH stimuli. These studies may not necessarily fully reflect the general dental population when challenged with real world sensitivity stimuli.

Based on these assumptions, this will be a real-world evidence study which will include subjects among a general population who suffer from dentin hypersensitivity (self-reported symptoms). This study will aim to evaluate the impact of a recommended daily use of desensitizing toothpaste on oral health related quality of life. Data generated will give real world information on the impact of a daily use DH treatment on oral health related quality of life.

2.3 Mechanism of Action/Indication

Potassium ions (K^+) are thought to relieve DH by reducing the excitability of the intra-dental

nerves. During brushing with a K^+ containing toothpaste, the concentration of K^+ ions at the tooth surface is raised and K^+ ions diffuse through the dentin through the tubules and raise the concentration of potassium around the odontoblast and associated nerve. Repeated exposure of the odontoblast and neve to elevated levels of potassium maintains the nerve in a depolarized state (Addy and Smith, 2010).

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To describe subjects' oral health related quality of life over a 24 week period following the use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the Dentin Hypersensitivity Experience Questionnaire (DHEQ-48) in a population of DH sufferers.	Plot over time in DHEQ mean scores (0, 4, 8, 12, 16, 20 and 24 weeks): Section 1 – Impact on everyday life (Q1-3) Section 2 – Total Score (Q1-34) – Individual Domain scores o Restrictions (Q1-4), o Adaptation (Q5-16), o Social Impact (Q17-21), o Emotional Impact (Q22-29) o Identity (Q30-34) – Global oral health score (Q35) – Effect on life overall score (Q36-39)
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To characterise subjects' change in oral health related quality of life over 24 weeks compared to baseline, following use of a sensitivity toothpaste containing 5% potassium nitrate, as measured by the DHEQ-48, in the overall population of DH sufferers and in 4 subgroups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	DHEQ Mean score over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall population of DH sufferers and each sub-group: Section 1 – Impact on everyday life (Q1-3) Section 2 – Total Score (Q1-34, section 2) – Individual Domain scores (section 2) o Restrictions (Q1-4), o Adaptation (Q5-16), o Social Impact (Q17-21), o Emotional Impact (Q22-29) o Identity (Q30-34) – Global oral health score (Q35) – Effect on life overall score (Q36-39)
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To explore the potential impact a sensitivity toothpaste containing 5% potassium nitrate has on subjects' reported pain in relation to DH in the overall population of DH sufferers and in 4 sub-groups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	For overall population of DH sufferers and each sub-group: • Numeric Pain Rating Scale (NPRS) mean score over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) • Plot over time in NPRS mean scores (0, 4, 8, 12, 16, 20 and 24 weeks) • Percentage of DH sufferers who achieve pain reduction identified as clinically important (pain reduction NPRS > 30%)
To explore subjects' overall satisfaction with DH treatment in the overall population of DH sufferers and in 4 sub-groups: **Age group** **Diagnosis** **Use of sensitivity toothpaste** **Self-reported DH frequency**	At week 24, Satisfaction Numerical rating scale (NRS) mean scores for overall population of DH sufferers and each sub-group
To describe oral hygiene habits of DH sufferers according to oral hygiene questionnaire	At baseline, summary of oral hygiene habits

In this study is expected to observe a trend in favor of improvement in QoL over time after 24 week treatment period in a general population of DH sufferers, in particular the total DHEQ score.

4 STUDY DESIGN

4.1 Overall Design

This will be a virtual, prospective, twenty-four weeks, open label study in subjects with DH (self-reported symptoms).

This study will aim to evaluate changes in oral health-related quality of life (OHrQoL) in subjects suffering from DH symptoms following the use of anti-sensitivity toothpaste for 24 weeks. Subjects' self-perception of DH will be evaluated by completion of a validated OHrQoL questionnaire (DHEQ-48) at baseline, 4, 8, 12, 16, 20 and 24 weeks.

Sufficient number of subjects (estimated 50% screen failure) aged between 18-65 years, who suffer from tooth sensitivity, will be screened to enroll approximately 650 to ensure 400 consumers complete the entire study (estimated 40% drop out).

Subjects will be recruited through social media and other digital platforms. Subjects interested in the study will be sent to a landing page after clicking on an "Ad" or study link where they fill-out an initial pre-screening questionnaire and if they are eligible, they will be sent an email with provided unique participant ID and the link to download the app. After downloading the PPD and logging in using a unique participant ID provided, they will review the electronic Inform Consent (eIC), they will be able to communicate with the PPD virtual site team via the PPD app's chat, via phone (study number linked to the study chat) or email. Subjects can use any or all of these methods as often as they need to until they are comfortable with their decision and may accept or decline the eIC. No study-specific data collection will occur prior to subject consent. Subjects who do not actively access the study-specific website/app and provide consent will not have the possibility to contribute study data.

Once the subjects accept/sign the eIC, they will be able to fill-out a screening questionnaire which will aim to identify and exclude individuals whose sensitivity could be caused by other factors/clinical pathology for which dental healthcare professional advice should be sought. Subjects who qualify based on inclusion/exclusion criteria and the screening questionnaire will be enrolled and will be sent a desensitizing toothpaste (5% potassium nitrate). They will be asked to use it for 24 weeks, following the commercial tube instructions, recommended daily use and their normal oral healthcare habits, and to fill in DHEQ form on 7 different occasions (Baseline (prior to any product use), 4, 8, 12, 16, 20 and 24 weeks).

At each DHEQ timepoint, subjects will receive reminders according to the schedule of activities.

Safety will be assessed by evaluation of AEs and will be collected remotely via an online, subject portal.

4.2 Scientific Rationale for Study Design

GSK CH has generated robust and positive efficacy results on the relief and management of DH in clinical measurements and OHrQoL. However, these results have been obtained from randomized controlled trials which include a very well-defined DH sufferers' population and

strict study procedures. These studies do not necessarily fully reflect the general dental population's behavior.

RWE studies have the potential to reflect users of products in everyday life therefore more accurately representing responses to an intervention and increasing their generalizability. They offer opportunities to gather information on marketed products in order to bolster existing clinical evidence and gain additional insights in the target population.

There are limited number of published RWE studies focusing on DH and most of them are part of a large observational dental practice-based study which focused on the diversity of methods available for diagnosing and treating DH (Cunha-Cruz *et al*, 2010; Heft *et al*, 2018; Kopycka-Kedzierawski *et al*, 2017a; Kopycka-Kedzierawski *et al*, 2017b; Litaker *et al*, 2019). Only one study has been identified which evaluated quality of life improvement using the validated Oral Health Impact Profile – 49 questionnaire, showing significant improvements at 24 weeks versus a negative control (https://www.colgatetalks.com/dentin-hypersensitivity-life-quality/), however the information available for this study is very limited.

This will be a virtual, prospective, twenty-four weeks, open label study in healthy DH sufferers (self-reported symptoms) among the general population.

In GSK CH randomized controlled trials (RCTs), an examiner clinically diagnoses DH in self-reported DH sufferers and selects two 'test teeth' from those that qualify as sensitive teeth for clinical assessments at all study visits. In this study, subjects will be identified as DH sufferers in the general population using a screening questionnaire (as previously done in (Porritt *et al*, 2016)) which will aim to identify and exclude individuals whose sensitivity could be caused by other factors/clinical pathology. They will be recruited between 18 and 65 years of age as DH is most frequently diagnosed between the ages of 20 and 40 years and is known to decrease with age above 40 years (Dababneh *et al*, 1999; West, 2006).

Eligible subjects will complete the Dentine Hypersensitivity Experience Questionnaire (DHEQ), a validated, condition specific measure of impacts on everyday life for DH sufferers (Baker *et al*, 2014) (Boiko *et al*, 2010), at baseline and over 24-week period. This will the first study where the DHEQ will be used in a real-world setting, therefore the choice of the time points (0, 4, 8, 12, 16, 20 and 24 weeks) relates to published GSKCH data (Mason *et al*, 2019), which showed statistically significant changes from baseline at least after 8 weeks for DHEQ total score, at least after 12 weeks for the slowest domain (Identity) and at least after 24 weeks for global oral health.

In addition, to assess effectiveness, the use of NPRS scale will be used to evaluate the percentage of subjects who achieve pain reduction from the participant perspective (pain reduction NPRS > 30% has been identified as clinically important in previous pain studies (Hawker *et al*, 2011). Furthermore, subjects will be asked to rate their satisfaction with treatment after 24 weeks (Heft *et al*, 2018; van Berckel *et al*, 2017).

The rationale for a single arm design in a long-term DH study which evaluates the participant-reported OHrQoL outcomes was previously described by Mason and colleagues (Mason *et al*, 2019). A commercially available toothpaste will be used in this open label study; and the dosage regimen will allow the subjects to use the product as recommended for sensitivity relief according to commercial tube instructions, as per nature of the RWE study.

4.3 Justification for Dose

Consistent with all marketed toothpastes, directions as recommended for sensitivity relief are stated on the commercial tube.

4.4 Duration of Study Definition

The duration of the study is defined for each subject as the date that the signed eIC is provided through the end of the study follow-up period (168 days [+ 7days] post-baseline), subject death, early withdrawal from the study, lost to follow-up or overall study termination.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Sufficient number of subjects will be screened (estimated 50% failure rate) to enroll approximately 650 to ensure approximately 400 evaluable subjects complete the entire study (estimated 40% drop out).

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process directly and successfully met eligibility criteria to proceed beyond screening as applicable for the protocol design.

5.2 Inclusion Criteria

An individual must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Provision of consent indicating that the subject has been informed of all pertinent aspects of the study.
2. All genders (male, female, not specified) aged between18 and 65 years, inclusive at the time of screening, willing to complete all activities as shown in the Schedule of Activities.
3. The subject must be able to complete all activities as shown in the Schedule of Activities independently on their smart devices.
4. Subject who has tooth sensitivity (self-reported symptoms).

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will not be eligible for enrollment into the study:

1. A subject whose sensitivity could be caused by other factors or clinical pathology as established by the screening questionnaire, which also includes:
    - A subject who has been/is on multiple prescription medications to treat severe acid reflux on regular basis or considered surgery for acid reflux
    - A subject with full or partial denture
    - A subject who has undergone treatment within 6 months of screening or is currently under treatment for periodontal or gum disease
    - A subject with active periodontitis

- A subject with active caries
- A subject with any chronic and/or severe painful health conditions which lead to regular use pain medications (more than 3 days a week)

2. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients: potassium nitrate (5%), sodium fluoride (0.15% w/v fluoride ion), water, sorbitol, hydrated silica, glycerin, cocamidopropyl betaine, flavor, xanthan gum, titanium dioxide, sodium saccharin, sodium hydroxide, sucralose, yellow 10, blue 1.

5.4 Randomization Criteria

There is no randomization in this study. All subjects eligible (subject who meet eligibility criteria based on inclusion/exclusion criteria and screening questionnaire) will be provided with the same study product.

5.5 Lifestyle Considerations

This study will not include any lifestyle considerations.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study i.e. do not fulfill all the screening criteria. To ensure transparent reporting of screen failure participants, a minimal set of screen failure information will include demography (year of birth, gender, region/state, ethnicity, race and education), screen failure details (e.g. withdrawal of consent) and eligibility criteria.

Subjects who do not meet the criteria for participation in this study (screen failure) may not be re-screened, unless due to technical issues within the PPD app/portal. If re-screening is applicable, subjects will be re-invited with a new participant ID to download the PPD app.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the Study Contact List held by PPD

The contact number is only to be used by PPD seeking advice on medical/ dental questions or problems in the event that the established communication pathways are not available. The contact number is not intended for direct use by study subjects.

To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact information in the PPD app or will be able to use the chat function in the PPD app.

5.8 Rater/Clinical Assessor Qualifications

N/A

6 STUDY PRODUCT

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Product Supplies

The following study product will be supplied by the Clinical Supplies Department, GSK CH:

Table 6-1 Study Product Supplies

	Study product
Product Name	Sensodyne Fresh Mint (USA marketplace toothpaste)
Pack Design	Carton of 12 tubes
Dispensing Details	One carton shipped to subject (baseline)
Product Master Formulation Code (MFC)	Commercial Product in the market where the study is done (CCI [redacted])
Dose/Application	As per directions stated on the commercial tube
Route of Administration	Oral Topical
Usage Instructions	As per directions stated on the commercial tube
Return Requirements	Subjects can keep unused product and can dispose of used product at the end of the study, after defacing or removing the study label. Subjects will confirm via the PPD app that the instructions above have been followed and how many unused tubes they have remaining.

6.1.1 Dosage Form and Packaging

The study product will be supplied to PPD preferred vendor by GSK CH. Products will be supplied in commercial tubes which will be placed into a carton. Study labels will be applied on the tubes and on the carton by GSK CH.

The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number and 'clinical trial use only' statement.

Care should be taken by PPD preferred vendor and subjects with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study.

6.1.2 Preparation and Dispensing

The study product will be prepared and/or dispensed by PPD preferred vendor according to instruction and their procedures. The PPD preferred vendor staff members will ensure the dispensing procedures are completed accurately.

Each eligible subject will receive sufficient tubes of product to cover usage during the study period.

6.2 Administration

Only subjects enrolled in the study (subjects who meet inclusion/exclusion criteria) may receive study products. Product shipment will be tracked, subjects will be asked to confirm that they have received the product via the PPD app and to follow commercial tube instructions as recommended for sensitivity relief. Subjects will be also asked to confirm the first use of the product.

6.2.1 Medication/Dosing Errors

N/A

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol (use of the product as per commercial tube instructions). Overdose is not likely to occur in this study.

6.3 Study Product Storage

As per nature of RWE studies, no specific temperature monitoring is required at the PPD preferred vendor sites.

6.4 Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

PPD preferred vendor must maintain adequate records documenting the receipt, shipment, loss, or other disposition of all the product supplies. Only study products stored/non-dispensed in the PPD preferred vendor site will be accounted for using the study product accountability form/record. PPD preferred vendor is responsible for accountability, reconciliation, and record maintenance of study products stored/non-dispensed in the PPD preferred vendor site.

6.4.1 Destruction of Study Product Supplies

At the end of the study, an appropriate designee, with the guidance from the GSK CH Clinical supply specialist will inventory only unused study products stored/non-dispensed in the PPD preferred vendor site on the accountability record. Only unused study products stored/non-dispensed in the PPD preferred vendor site for this clinical study will be

returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit. Study subjects can keep the unused products.

6.5 Blinding and Allocation/Randomization

This is an open label study, and no blinding is required.

6.6 Breaking the Blind

N/A

6.7 Compliance

The subjects will be asked to follow commercial tube instructions as recommended for sensitivity relief. In order to maintain adherence, the PPD app will send notifications/reminders to the subjects on pre-defined basis, and virtual study team may reach out to them if there is still lack of adherence. Also, considering the virtual nature of this study, subjects will be doing the study from the comfort of their home via guidance from the PPD app and virtual study team may also intervene if drop out is likely. The PPD app will also send weekly check ins (e.g. have you used the study product every day? Has the commercial tube instructions been followed?) and subjects will confirm how many unused tubes they have remaining at the end of the study.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

7.1 Participant Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request. These rights and information on how to withdraw consent will be included in the electronic informed consent form (eICF). Should the subject withdraw from the study, all further scheduled communication will be discontinued (e-mail and/or text message and/or notifications).

The reasons for subjects not completing the study will be recorded in the electronic Case Report Form (eCRF) (PPD portal), if available.

If the subject withdraws from the study and withdraws consent for disclosure of future information, no additional data should be collected. GSKCH may retain and continue to use any data collected before such withdrawal of consent.

7.2 Lost to Follow up

A subject will be considered lost to follow up if he or she repeatedly is unable to be contacted by PPD within the permitted missed reminders (logins) and up to 168 days (+7 days). Before a subject is deemed lost to follow up, PPD must make every effort to regain contact with the participant (where possible, 3 notifications). These contact attempts should be documented if occurred outside PPD app.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study and lost to follow up.

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study time point. However, as per nature of RWE studies, if a subject fails to complete DHEQ-48 questionnaire or NPRS scale at any timepoint post baseline, subject will be permitted continuing in the study.

The timing of each procedure is listed in the Schedule of Activities.

8.1 Screening

The following data will be collected within PPD app:

- Informed Consent
- Demographics
- Inclusion/exclusion criteria
- Screening questionnaire
- Subject eligibility
- Medical history
- Adverse events (*SAEs will be collected from immediately after a subject provides consent signature until last administration of the study product*)

8.1.1 Informed Consent

The electronic Informed Consent (eIC) process will be performed via the PPD app on the subject's mobile device. This system will be used to consent the subjects with the benefit of helping them understand the research they are taking part in and to control the consent process. Once they have had the opportunity to read the consent, subjects will be able to communicate with the PPD virtual site team via the PPD app's chat, via phone (study number linked to the study chat) or email. Participants can use any or all of these methods as often as they need to until they are comfortable with their decision, and then they can electronically sign the eIC in PPD app. Once a decision has been rendered by the participant in the PPD app, a screen message will promptly appear and present the participant with an opportunity to request an emailed copy of their signed eIC. This option will also be available at all times within the PPD app for immediate access. All consent forms are uniquely password protected on both the subject and PPD virtual site team side. A limited number of virtual study team members will have access to the online portal where the signed eICs are stored so they may perform their assigned duties, such as ensuring consent signatures are properly completed by each enrolled subject.

PPD and its PPD app will be used to provide the system and training. A help desk will be provided and subjects can access it as needed.

If, during participation in the study, any new information becomes available that may affect the subject' willingness to continue with the study, each ongoing subject should receive this new information and be re-consented into the study.

After signing the eIC, subjects will undergo the screening procedures. If the subject is confirmed eligible, the subject is considered enrolled in the study.

8.1.2 Demographics

The following demographic information will be recorded within PPD app: year of birth, gender, region/state, ethnicity, race and education (did not graduate high school, high school graduate or GED, Technical school or associates degree, 4 year degree, postgraduate degree).

8.1.3 Medical History and Medications

Details of relevant medical and surgical history, including allergies or drug sensitivity, will be collected in the eCRF (PPD app).

Medical occurrences and AEs which subjects experience from the time of consent signature, but prior the use of the study product, will be recorded in the Medical History section of the eCRF (PPD portal).

Medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, and recent vaccines taken from signing the ICF will be documented as concomitant medication/treatments in the eCRF (PPD app).

Details of any medications used by the subjects throughout the study will be collected in the eCRF (PPD app) with reason for use, unit dose, daily dose, and start and stop dates of administration.

8.2 Baseline Week 0

Baseline activities must be conducted within 14 days from subject eligibility and collected within PPD app:

- Medical History
- Medications
- DHEQ-48 questionnaire
- NPRS scale
- Oral hygiene questionnaire
- Product shipment (*only after baseline assessments have been completed*)
- Adverse events (*AEs which subjects experience from the first use of the product until last administration of the study product, and SAEs*)

8.3 Week 4, 8, 12, 16 and 20

The following data will be collected within PPD app:

- Concomitant Medications
- DHEQ-48 questionnaire
- NPRS scale
- Adverse events

8.4 Week 24

The following data will be collected within PPD app:

- Concomitant Medications
- DHEQ-48 questionnaire
- NPRS scale
- Patients' satisfaction with treatment (NRS)
- Adverse events

8.5 Study Conclusion

The Study Conclusion page of the eCRF (PPD portal) will be completed for all subjects by PPD virtual site team. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page, if available.

If a subject has any AEs at the end of the study, GSKCH should be notified. AEs will be marked as unresolved and study PI/doctor will ask the subject to seek appropriate healthcare professional care, if applicable.

8.6 Follow-up phone call

PPD will contact a subject to follow up on SAE post-study completion/withdrawal to ensure any issues are resolved. PPD must make every effort to regain contact with the subject (where possible, 3 notifications). Should the subject continue to be unreachable, the SAE will be considered unresolved.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required activities are completed as described.

9.1 Screening Assessments

Subject eligibility will be determined based on the inclusion/exclusion criteria and screening questionnaire.

9.2 Quality of life Assessment

9.2.1 Dentine Hypersensitivity Experience Questionnaire (DHEQ)

The DHEQ-48 is a condition-specific questionnaire that has been previously validated in longitudinal studies and shown to be responsive to treatments (Baker *et al*, 2014). The breakdown of the DHEQ total score into 5 separate domain scores allows for a more granular understanding of which specific areas of improvement subjects experience in their oral health related quality of life (OHrQOL). The 5 domains, from a subject's perspective, are:

- **Restrictions** (the ways in which any sensations in your teeth affect you in your daily life: compiled from subject responses to Section 2, Q1-4)
- **Adaptation** (the ways in which the sensations in your teeth have forced you to change things in your daily life: compiled from subject responses to Section 2, Q5-16)

- **Social Impact** (the ways the sensations affect you when you are with other people or in certain situations: compiled from subject responses to Section 2, Q17-21)
- **Emotional Impact** (the way the sensations in your teeth make you feel: compiled from subject responses to Section 2, Q22-29)
- **Identity** (about what the sensations in your teeth mean for you: compiled from subject responses to Section 2, Q30-34).

In addition, the DHEQ provides further specific information through:

- The **Global Oral Health Rating** (the subject's perception of the overall health of their gums, mouth and teeth: compiled from subject responses to Section 2, Q35)
- **Effect on Life Overall Rating** (the subject's perception of the impact of DH on their overall quality of life (QoL): compiled from subject responses to Section 2, Q36-39).

9.3 Safety and Other Assessments

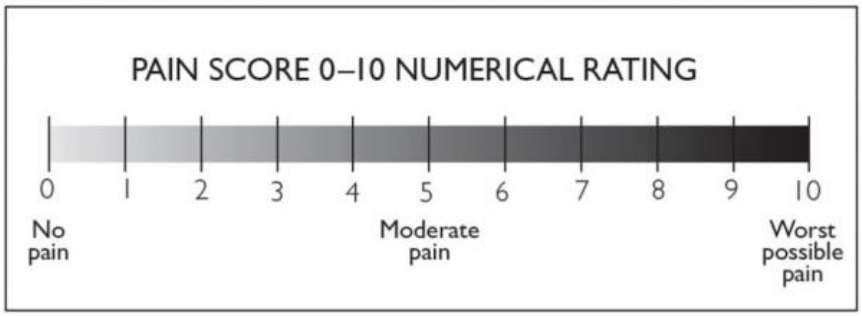
There will not be any safety assessment. AEs will be monitored, recorded and handled during the entire study.

9.3.1 DH Pain Assessment

The 11-item Numeric Pain Rating Scale (NPRS) is a segmented numeric version of the visual analog scale (VAS) in which a respondent selects a number (0–10) that best reflects the intensity of his/her pain (Hawker *et al*, 2011; ROCHA *et al*, 2020).

Similar to the VAS, the NPRS is anchored by terms describing pain severity extremes.

The 11-point numeric scale ranges from '0' representing one pain extreme (e.g. "no pain") to '10' representing the other pain extreme (e.g. "pain as bad as you can imagine" or "worst pain imaginable").



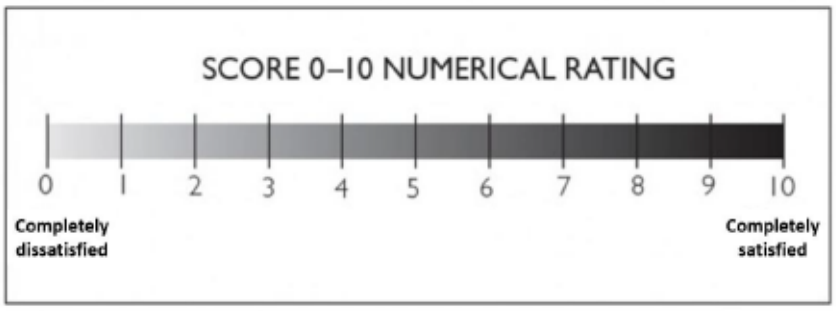
Subjects will be asked to indicate the numeric value on the segmented scale that best describes their pain intensity and to report pain intensity "in the last 24 hours".

Scores range from 0-10 points, with higher scores indicating greater pain intensity.

9.3.2 Patient satisfaction with treatment

The 11-item Numerical Rating Scale is an 11-point ordinal scale assessing satisfaction with the overall management of the condition for which the subjects sought help from treatment, from 0 (completely dissatisfied) to 10 (completely satisfied). Higher scores depict higher satisfaction (van Berckel *et al*, 2017).

Subjects will be asked to indicate the numeric value on the segmented scale that best describes their satisfaction with the treatment after 24 weeks of use.



Subjects will be also asked to record comments on their satisfaction with treatment (e.g. Please give more details on why you are satisfied or dissatisfied with the product)

10 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND PREGNANCY EXPOSURE

PPD is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study product or the study, or that caused the subject to discontinue the study product or study.

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including any washout or lead-in product (or medical device).

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a particular category of an adverse event where the adverse outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**

- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Definition of Human Safety Information (HSI)

HSI is defined as information relating to human health and/or wellbeing following exposure to GSK products. In addition to events meeting the AE definition, HSI can also include:

- Failure to produce expected benefits (i.e. lack of efficacy)
- Off-label use
- Drug abuse or effects of drug withdrawal
- Occupational exposure
- Patients taking GSK products whilst pregnant or breastfeeding
- Paternal exposure to a GSK product before and during pregnancy
- Transmission of an infectious agent via a medicinal product
- Safety information received as part of a product quality complaint
- Unexpected therapeutic benefits (i.e. an unexpected improvement in a concurrent condition other than the one being treated)

10.4 Time Period and Frequency for Collecting AE and SAE Information

Any adverse events the subject experiences immediately after they provide consent to participate in the study, by the completion (signature) of the eIC, but prior the use of the study product will be collected as Medical History in the eCRF (PPD app).

Any events experienced from the first use of study product until last administration of the study product will be recorded as Adverse Events. All SAEs will be collected immediately after a subject provides consent signature until last administration of the study product.

Details recorded by the subject on the PPD app that meet the definition of an AE must also be discussed with the subjects.

All SAEs will be recorded and reported to GSKCH immediately and under no circumstance should this exceed 24 hours. PPD will submit any updated SAE data to GSKCH within 24 hours of it being available.

PPD is not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if PPD learns of any SAE, including a death, at any time after a subject has been discharged from the study, and considers the event to be reasonably related to the study product or study participation, PPD must promptly notify GSKCH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box PPD. The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Safety group mailbox at GSK PPD.

PPD will submit any updated SAE data to GSK CH within the designated reporting time frames.

10.5 Procedures for Reporting AEs and SAEs

Spontaneous reporting of adverse events will be recorded in the PPD app and reported appropriately. Care will be taken not to introduce bias when questioning a subject about any changes in their health. Participants will have the ability to report changes to their health via the PPD app through the Health Change Form or chat. Participant may also choose to communicate with the virtual site study team via email or phone call to report a change to their health. Upon reporting of health change by the participant through these methodologies, study doctor or designee will be alerted to reach out to the participant to follow-up for a possible adverse event and document their findings within the PPD study portal.

Each AE is to be assessed by the virtual PI to determine if it meets the criteria for a SAE. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

The AEs/SAEs will be recorded within PPD app. It is not acceptable for PPD to share any subject's medical records to GSK CH in lieu of completion of the AE form.

In addition to the subject recording the event on the PPD app, all SAEs will be reported to Case Management Group (CMG), Global Safety at GSK CH (GSK CMG).

Following completion of the subject AE page within PPD app, PPD medical qualified person will review the self-reported information and assess if the AE meets the definition of an SAE. PPD will enter available information into the SAE form and will forward the completed SAE form to GSK CMG within 24 hours of receiving the questionnaire data.

If additional details are required from the subject in order to determine if the reported AE meets SAE criteria, PPD will re-contact the subject to query the AE details. If it is not possible to re-contact the subject within 24 hours, PPD will complete the SAE form to the extent possible with the available information and will send to GSK CMG within the 24 hour time frame. PPD will contact the subject on a further 3 occasions to attempt to collect further details and will share additional information with GSK CMG.

All collected SAE-related data should be sent to GSK CMG PPD, GSK CH Clinical Operations Safety Reporting email box PPD and the GSK clinical study manager associated with the present study.

In order to maintain compliance with international and national regulatory bodies, the subject will be notified in the eIC that they may be further contacted in order to collect additional information required to evaluate the potential event.

AEs/SAEs will be reported to local and regional health authorities by GSKCH, when appropriate, in accordance with applicable local and regional regulations. Prompt notification of SAEs by PPD to GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, etc. Both PPD and GSKCH will comply with all local medical device reporting requirements Safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy.

10.6 Procedures for Reporting HSI

HSI will be monitored on social media during subject recruitment. If PPD identifies HSI in comments/posts under advertisement material which relate to subject participation to the study, PPD is responsible to ensure the HSI will be submitted using reporting form provided by GSKCH within 24 hours of awareness (or next working day if over a weekend) via a secure email or fax to:

Email address: PPD

Fax: PPD

GSK CMG PPD and the GSK clinical study manager associated with the present study will be copied in the email.

PPD **is responsible to retain record that the HSI was sent/received for AE reconciliation at the end of the study.**

10.7 Procedure for reporting AEs after study completion

The study subjects will be allowed to retain unused products after completing the study. Subjects will be asked to remove the study label from the toothpaste tubes and they will be asked to report any issues/questions or comments as per commercial tube instructions.

10.8 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE eCRF (PPD app) page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.9 Pregnancy

For GSK CH studies in which no drug is utilized or studies of single-use marketed products that are classified as a non-medicinal product in the market where the testing is occurring and there is no pregnancy warning on labelling, a pregnancy test will not be required and it will not be an exclusion criteria for this study. Pregnancy information will be collected only for spontaneous pregnancy reports.

10.9.1 Action to be Taken if Pregnancy Occurs

PPD will record pregnancy information on the appropriate form and e-mail it to the GSK CH Clinical Operations Safety Reporting email box PPD within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Safety mailbox PPD.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by PPD to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group, Global Safety group mailbox at GSK PPD. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported. While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

11 DATA MANAGEMENT

As used in this protocol, the term eCRF is understood to refer to an electronic data record (PPD portal).

For this study, subject data will be entered into the PPD app, a validated system. Data relating to SAEs and pregnancy will also be collected on specific forms.

PPD is responsible for verifying that data entries are accurate in the eCRF.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

A CRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent the eCRF (PPD portal) must be completed and reviewed for completion and accuracy. PPD must maintain accurate documentation that supports the information entered in the eCRF.

Management of clinical data will be performed in accordance with PPD applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or full birth date) is to be recorded in the eCRF or as part of the query text.

Data collection, processes as outlined in PPD processes and SOPs will be documented via Data Management Plan.

All eCRF (PPD portal) pages should be completed by subjects when the eCRF has been designated as the source.

GSK CH will obtain and retain all eCRFs and associated study data as applicable at the completion of the study.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, PPD app, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by PPD

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary, CCI .

11.2.1 Data Queries

The PPD data management team will perform edit checks as the data are being entered into the system, and queries will be entered on a data issues log for the decentralized site staff to address. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

11.3 Processing Patient Reported Outcomes

Electronic Patient reported outcome (ePRO) data will be collected using electronic devices and transferred electronically to GSKCH or PPD

To protect the privacy of subjects, no PII (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO that will be forwarded to GSK CH or PPD

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

No formal sample size calculation has been performed for this study however sufficient subjects will be screened (estimated screen failure 50%) to have approximately 650 subjects enrolled and 400 completers (estimated 40% drop-out).

There is no prior information for the use of DHEQ in DH sufferers in a RWE setting. It is believed that for this study 400 subjects are deemed sufficient to observe a trend over time from baseline at 24 weeks in total score.

12.2 Populations for Analysis

The Screened population will include subjects who sign the eIC and enter the screening process of assessment of inclusion and exclusion criteria.

The Enrolled population will include all subjects who meet the inclusion/exclusion criteria and identified by the screening questionnaire

The Safety population will include all subjects who receive at least one dose of study product. Safety population will be used of safety variables.

The modified Intent-To-Treat (mITT) population will include all subjects who receive at least one dose of study product and have at least one post baseline DHEQ-48 questionnaire data. Efficacy data will be summarized using the mITT population only.

12.3 Sub-Group classification

A total of 4 different groups will be identified at screening for the purposes of sub-group analyses:

- Age group
  - ≤ 40 years old
  - > 40 years old
- Diagnosis
  - self-reported DH without previous diagnosis by a dentist
  - self-reported DH with previous diagnosis by a dentist
- Use of sensitivity toothpaste
  - Non-users – will include subjects who are not currently using a sensitivity toothpaste e.g. first-time user
  - Intermittent users – will include subjects who sometimes use a sensitivity toothpaste
  - current users – will include subjects who regularly (daily) use a sensitivity toothpaste
- Self-reported DH frequency
  - frequent = Several times a day, Once a day, Several times a week
  - less frequent = Once a week, Several times a month, once a month, less than once a month

12.4 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (RAP), which will be written following finalization of the protocol and prior to study analysis (as appropriate). This section is a summary of the planned statistical analyses including primary and exploratory endpoints. Additional details for exploratory endpoints will be further described in detail in the RAP.

12.4.1 Primary Analysis

For the primary objective, plots of the mean values for section 1 questions Q1-3, and questions in section 2 for total DHEQ score – section 2 (sum Q1-34), each of the domain's mean values (Restrictions – sum Q1-4, Adaptation – sum Q5-16, Social Impact – sum Q17-21, Emotional Impact – sum Q22-29, Identity – sum Q30-34), Global oral health (Q35) and Effect on life overall (sum Q36-39) will be presented over 24 weeks to assess QoL over time in the overall population of DH sufferers, graphically.

12.4.2 Safety Analyses

All AEs will be coded using MedDRA. AEs will be categorized as oral and non-oral by PPD prior to database lock. The number of AEs/SAEs and number of subjects with AEs/SAEs will be listed and tabulated.

12.4.3 Other Analyses

The exploratory endpoints will be analyzed as follows. Further details will be provided in the RAP.

- Plot over time in DHEQ mean scores for each sub-group

For the exploratory objective relating to sub-groups, plots of the mean values for section 1 questions Q1-3, and questions for section 2 total DHEQ score – section 2 (sum Q1-34), each of the domain's mean values (Restrictions – sum Q1-4, Adaptation – sum Q5-16, Social Impact – sum Q17-21, Emotional Impact – sum Q22-29, Identity – sum Q30-34), Global oral health (Q35) and Effect on life overall (sum Q36-39) will be presented over 24 weeks to assess QoL over time in the further characterisation of DH sufferers by sub-group classification, graphically.

- DHEQ Mean scores over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall DH sufferers and each sub-group

The exploratory response variable is the DHEQ mean score at 0, 4, 8, 12, 16, 20 and 24 weeks respectively in total score, each of the DHEQ domain scores, questions Q1-3, Global oral health and Effect on life overall.

An Analysis of Variance (ANOVA) model will be used to analyze the DHEQ score as the response variable and timepoint as the dependent variable. Subject will be included as a random effect. Each post baseline timepoint will be compared to baseline using the adjusted means from the time variable from the model.

For the analysis of the 4 subgroups, an extra factor for the subgroup will be included along with the subgroup*timepoint interaction. This will enable to look at the differences between sub-group and the interaction term will enable adjusted means of each subgroup over time.

For the ANOVA if the underlying assumptions are not met, alternative methods will be sought, including transformations or non-parametric methods.

- Percentage of DH sufferers who agree (score 5-7) to items in each respective domain at baseline and week 24

A table for percentage of consumers who agree (score 5-7) to items in each domain at baseline and at week 24 respectively will also be presented as part of this objective

- Numeric Pain Rating Scale (NPRS) Mean scores over time compared to baseline (0, 4, 8, 12, 16, 20 and 24 weeks) to be analysed for overall DH sufferers and each sub-group

The exploratory response variable is the NPRS mean score at 0, 4, 8, 12, 16, 20 and 24 weeks. An Analysis of Variance (ANOVA) model will be used to analyze the NPRS score as the response variable and timepoint as the dependent variable. Subject will be included as a random effect. Each post baseline timepoint will be compared to baseline using the adjusted means from the time variable from the model.

For the analysis of the 4 subgroups, an extra factor for the subgroup will be included along with the subgroup*timepoint interaction. This will enable to look at the differences between sub-group and the interaction term will enable adjusted means of each subgroup over time.

For the ANOVA analyses if the underlying assumptions are not met, alternative methods will be sought, including transformations or non-parametric methods.

A plot over time in NPRS mean scores will also be presented along with a table reporting the percentage of participants who achieve pain reduction identified as clinically important (pain reduction NPRS > 30%)

- Satisfaction Numerical rating scale (NRS)

The satisfaction Numerical rating scale will be summarized using frequencies at week 24. Similar summaries will be presented for overall population and each of the subgroups.

- Oral hygiene habits of DH sufferers according to oral hygiene questionnaire

A summary of oral hygiene habits at baseline will be provided as part of this objective

12.4.4 Exclusion of Data from Analyses

Exclusion of any data from the analyses will be determined during a data review meeting prior to database lock and pre-defined in the RAP. Any reasons for exclusion from an analysis population will be listed, if applicable. As there is no PP analysis planned, only an assessment of subjects being in the safety and mITT populations will be made.

12.4.5 Demographic and Baseline Characteristics

Age and other continuous demographic and baseline variables will be summarized using descriptive statistics such as mean, range, median and standard deviation. Gender, race, ethnicity and other categorical demographic and baseline variables will be summarized using frequency counts and percentages for the safety and mITT populations.

12.4.6 Study Product Compliance and Use of Other Therapies

12.4.6.1 Study Product Compliance

Study product compliance and compliance to the study schedule will be tabulated and summarized for the safety population.

Summaries will include a simple yes/no frequency (and percent) count at each timepoint:

- Summary of completion to study schedule and assessments (yes/no)
- Summary of product usage according to product instructions (yes/no)
- Summary of number of tubes remaining at the end of the study (number remaining)

12.4.6.2 Prior and Concomitant Medications

Concomitant medications taken during the study will be listed for the safety population.

12.4.7 Handling of Dropouts and Missing Data

Missing data due to general dropout/withdrawals will be assessed on an ongoing basis during the study. Any further sensitivity analyses needed due to missing data will be reviewed at the time of data review.

For the DHEQ data, for any timepoint if response is missing will be excluded from the primary analysis however the data available for each subject (even though some time points may be missing) will still be included in the analysis.

12.4.8 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

During the study, the data will be monitored to verify that:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH may conduct a quality assurance assessment and/or audit of the PPD records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, PPD must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

PPD will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study.

The GSK CH will be available to help PPD prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of PPD to have prospective approval of the study protocol, protocol amendments, inform consent documents, and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the

IRB/EC should be retained in the eTMF. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

PPD will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The inform eIC documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The inform eIC documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

PPD must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs may be used as recruitment procedures. Use of ethics committee approved, generic, pre-screening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This pre-screening questionnaire will be accessed by subjects clicking on ads on social media, which will direct them to a landing page.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

13.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH-sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if PPD is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, PPD will inform GSK CH immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that PPD becomes aware of.

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK CH processes.

GSK intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

13.5 Provision of Study Results to Investigators

N/A

13.6 Records Retention

Following closure of the study, PPD must assure that the subject's anonymity will be maintained. On eCRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. PPD should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, should be maintained by PPD in strict confidence.

Records and documents, including signed eIC, pertaining to the conduct of this study must be retained by PPD as per the signed contractual agreement, from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study (US requirement is 30 years), as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and PPD. PPD must notify GSK CH of any changes in the archival

arrangements, including, but not limited to, transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH.

If a study is prematurely terminated, GSK CH will promptly notify PPD After notification, PPD must promptly contact all participating subjects and should assure appropriate follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and PPD should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, PPD should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH study accountable person will conduct closure activities with PPD as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

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15 APPENDICIES

15.1 ABBREVIATIONS

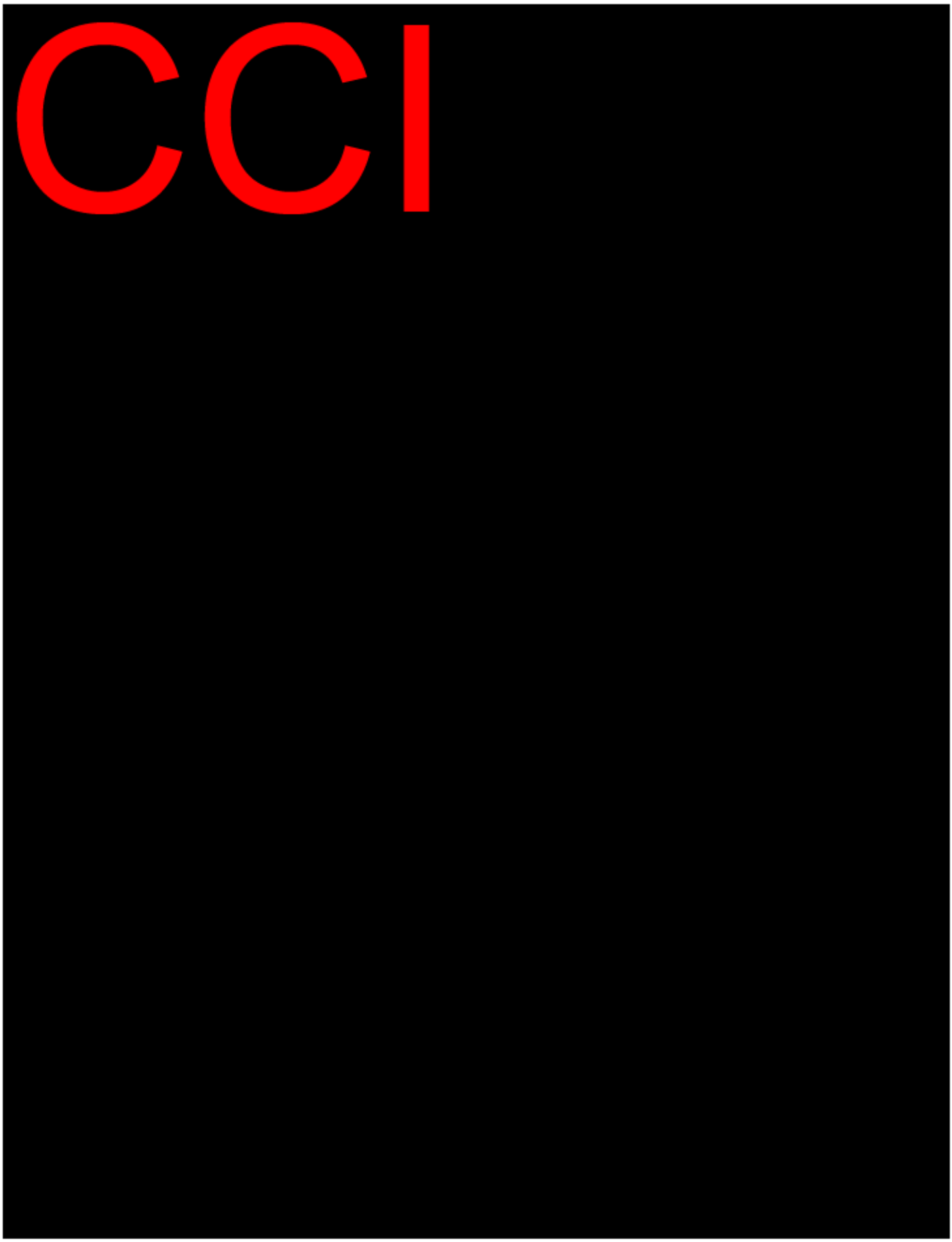
The following is a list of abbreviations that may be used in the protocol.

Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
CMG	Case Management Group
CSR	Clinical study report
DH	Dentin hypersensitivity
DHEQ	Dentin hypersensitivity experience questionnaire
EC	ethics committee
ECG	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eICF	Electronic informed consent form
ePRO	Patient reported outcome
eTMF	Electronic trial master file
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
HSI	Human subject information
ICH	International Conference on Harmonization
IRB	institutional review board
K	potassium
MedDRA	Medical dictionary for regulatory activities

Abbreviation	Term
MFC	Master Formulation Code
N/A	not applicable
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
OHrQoL	Oral health related quality of life
PII	Personal Identifiable Information
RAP	reporting and analysis plan
RCTs	Randomized controlled trials
RWD	Real world data
RWE	Real world evidence
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse event
VAS	Visual analogue scale

15.2 Screening questionnaire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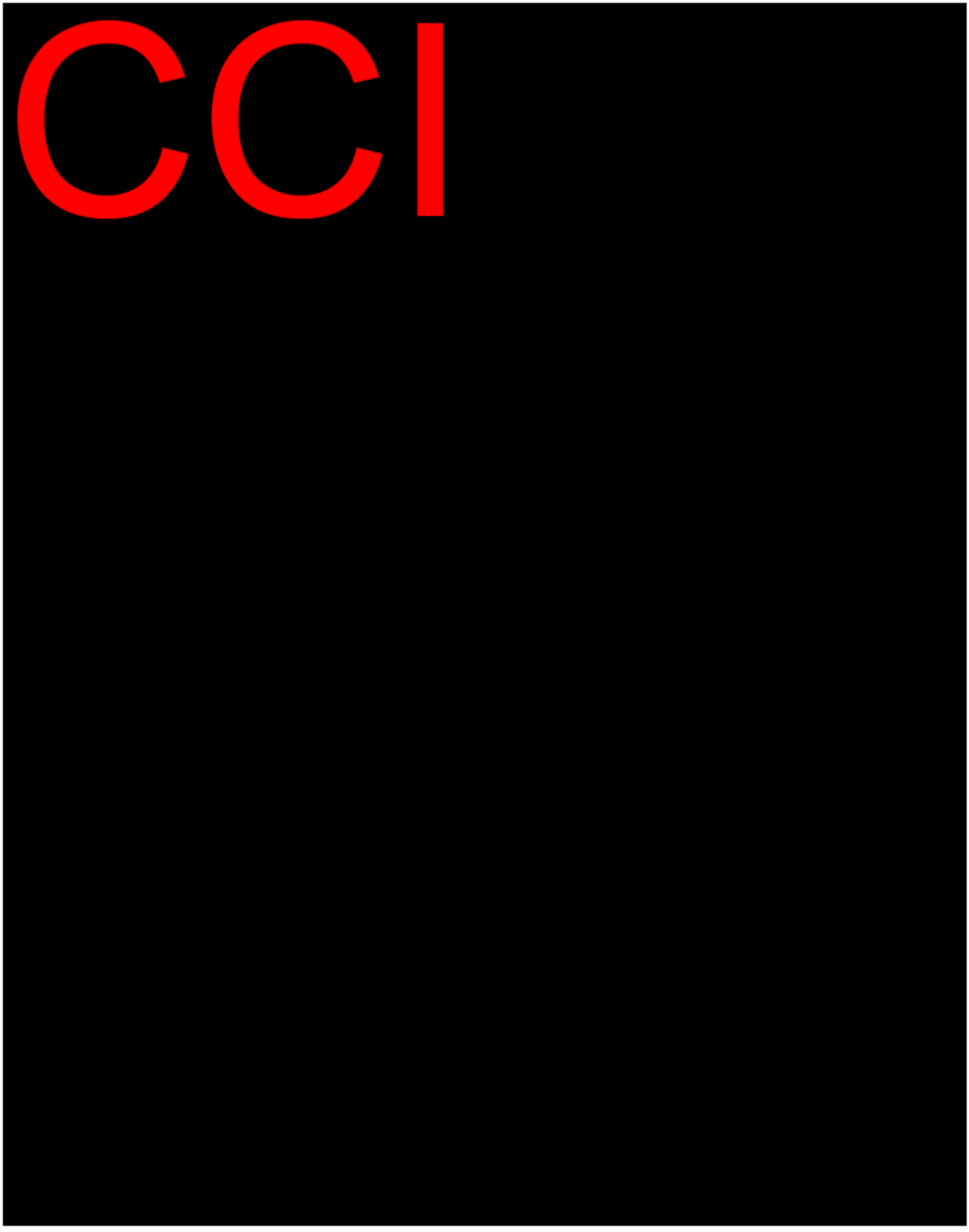
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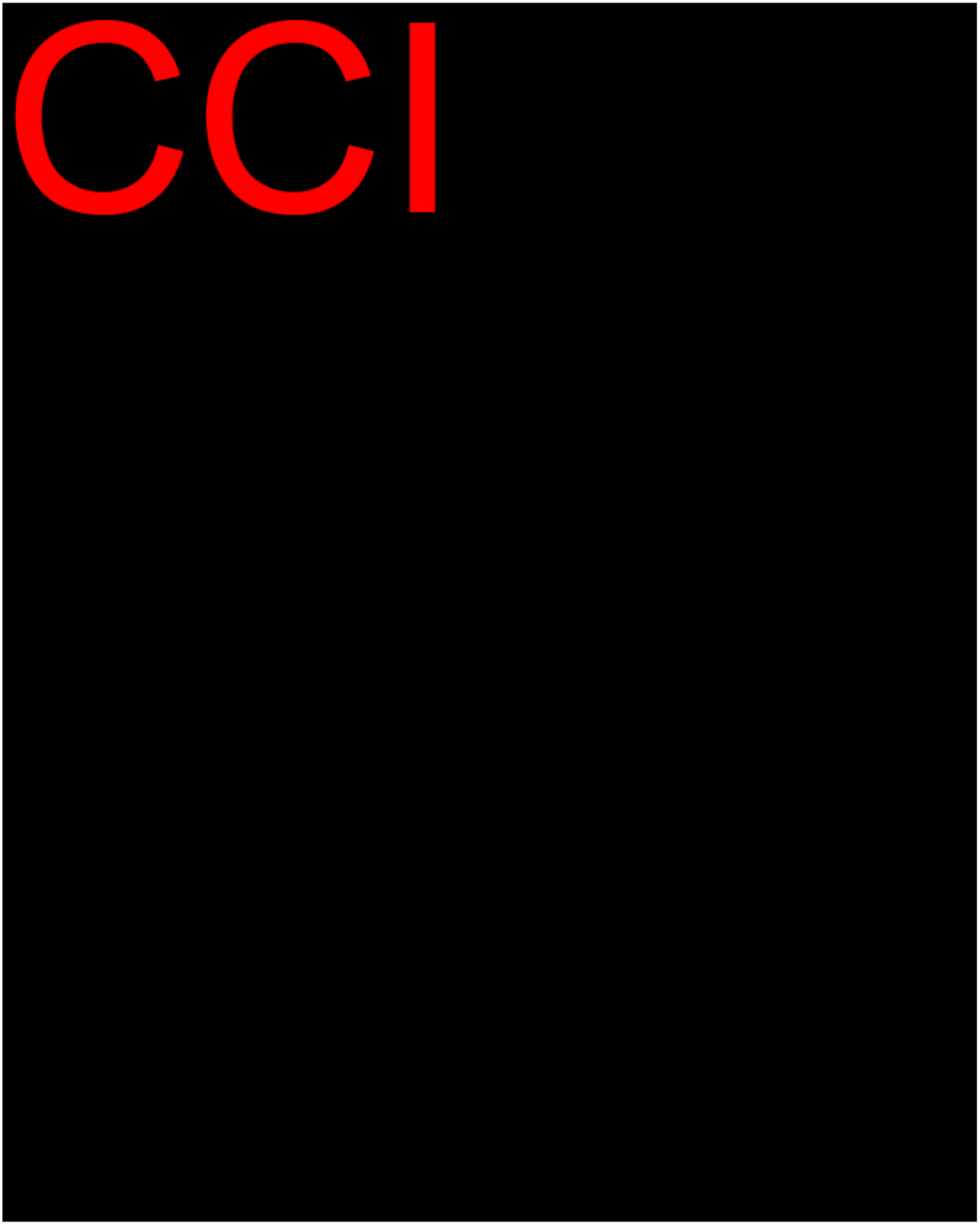
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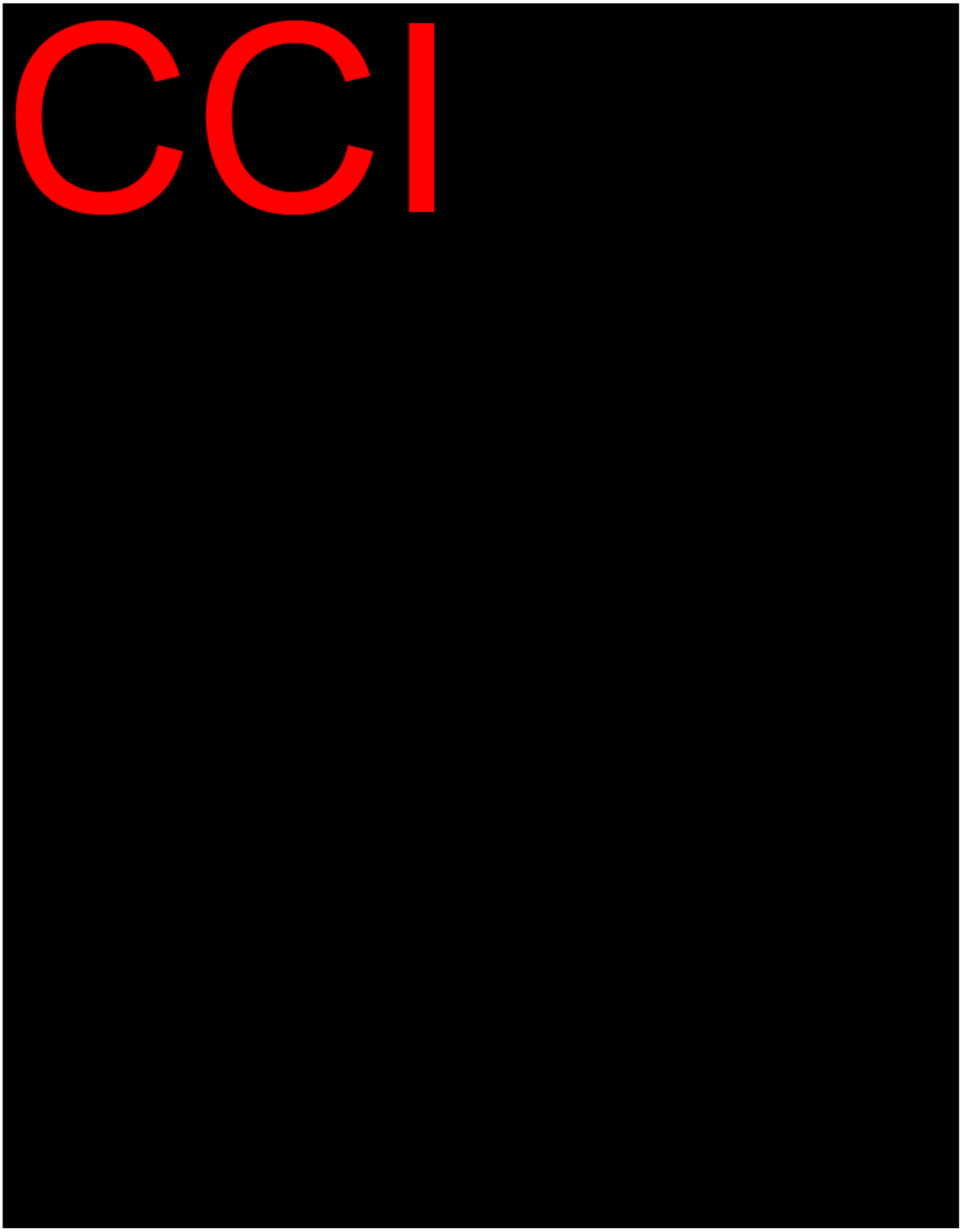
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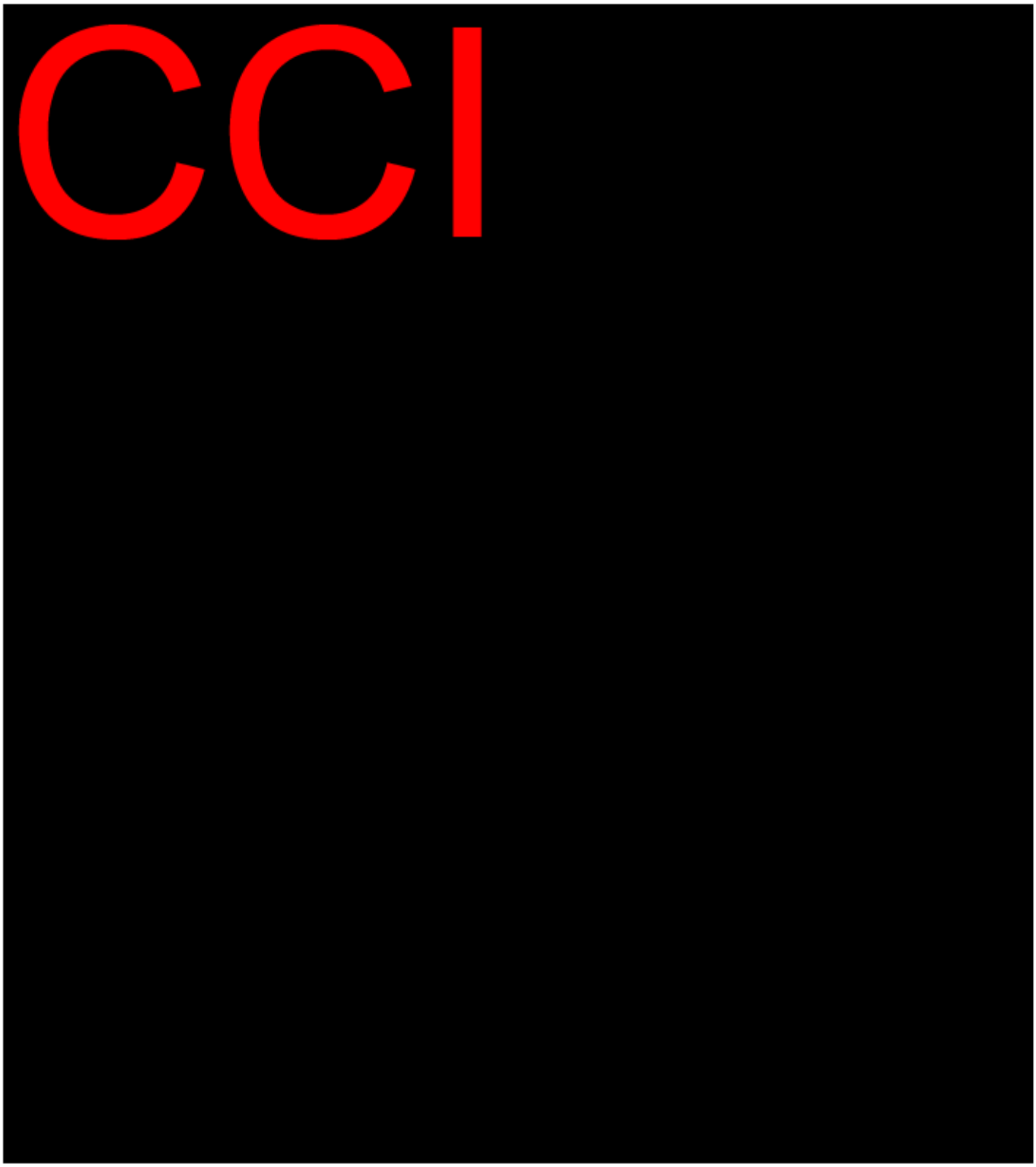


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