CLINICAL PROTOCOL

A randomized, controlled clinical study to evaluate the efficacy of a range of dental/denture products for improved oral health, compared to existing oral hygiene, in a population of partial denture wearers with generalized mild-moderate plaque-induced gingivitis

Protocol Number:	212401
Compound/Product Name:	Dental/Denture Cleansing Range
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Phase:	IV

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** PPD
Sponsor Contact Details	GlaxoSmithKline Consumer Healthcare (GSK CH) PPD

This document contains confidentiality statements that are not relevant for this publicly available version

Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Removal of microbiology endpoints Addition of oral hygiene index endpoints Change in product usage instructions (for foam) to align with new GDS Update to inclusion/exclusion criteria. Change in overall language to align with study running in UK rather than US. Change in PDCI objective from exploratory to secondary
Amendment 2	3.0	Change in diary dispensation which will now only be performed once. Correction of the descriptive terms in Table 9.6. Reinstatement of Lifestyle Consideration regarding interproximal cleaning. Clarification in study design that subjects should have only 1 RPD. Clarification in section 12.2.3 that Medical history will be listed rather than tabulated. Removal of requirement for daily text messages reminding subjects to use treatment products. Correction of stability criterion in section 9.1.4.
Amendment 3	4.0	Addition of oral care advice to be given to all randomized subjects at Visit 2 (section 8.2.1). Definition of mITT included in Synopsis Changes to compliance text (section 6.7) to clarify that failure to follow the oral care advice given at Visit 2 (as detailed in section 8.2.1) will not qualify as a deviation. Change to compliance text (section 6.7) to clarify that for subjects in the non-intervention group, a deviation will be recorded if, in the opinion of the investigator or designee, they significantly and consistently change their oral hygiene routine. Clarification in instructions for use and sections 4 and 6 that subjects will use treatment products twice per day. Clarification in section 12.2.8 that photographs of RPDs will be included in the clinical report for illustration of the scale only.

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

Principal 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

Background and Rationale

The study will examine the effects of an intervention with a range of dental/denture products (comprising use of 3 products, a dentifrice, a mouthrinse and a denture cleanser) compared to no intervention (use of existing oral hygiene) in a population with mild-moderate generalized gum problems and who wear a removable partial denture (RPD). The study will evaluate subjects' oral and gum health using established clinical indices for gingivitis, plaque and oral hygiene endpoints, denture cleanliness will be assessed by the partial denture cleanliness index and subjects' perceptions towards dental/denture cleaning will be explored *via* a questionnaire. This study is required to support the efficacy and safety of the sequential use of these 3 products.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the Bleeding Index (BI), compared to no intervention (existing oral hygiene), when used twice daily for 12 weeks.	BI at 12 weeks.
Secondary	
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the number of bleeding sites, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	Number of bleeding sites at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival inflammation (following dental prophylaxis), as measured by the Modified Gingival Index (MGI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	MGI at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival plaque formation (following dental prophylaxis), as measured by the Turesky Plaque Index (TPI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	TPI (overall and interproximal) at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the Bleeding Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 weeks.	BI at 6 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining the cleanliness of partial dentures, as measured by the Partial Denture Cleanliness Index (PDCI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	PDCI scores at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival calculus formation (following dental prophylaxis), as measured by the calculus index (CI)component of the oral hygiene index (OHI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	CI scores at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing oral debris (following dental prophylaxis), as measured by the oral debris index component of the OHI, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	ODI scores at 6 and 12 weeks.

To evaluate the clinical efficacy of a range of dental/denture products in improving oral hygiene (following dental prophylaxis), as measured by the OHI score (composite score of calculus and oral debris indices), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	OHI scores at 6 and 12 weeks.
Exploratory	
To evaluate subject's perceptions of dental/denture cleaning at 6 and 12 weeks.	Scores from Cleaning Perceptions Questionnaire at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the Bleeding Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	BI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the number of bleeding sites, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	Number of bleeding sites associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the Modified Gingival Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	MGI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival plaque formation associated with denture abutment teeth (following dental prophylaxis), as measured by the modified Turesky Plaque Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	TPI associated with abutment teeth (overall and interproximal) at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival calculus formation associated with denture abutment teeth (following dental prophylaxis), as measured by the calculus index (CI) component of the oral hygiene index (OHI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	CI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing oral debris associated with denture abutment teeth (following dental prophylaxis), as measured by the oral debris index component of the OHI, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	ODI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in improving oral hygiene associated with denture abutment teeth (following dental prophylaxis), as measured by the OHI score (composite score of calculus and oral debris indices), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	OHI associated with abutment teeth at 6 and 12 weeks.
To capture photographic images of RPDs for each of the scores in the PDCI scale to assist study site staff with consistent evaluation of the PDCI over the duration of the study, to assist with future studies that might use this scale, and to aid to interpretation of results (including publication of the study outcomes).	Photographs of RPDs.
Safety	
To assess the safety and tolerability of a range of dental/denture products when used twice daily for 12 weeks.	Treatment emergent adverse events and incidents.

Study Design

This will be a single-center, single-blind (to the examiner(s) performing the plaque, gingivitis, denture cleanliness and oral hygiene assessments), randomized, stratified (by denture material type and baseline mean overall MGI score), two-treatment, parallel group, 12 week clinical study in generally healthy, adult volunteers with one conventional RPD and generalized, mild-moderate, plaque-induced gingivitis (as determined by clinical examiner) and ≥4 natural teeth in each arch that meet all study criteria at both the Screening and Baseline visits (including ≥ 30 evaluable surfaces for clinical evaluation of gingivitis and plaque). The study will examine the effects of twice daily use of a range of dental/denture products (comprising use of a dentifrice, a mouthrinse and a denture cleanser) compared to no intervention (subjects who continue with their existing oral hygiene habits). There will be four visits to the study site: Screening, Baseline (when subjects are randomized), and after 6- and 12-Weeks use of the range of dental/denture products. Gingivitis will be assessed using the Modified Gingival Index (MGI) (Lobene, 1986) and a Bleeding Index (BI) (Saxton and Ouderaa, 1989). Plaque will be assessed by the Turesky modification of the Quigley & Hein Plaque Index (TPI) (Lobene et al, 1982). These indices are intended as markers of overall oral health. The cleanliness of the denture will be assessed by the examiner using the Partial Denture Cleanliness Index (PDCI) and overall oral hygiene will be assessed by the Oral Hygiene Index (OHI) (Greene and Vermillion, 1960). The subject's perception of denture/dental cleanliness will be determined through a questionnaire. Safety will be assessed through examination of the subject's oral hard and soft tissues throughout the study, recorded AEs and Incidents.

Study Products

Usage of a range of dental/denture products comprising of:

- Experimental dentifrice containing 0.454% stannous fluoride (currently non-marketed)
  - A strip of the dentifrice (full brush head) will be applied to the full length of the toothbrush head and used to brush the teeth for 2 timed minutes.
- Denture cleansing foam (COREGA Purfrisch Reinigungsschaum - German Marketplace product).
  - The subject will clean their denture using 2 pumps of the denture cleansing foam and a denture cleaning brush for 90 timed seconds outside of the mouth.
- Experimental mouthrinse containing 90ppm fluoride as sodium fluoride (currently non-marketed)
  - 10ml of the mouthrinse will then be swished around the mouth for 1 timed minute.

Interventional group subjects will use the above products twice daily (morning and evening) for 12 weeks.

Type and Planned Number of Subjects

Sufficient subjects will be screened to randomize approximately 150 (maximum 175) to ensure approximately 128 evaluable subjects complete the entire study. Subjects will be generally healthy, have mild-moderate generalized plaque-induced gingivitis at Baseline and wear one conventional RPD.

The modified intent to treat (mITT) population (defined as those subjects who are randomized, receive at least one dose of study product and have at least one post-baseline efficacy measurement performed) will be used for all primary and secondary analyses. The primary efficacy endpoint will be the Bleeding Index (BI) score after 12 weeks of study treatments. The BI score will be calculated as the average index over all tooth sites. An analysis of covariance (ANCOVA) model will be used for the primary analysis with treatment, gender, denture material type (acrylic or cobalt/chrome), and the baseline mean overall MGI score (low: ≤2.0; high >2.0) as factors and the baseline BI score as a covariate. The adjusted means of the two

treatments and the treatment difference will be provided together with 95% CI and P-values. The proportionate reduction will be calculated for BI and MGI endpoints.

The null and alternative hypotheses to be tested in the primary analysis are;

H_0: There is no treatment difference in mean BI score after 12 weeks

H_1: There is a treatment difference in mean BI score after 12 weeks

Secondary efficacy endpoints will be:

- Number of bleeding sites at Week 6 and Week 12
- MGI score at Week 6 and Week 12
- Overall TPI score at Week 6 and Week 12
- PDCI score at Week 6 and Week 12
- Interproximal TPI score at Week 6 and Week 12
- Overall calculus and oral debris scores and the composite OHI score at week 6 and week 12
- BI score at Week 6

The BI score, MGI score, OHI score (and individual scores of calculus and oral debris) and overall TPI scores will be calculated as the average index values over all tooth sites. The interproximal TPI score will be calculated as the average index value over all interproximal tooth sites. The number of bleeding sites will be calculated as the number of tooth sites with a BI score of 1 or 2. The PDCI will be calculated as the average index values over all subjects.

The number of bleeding sites, OHI score (and individual scores of calculus and oral debris), PDCI score, overall TPI score, interproximal TPI score, and BI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt/chrome), and baseline mean overall MGI score (low: $\leq$2.0; high >2.0) as factors and the baseline score as covariate. The adjusted means of the two treatments, the treatment difference and the proportionate reduction for each treatment group will be provided together with 95% CI and P-values.

The MGI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt/chrome) as factors and baseline MGI score as covariate. As baseline MGI score is included as a covariate, baseline mean overall MGI score (low: $\leq$2.0; high >2.0) will not be included. The adjusted means of the two treatments and the treatment difference will be calculated together with 95% CI and P-values. The proportionate reduction will also be calculated for BI and MGI endpoints.

For both primary and secondary analyses, the assumption of normality and homogeneity of variance in the ANCOVA model will be investigated and if violated, data transformations will be investigated. If suitable transformations cannot be found, non-parametric tests will be performed, and results will be compared with the ANCOVA results. If the inferences from the two analyses are similar, then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between inferences of the ANCOVA and non-parametric analysis, results will be drawn on the non-parametric analysis.

1.1 Schedule of Activities

The schedule of activities table provides an overview of the subject visits and study procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Visit 1	1 – 28 days between Visit 1 and Visit 2[5]	Visit 2	Visit 3	Visit 4
	Screening (Day -28 to -1)		Baseline (Day 0)[1]	Week 6 (Day 42±3)[1]	Week 12 (Day 84±3)[1]
Informed consent	X				
Demographics	X				
Medical history[2]	X				
Current / concomitant medication	X		X	X	X
Dental history	X				
Well-fit assessment of RPD	X				
Collect used study products & diary				X	X
Compliance checks including diary review				X	X
Subject completes questionnaire			X	X	X
Remove Removable Partial Denture (RPD)	X		X	X	X
Well-made assessment of RPD	X				
Partial denture cleanliness index (PDCI)			X	X	X
Photography of RPDs representing the range of PDCI scores [9]			X	X[8]	X[8]
Full oral soft tissue (OST) examination	X[3]		X	X	X
Full oral hard tissue (OHT) examination	X[3]				X
Gross gingival assessment	X				
Subject continuance				X	X
Modified Gingival Index (MGI) and Calculus Index (CI)			X	X	X
Disclosing followed by Plaque Index (TPI), Oral Debris Index (ODI) and Bleeding Index (BI)[11]			X	X	X
Inclusion / exclusion criteria	X		X		
Subject eligibility	X		X		
Stratification / randomization			X		
Repeat MGI and TPI assessments[7]			X	X	X
RPD cleansing and sub- & supra-gingival prophylaxis and flossing (with second clinician check after disclosing & residual plaque removal, if applicable i.e. confirmed plaque score of zero)			X		
Return RPD to subject	X		X	X	X

Dispense study products, toothbrush, product usage instructions, diary & timer[4]			X	X[12]	
Supervised subject brushing, mouth rinsing and denture cleansing at site including instruction in correct product usage[6]			X	X	
Optional dental prophylaxis and RPD cleansing					X[10]
Adverse events / incidents	X		X	X	X
Study conclusion					X

Abbreviations: OST = Oral Soft Tissue, OHT= Oral Hard Tissue, RPD = Removable Partial Denture, TPI= Turesky Plaque Index, BI= Bleeding Index, MGI= Modified Gingival Index, PDCI= partial denture cleanliness index, OHI= oral hygiene index, CI= calculus index, ODI= oral debris index.

Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) and medical device incidents will be collected immediately after a subject provides consent to participate in the study by the completion of the Informed Consent Form (ICF).

[1.] Subjects will abstain from overnight toothbrushing for a minimum of 12 hours (maximum of 18 hours) immediately prior to the assessment visits (Visits 2, 3 & 4).

[2.] Including smoking / tobacco-use status.

[3.] In relation to the general dentition exclusion criteria.

[4.] Timer and diary only dispensed once, at Visit 2 only. Subjects randomized to the no intervention group will receive only the diary. All randomized subjects to receive standard oral care advice.

[5.] Subjects will be instructed to brush their teeth using their normal dentifrice, use their existing denture cleansing procedure following their normal routine between screening and baseline visits.

[6.] For subjects randomized to the interventional group only.

[7.] At least 2 repeatability assessments should be performed each day (≥1 in the morning; ≥1 in the afternoon).

[8.] Photographs should only be obtained at Visits 3 and 4 should insufficient photographs of sufficient quality not been obtained at Visit 2.

[9.] For a subset of subjects only (in accordance with Section 8.2.5).

[10.] After completion of all assessments if deemed necessary by the clinical examiner.

[11.] ODI to be assessed after TPI and BI to be assessed after ODI.

[12.] At Visit 3 the diary is returned to the subject following review by the study site.

2 INTRODUCTION

In this study, a range of products specifically for removable partial dentures (RPD) wearers to utilize for oral and denture cleansing will be tested for their effect in maintaining oral health. RPDs are considered a non-invasive and cost-effective treatment option indicated for the replacement of missing teeth in partially edentulous individuals. Fixed prostheses or dental implants may not be available for some patients due to anatomic, systemic, or economic reasons (Costa et al, 2017), therefore RPDs may be considered a non-invasive and relatively cheap treatment with a predictable long-term success, achieving appropriate aesthetics, increasing the masticatory efficiency, and improving phonetics (Bohnenkamp, 2014; Nassani et al, 2013). However, RPDs can represent a risk for the remaining teeth, mainly abutment teeth, depending on the prosthesis design, health of the supporting periodontal tissues and the oral hygiene level (Preshaw et al, 2011). The most common complication associated with RPDs is poor oral hygiene. About 64% of RPDs wearers showed signs of poor oral hygiene in a 10-year follow-up study (Wagner and Kern, 2000). According to a clinical examination in another study, only 39.8% of participants were viewed to have a good level of denture cleanliness, with the remaining 60.2% having a poor to moderate level (Milward et al, 2013). RPDs have the potential to negatively impact on different aspects of oral health. There is clear evidence that RPDs increase plaque and gingivitis (Knezovic Zlataric et al, 2003; Preshaw et al, 2011). The presence of a prosthesis in the oral cavity increases the retention sites for microorganisms; this is particularly the case with an RPD, which has a design that favors food retention, biofilm accumulation and colonization of microorganisms such as *Streptococcus mutans* (Rocha et al, 2008). In a separate randomized clinical trial (Jepson et al, 2001), RPD wearers were found to have nearly five times more caries lesions when compared to those with fixed prostheses. *S. mutans* and *lactobacilli* are found in higher levels in patients wearing RPDs than in patients with fixed prostheses & natural dentition (Beighton et al, 1990; Tanaka et al, 2009). All these risks are more likely to affect the abutment teeth leading to potentially further tooth loss. Kern and Wagner (Kern and Wagner, 2001) reported in their 10-year follow up study that disproportionately higher number of abutment teeth were lost over that time (26.4%) compared with non-abutment teeth (14.2%).

Regular denture hygiene by individuals with RPDs is an important component of overall good oral health and for prevention of periodontal problems, dental caries and denture stomatitis. It is therefore essential that individuals with RPDs are provided with instructions on oral and denture hygiene and maintenance on receiving their denture, to ensure good oral health and longevity of the individual's remaining natural teeth. However, several studies showed that there is a lack of knowledge surrounding denture hygiene among patients (Collis and Stafford, 1994; de Castellucci Barbosa et al, 2008; Milward et al, 2013). While 91.8% of study participants (RPD wearers) stated they were provided with instructions on denture hygiene when provided with their current prosthesis, 60.2% were shown to have less than an appropriate level of denture cleanliness (Milward et al, 2013). Additionally, the issue of denture hygiene has been the focus of a Cochrane review which was unable to clearly identify the most effective way of removing plaque from dentures due to the paucity of available literature to answer the question (de Souza et al, 2009). It is noteworthy that adherence of RPD patients to oral hygiene and denture hygiene instruction tends to decline as time goes by, indicating a requirement for continual reinforcement of oral hygiene messages (Preshaw et al, 2011). All published RPDs

guidelines emphasize on the importance of maintaining optimal oral hygiene and denture hygiene in RPD wearers (bsspd, 1996; Felton et al, 2011; NHS Trust, 2006; NICE, 2016).

Gum disease describes a group of conditions affecting the periodontium (the supporting structures around the teeth) and includes gingivitis. Gingivitis is an inflammatory response to the presence of dental plaque (Kinane, 2001), which typically presents as redness, swelling (edema) and/or bleeding of the gums at the gingival margin surrounding the tooth. The high prevalence of gingivitis worldwide is reported in large population surveys and is recognized by the World Health Organization (Albandar, 2002; Chapple et al, 2002; Petersen and Ogawa, 2012). In the USA, it has been reported in > 50% of the population, with some population groups approaching 100% (Brown et al, 1996; Oliver et al, 1998).

Gingivitis is a reversible condition but, if left untreated, it can progress to the irreversible phase of periodontitis, where inflammation extends to the underlying tissues, periodontal ligament and alveolar bone. The resulting net loss of these structures can eventually lead to tooth loss through destruction of the periodontal tissues supporting the tooth (Petersen et al, 2005). Periodontitis is reported to affect 5-20% of the world's population (Petersen et al, 2005). The maintenance of good gingival health is therefore important in preventing gingivitis and the development of periodontal disease (Tai et al, 2006).

Dental plaque is a soft, sticky, colourless deposit of bacteria which collects on the teeth and along the gingival margin; it is the causative agent of gingivitis and periodontitis (Davies, 2008; Kinane, 2001; Silness and Loe, 1964; Theilade et al, 1966). Gingivitis develops when the plaque elicits a local inflammatory response in the gingivae at the site of its accumulation (Davies, 2008; Marsh, 1992). Gingivitis is prevented and resolved through effective plaque control, primarily via mechanical plaque removal (i.e. toothbrushing) (Davies, 2008; Marsh, 1992; Ower, 2003; van der Weijden and Hioe, 2005).

In this study, a range of products specifically for RPD wearers to utilize for oral and denture cleansing will be tested for their effect in maintaining oral health. Owing to the lack of clinical measures to probe oral health, gingivitis and plaque measurements (e.g. bleeding index, modified gingival index, Turesky plaque index) will be utilized as markers of general oral health. The product range will be used twice daily (morning and evening) and consists of a stannous fluoride-containing dentifrice, a sodium fluoride containing mouthrinse, and a denture cleanser foam. RPD wearers are known to be high-risk for plaque accumulation, gingivitis and caries and this study will therefore investigate the ability of usage of the product range to reduce dental plaque and reduce gingivitis measures compared to a no intervention group (subjects will continue with their existing oral hygiene measures). The impact of use of the product range on the subject's perceptions of dental/denture cleanliness will also be explored via a questionnaire. This study will therefore provide the first evidence on the efficacy of a specific range of dental/denture products for wearers of RPD.

2.1 Study Rationale

This clinical study is the first known design to explicitly investigate the efficacy and safety of the use of a range of dental/denture products on the maintenance of oral health. The endpoints utilized in this study have been chosen as markers of general oral health of subjects who wear removable partial dentures. This study is required to evaluate whether potential claims associated with the use of the range of dental/denture products are valid as well as to inform the dental practitioner on the potential benefits to oral health of the range of dental/denture products.

Whilst the product range itself has not been previously clinically tested, the toothpaste and denture cleanser foam have been tested as individual products (or products very similar to those being tested) in a number of clinical studies (see Background Section 2.2). These studies demonstrate the efficacy and safety of the individual study products. Additionally, the experimental dentifrice and mouthrinse are also very similar to existing marketed products that have an acceptable risk-benefit ratio. In conclusion, therefore, the benefits outweigh the risks identified for the intended use of the products comprising the interventional range of products.

Complete information for the products used in this range of dental/denture products may be found in the single reference safety document (SRSD), which for this study is the safety statement.

2.2 Background

This study is designed to investigate the efficacy of the use of a product range comprising a dentifrice, a mouthrinse and a denture cleanser foam in maintaining general oral health as evidenced through improved signs of gum health and reducing plaque in a population of subjects who wear a removable partial denture. Whilst the sequential use of the 3 products has not been previously evaluated, clinical data does exist on formulations very similar to the dentifrice and the dental cleaning foam when used individually.

The experimental dentifrice contains stannous fluoride, an active with an extensive history of gum-health efficacy (Makin, 2013; Paraskevas and Van der Weijden, 2006; Rølla and Ellingsen, 1994; Twetman et al, 2003). Very similar formulations to the experimental dentifrice to be evaluated in this study (varying only in differences in flavorings), have been evaluated previously both for dentine hypersensitivity (Parkinson et al, 2013; Parkinson et al, 2015; Parkinson et al, 2016) and gingivitis endpoints (Parkinson et al, 2018a; Parkinson et al, 2018b). Additionally this formulation has been shown not to exhibit dental staining that has previously been observed with stannous fluoride-based dentifrices (Nehme et al, 2013). Stannous fluoride has been recognized as safe and effective for the treatment of gingivitis by the US Food and Drug Administration (FDA) (FDA, 2003).

The usage of the marketed denture cleanser foam has been clinically demonstrated to remove denture plaque (CCI [redacted]) and denture stain (CCI [redacted]). These studies demonstrated the cleaning ability of the cleanser foam when used as directed by brushing the foam on the denture.

2.3 Mechanism of Action/Indication

Dentifrices function by facilitating plaque removal through tooth brushing. Additionally, the product range under investigation utilizes an experimental dentifrice that contains Stannous fluoride (SnF_2), a well-known chemotherapeutic agent, incorporated into dentifrices since the 1940s for its oral health benefits (Makin, 2013; Miller et al, 1994; Van Loveren, 1990; Van Loveren, 2001). The stannous ion (Sn^{2+}) is a broad-spectrum antimicrobial with bacteriostatic and bactericidal properties (Archila et al, 2004; Bellamy et al, 2012; He et al, 2012; Tinanoff, 1995). It has been shown to interfere with the development and maturation of the plaque biofilm, inhibiting bacterial adherence and colonization of the oral surfaces, and penetrating the cell wall to interfere with bacterial metabolism (Tinanoff, 1990; Wilson and Pratten, 1999). These effects have been shown to carry through to *in vivo* effects on a range of microbial activities, resulting in anti-plaque benefits (Bacca et al, 1997; Kasturi et al, 1995; White et al, 1995).

Usage of the denture cleanser foam has been clinically demonstrated to remove denture plaque (CCI [redacted]) and denture stain (CCI [redacted]). The mode of action is reported to be physical, through brushing, augmented by the surfactants present in the foam.

The clinical oral health efficacy of the range of dental/denture products will be investigated in subjects with clinically diagnosed mild-moderate gingivitis.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the Bleeding Index (BI), compared to no intervention (existing oral hygiene), when used twice daily for 12 weeks.	BI at 12 weeks.
Secondary	
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the number of bleeding sites, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	Number of bleeding sites at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival inflammation (following dental prophylaxis), as measured by the Modified Gingival Index (MGI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	MGI at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival plaque formation (following dental prophylaxis), as measured by the Turesky Plaque Index (TPI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	TPI (overall and interproximal) at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gingival bleeding (following dental prophylaxis), as measured by the Bleeding Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 weeks.	BI at 6 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining the cleanliness of partial dentures, as measured by the Partial Denture Cleanliness Index (PDCI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	PDCI scores at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival calculus formation (following dental prophylaxis), as measured by the calculus index (CI)component of the oral hygiene index (OHI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	CI scores at 6 and 12 weeks.

To evaluate the clinical efficacy of a range of dental/denture products in reducing oral debris (following dental prophylaxis), as measured by the oral debris index component of the OHI, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	ODI scores at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in improving oral hygiene (following dental prophylaxis), as measured by the OHI score (composite score of calculus and oral debris indices), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	OHI scores at 6 and 12 weeks.
Exploratory	
To evaluate subject's perceptions of dental/denture cleaning at 6 and 12 weeks.	Scores from Cleaning Perceptions Questionnaire at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the Bleeding Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	BI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the number of bleeding sites, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	Number of bleeding sites associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in maintaining gum health by reducing gum problems associated with denture abutment teeth (following dental prophylaxis), as measured by the Modified Gingival Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	MGI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival plaque formation associated with denture abutment teeth (following dental prophylaxis), as measured by the modified Turesky Plaque Index, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	TPI associated with abutment teeth (overall and interproximal) at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing supra-gingival calculus formation associated with denture abutment teeth (following dental prophylaxis), as measured by the calculus index (CI) component of the oral hygiene index (OHI), compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	CI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in reducing oral debris associated with denture abutment teeth (following dental prophylaxis), as measured by the oral debris index component of the OHI, compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	ODI associated with abutment teeth at 6 and 12 weeks.
To evaluate the clinical efficacy of a range of dental/denture products in improving oral hygiene associated with denture abutment teeth (following dental prophylaxis), as measured by the OHI score (composite score of calculus and oral debris indices),	OHI associated with abutment teeth at 6 and 12 weeks.

compared to no intervention (existing oral hygiene), when used twice daily for 6 and 12 weeks.	
To capture photographic images of RPDs for each of the scores in the PDCI scale to assist study site staff with consistent evaluation of the PDCI over the duration of the study, to assist with future studies that might use this scale, and to aid to interpretation of results (including publication of the study outcomes).	Photographs of RPDs.
Safety	
To assess the safety and tolerability of a range of dental/denture products when used twice daily for 12 weeks.	Treatment emergent adverse events and incidents.

This study will be considered successful if a statistically significant improvement in BI, compared to the no intervention group (existing oral hygiene) at an alpha level of 0.05, is observed following 12 weeks twice daily use of a range of dental/denture products.

4 STUDY DESIGN

4.1 Overall Design

This will be a single-center, single-blind (to the examiner(s) performing the plaque, denture cleanliness, oral hygiene and gingivitis assessments), randomized, stratified (by denture material type and baseline mean overall MGI score), two-treatment, parallel group, 12 week clinical study in generally healthy, adult volunteers with one conventional RPD and generalized, mild-moderate, plaque-induced gum problems (as determined by clinical examination) and ≥4 natural teeth in each arch that meet all study criteria at both the Screening and Baseline visits (including ≥ 30 evaluable surfaces for clinical evaluation of gum problems and plaque). The study will examine the effects of the use of a range of dental/denture products (comprising use of a dentifrice, a mouthrinse and a denture cleanser) compared to the use of no intervention (existing oral hygiene). There will be four visits to the study site: Screening, Baseline, and after 6 and 12 Weeks products use. Gum problems will be assessed using the Modified Gingival Index (MGI) (Lobene, 1986) and a Bleeding Index (BI) (Saxton and Ouderaa, 1989). Plaque will be assessed by the Turesky modification of the Quigley & Hein Plaque Index (TPI) (Lobene et al, 1982), oral hygiene by the Oral Hygiene Index (OHI) (Greene and Vermillion, 1960) and the cleanliness of the denture assessed using the Partial Denture Cleanliness Index (PDCI) (Blair et al, 1995). Additionally, the subject's perceptions to denture/dental cleanliness will be determined through a questionnaire.

Sufficient subjects will be screened in order to randomize approximately 150 (maximum 175) to ensure approximately 128 evaluable subjects complete the entire study.

Study subjects will be aged at least 18 years, in good general health, non-smokers (defined as not having smoked [including e-cigarettes] for the previous 12 months), with generalized, mild-moderate, plaque-induced gingivitis (as determined by clinical examination) and ≥ 4 natural teeth in each arch that meet all study criteria at both the Screening and Baseline visits (including ≥ 30 evaluable surfaces for MGI, BI, OHI and TPI) and who wear a single conventional acrylic or cobalt chrome RPD.

At the Screening visit (Visit 1), subjects will give their written informed consent to participate in the study. Demographics, medical history, dental history, current medications will be recorded, followed by an oral and RPD examination and a gingival assessment. Screening

assessments will include full oral soft tissue (OST) and oral hard tissue (OHT) examinations (including dentition exclusions and gingival status), the fit of the RPD and whether it is well-made. Inclusion and Exclusion criteria as well as Subject eligibility will be assessed. Subjects will be instructed to continue to brush using their usual dentifrice and following their usual dental/denture cleaning routine between screening and baseline.

Within 1-28 days of Screening (Visit 1), eligible subjects will return to the site for the Baseline visit (Visit 2) with overnight plaque (subjects will abstain from any oral/denture hygiene for a minimum of 12 hours [maximum 18 hours] i.e. overnight, immediately before the visit). Subjects will have their medications recorded and will undergo, in the following order, completion of the questionnaire, removal of their denture with PDCI assessment, RPD photography (for a subset of subjects only in accordance with Section 8.2.5) then undergo a full OST examination and assessments of gingival inflammation (MGI followed by BI). Following the MGI and CI assessments, and after rinsing with approximately 20ml of water, subjects will have their dental plaque disclosed before undergoing the TPI, ODI and BI assessments (in that order).

Eligible subjects will continue in the study. Subjects with a mean overall BI, MGI or TPI scores outside the study range will no longer be eligible to continue in the study and will be discontinued from the study at this visit. To control inter-examiner variability, the same suitably qualified examiner will be used throughout the study for each of the dental assessments as far as possible. The same examiner can perform more than one assessment, but as far as possible the same examiner must perform each of these assessments for all subjects throughout the study.

Eligible subjects will be stratified based on denture material type (acrylic or cobalt chrome) and baseline mean overall MGI score (low: $\leq$2.0; high >2.0) to ensure a balance in treatments across the strata, and then randomized into one of two treatment groups. A dental prophylaxis will be performed by a suitably qualified member of site staff for each eligible subject using a standard fluoride-free dental prophylaxis paste followed by flossing. Subject's teeth will be disclosed using a disclosing solution to check for residual plaque. A second clinician will check to ensure all plaque has been removed. Any residual plaque & calculus remaining will be removed by the second clinician by dental polishing with a standard fluoride-free dental prophylaxis paste, to bring the subject to a confirmed score of zero visible plaque (TPI=0). The subject's RPD will also be cleaned by a suitable qualified member of clinical staff using the supplied denture cleaning paste and brush so that there is no visible plaque and no matter adherent to the dental probe on light scraping (i.e. a PDCI score of 0).

Following dental prophylaxis and RPD cleansing, subjects randomized to use of the range of dental/denture products will receive their assigned study products (including sundry items), a diary and instructions on product usage. These subjects, under supervision, will brush their teeth with the dentifrice provided, in their usual manner for two timed minutes, clean their RPD with the supplied denture foam cleanser and brush in accordance with the product usage instructions and then rinse their mouths with the mouthrinse for 1 timed minute. The subjects will then re-fit their RPD in their mouth. Subjects will continue to use their supplied products twice per day, recording each use in their study diary. Subjects randomized to the no intervention group will continue with their usual dental/denture cleansing habits. All randomized subjects will receive general oral care advice and should record details of each of their tooth brushing/ mouth rinsing and denture cleansing activities in their study diary along with any new medications taken or change to their existing medication.

Subjects will return to the study site 6 and 12 weeks after randomization (Visits 3 and 4, respectively) having abstained from oral hygiene for a minimum of 12 hours (maximum of 18 hours) i.e. from overnight, immediately before each assessment visit, if possible, at approximately the same time of day as the baseline visit. The study products will be collected (from subjects randomized to the Interventional product range only), and these and the diary reviewed for treatment compliance. Subjects randomized to the no intervention group will have their diary reviewed to ensure these subjects have continued with their usual oral hygiene. Subjects will complete the questionnaire, remove their denture which will be assessed using the PDCI. They will then have a full OST examination and then undergo, in the following order, MGI, CI, plaque disclosure, TPI, ODI then BI assessments. At Visit 3, subjects randomized to the interventional range of products will receive another supply of assigned study products and undergo supervised use of the study products per the usage instructions and all subjects will have their diary returned to them. At Visit 4, subjects will return all study materials, undergo an OHT examination and have a dental prophylaxis and their denture cleaned if deemed appropriate by the investigator/examiner and/or requested by the subject.

At Visits 2, 3, 4, repeatability data will be generated for MGI & TPI assessments from replicate examinations on the same subject. Depending on subject visit scheduling, every effort will be made to complete one repeatability examination for each clinical measure during each clinical session, that is, at least one in the morning and at least one in the afternoon on each assessment day. Repeatability examinations will be separated by a minimum of 10 minutes and, where possible, separated by another subject.

All evaluable teeth (in relation to the inclusion/ exclusion general dentition criteria) will be assessed for MGI, CI, TPI, ODI and BI at baseline, 6 and 12 weeks.

To aid study compliance, all subjects currently active in the study will receive an SMS (text message) reminder from the study site before a scheduled visit (Visits 2-4) to remind them of the requirement for no oral hygiene on the morning prior to their visit.

4.2 Rationale for Study Design

The clinical design employed here is typical of many studies conducted to evaluate the clinical efficacy of oral healthcare products in the treatment of gum problems, albeit this design is generally employed in non-denture wearers. Owing to the lack of clinical measures to probe oral health, gingivitis and plaque measurements (e.g. bleeding index, modified gingival index, Turesky plaque index) will be utilized in this study as markers of general oral health. Study subjects with a pre-specified level of gum problems are randomized to either the intervention range of products group or a no intervention group; efficacy is determined after professional dental cleaning and a period of twice-daily brushing. Dental prophylaxis removes all visible calculus and stain from the surface of the teeth (plaque retentive factors that could influence plaque accumulation) and ensures study subjects enter the treatment period with no visible plaque (TPI = 0). This clinical study design has been chosen as this is recommended by the dental research communities and is consistent with American Dental Association (ADA) guidelines for such studies (ADA, 2016).

A parallel group design has been selected as most appropriate for this investigation owing to the difficulties in ensuring an adequate latent period between study periods in a cross-over design.

Twelve weeks is deemed sufficient time to evaluate product effectiveness in this clinical design as demonstrated by numerous previous studies e.g. (Parkinson et al, 2018a; Parkinson et al, 2018b) and as recommended by ADA guidelines (ADA, 2016).

The application of twice daily tooth brushing, mouth rinsing and denture cleansing (morning and evening), the dose of the study products, method and duration of application are based on widely recommended oral hygiene practice, and typical consumer habits and is also in accordance with current or intended product labels. To facilitate compliance with product usage throughout the study, and to enable staff to confirm correct dosing, a supervised brushing for subjects randomized to the intervention group will be performed on site at the end of Visits 2 and 3; subjects will also be required to record each use of study product in the diary provided. Additionally, a timer will be provided to the subjects to aid compliance with the product usage instructions.

The MGI and the BI are established clinical measures of gingival inflammation and gingival bleeding, respectively (i.e. gingival health); the TPI is an established clinical measure of supra-gingival plaque accumulation. The OHI is an established and well-used clinical measure of overall dental cleanliness. To avoid inter-examiner variability, a single examiner will be responsible for the conduct of each clinical assessment for the duration of the study. To assess examiner reproducibility across the treatment period, repeat MGI and TPI assessments will be performed on selected subjects at Visits 2-4. Due to the invasive nature of the index, repeatability assessments are not feasible for the BI. TPI and MGI are both recommended indices for the evaluation of plaque and gingivitis by the ADA (ADA, 2016). Eligible subjects should have a mean whole mouth BI $\geq$ 0.1 to $\leq$ 1.3, a mean whole mouth MGI $\geq$ 1.75 to $\leq$ 2.30 and a mean overall TPI score $\geq$1.5 at the Baseline visit. These requirements are to ensure that appropriate subjects with mild-moderate gingivitis are recruited and are consistent with previous clinical studies of similar design (Parkinson et al, 2018a; Parkinson et al, 2018b) and follows FDA recommendation (FDA, 2005).

Early stages of gum disease, prior to loss of tissue attachment, is considered to be an essentially reversible condition (Chapple et al, 2018) and the generally accepted treatment option for the dental practitioner is to administer an oral prophylaxis (Lamont et al, 2018), which, in this study, is administered to all subjects at Visit 2 (baseline) and offered to all subjects at the end of the study. Therefore, assigning subjects with mild-moderate gingivitis to continued use of their existing oral hygiene is expected to result in improvement in their condition based upon the prophylaxis administered. However, it would be inappropriate to recruit subjects with severe gingivitis/periodontitis into this study since these subjects should undergo immediate appropriate medical treatment. A minimum of 4 teeth per arch is required in this study since it is considered a practical minimum number of teeth required to support an RPD adequately.

According to the International Conference on Harmonisation (ICH) guidelines (ICH, Nov 2016), for a study to be classified as truly double-blind, not only does the examiner (and any appropriate member of staff who may be involved in the dispensing of products, analysis of data etc.) need to be blind to the treatment a subject receives, but the products under test must be identical in every way (color, flavor, rheology, appearance, packaging). Given the subjects in the no intervention group will continue with their current oral hygiene practice and not be assigned any product to use, the level of blindness for this study is described as 'examiner blind' only. The same examiner will be used for each clinical index throughout the study to eliminate the possibility of inter-examiner variability.

The effects of smoking on periodontal health are well documented in the scientific literature. Smoking decreases blood flow within the gingival microvasculature and interferes with neutrophil function, suppressing the inflammatory response to dental plaque and masking the clinical signs of periodontal disease (Kinane, 2001; Lie et al, 1998; Machuca et al, 2000; Obeid and Bercy, 2000; Shearer et al, 2005). A 14-day experimental gingivitis model reported much less gingival bleeding in smokers compared to non-smokers, even though plaque levels and the composition of the oral microflora were similar between the two groups (Lie et al, 1998). Smokers (and tobacco users) will therefore be excluded from this investigation of product efficacy for the treatment of plaque-induced gingivitis. The RPD wearers that are going to be recruited for this study should be subjects who do not frequently use denture cleansers (defined as those subjects who do not use marketed denture cleanser tablets or liquids more frequently than once per month). These subjects form the largest group of the partial wearers, about 51% as shown in a GSK global segmentation study (GSK data on file) and thus will represent the behavior of the most typical partial denture wearer. Subjects should not be taking medication which alters gingival appearance/bleeding and in accordance with ADA guidelines (ADA, 2016) their use within one month (28 days) prior to Baseline is prohibited.

Gender is a known modifier of the initiation and outcome of conditions related to gingival health (Alam et al, 2012) and hormonal fluctuations through the female menstrual cycle may also influence response to dental plaque (Machuca et al, 1999; Raber - Durlacher et al, 1994) and lead to increased variability in the clinical assessment of gingival health (Kovar et al, 1985). In this study, both male and female subjects will be randomized to study product (in accordance with ADA guidelines (ADA, 2016)); gender will be included as a factor in the statistical analysis (Analysis of Covariance [ANCOVA]).

Eligible subjects will be stratified according to their baseline mean overall MGI score (low: $\leq$2.0; high >2.0) and according to their denture type (acrylic or cobalt chrome) to ensure treatment groups are balanced. Only subjects with an acrylic or cobalt/chrome RPD will be allowed in this study. Whilst other materials (e.g. flexible nylon) can be used in the manufacture of RPDs, these are far less commonly utilised, and are therefore excluded from this study.

Whilst the individual products being tested in this study are not contra-indicated for pregnancy and use of them would not be expected to cause harm either to the mother or foetus, pregnant females will be excluded from this study due to the increased prevalence and severity of gingivitis and periodontal disease along with increased amounts of calculus and plaque observed with pregnancy. The severity of these conditions is known to vary during the course of pregnancy (Samant et al, 1976), and thus pregnancy would be a confounding factor of the objectives in this study. Pregnant females and those intending to become pregnant are thus excluded in this study.

In order for the clinical site to be able to remind subjects of the protocol requirements, subjects will be required to own a cell phone capable of receiving text messages.

4.3 Justification for Dose

Use of the intervention range of products under investigation will involve subjects removing their RPD, brushing their natural teeth with the dentifrice, brushing their denture with the supplied denture foam then rinsing their mouth with a mouthrinse. This will be performed twice daily (morning and evening).

The application of twice daily brushing, with a brush length of dentifrice is based on consumer habit and common practice within oral care clinical trials. Subjects will apply a full ribbon of dentifrice to the study toothbrush and brush their teeth in their usual manner for two timed minutes twice daily (morning and evening). Two minutes is chosen as the brushing time since this is the length of time typically advocated by dental professionals (NHS, 2019). The denture cleanser will be applied to the RPD external to the mouth and brushed for 90s prior to thorough rinsing under running tap water twice-daily. The mouthrinse dose is typical (10ml) and will be swished in the mouth twice daily for 1 minute after toothbrushing. This aligns with common practice and the FDA anti-caries monograph (FDA, 1995). The dosing of the range of products is in agreement with the proposed product labelling (for the dentifrice and mouthrinse) and the current product labelling (for the denture cleanser foam).

Subjects in the non-intervention group will continue with their existing oral hygiene practices. This has been chosen as the relevant control for this study since the study objectives are to evaluate the improvement in overall oral hygiene through use of the interventional range of products and therefore comparing to a group that continues with their existing oral hygiene practice is appropriate.

No dose modification is permitted in this study. Any variation from the product usage instructions should be communicated to study site personnel and recorded as a deviation on the CRF.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (last subject last visit date).

The end of this study is defined as the date of the last subject last visit date.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

This study will recruit healthy volunteers of either gender aged 18 years or older with mild-moderate plaque-induced gingivitis who wear one removable partial denture. The individual products used by subjects in the intervention group, when marketed, will be indicated for the general population who wear removable partial dentures and who are therefore at risk of further tooth loss. The inclusion criteria allows for investigation of subjects typical to the indicated population.

Sufficient subjects will be screened to randomize at least 150 (maximum 175) subjects (equally distributed across the two treatment groups) to ensure approximately 128 evaluable subjects complete the entire study.

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 the screening visit as applicable for the protocol design.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is

considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol.

5.2 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 and 75 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. A subject with good general and mental health with, in the opinion of the investigator or medically qualified designee no clinically significant or relevant abnormalities in medical history or upon oral examination, or a condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study.
5. A subject who is a cell phone owner with text messaging capabilities.
6. Dental Criteria:
    a. A subject with a minimum of 4 natural teeth in each arch.
    b. A subject with a minimum of 30 scorable surfaces for MGI, BI, OHI and TPI. (A scorable surface is defined as a surface that has at least 2/3 of the surface gradable for each clinical index. Third molars, orthodontically banded/bonded, fully crowned or extensively restored or grossly carious teeth are not included in the tooth or scorable surface count. *Third molars can be included if, as a result tooth loss, they are functioning as second molars.* Tooth surfaces with calculus deposits which, in the opinion of the clinical examiner, would interfere with the assessments of the selected clinical indices are also excluded.)
    c. A subject with a minimum of 2 scorable abutment teeth, defined as teeth proximal to the RPD or impinged by an RPD clasp or rest.
    d. A subject with generalized mild-moderate plaque-induced gingivitis present at the screening visit (in the opinion of the clinical examiner from a gross visual examination).
    e. A subject with a mean whole mouth BI $\geq$ 0.1 to $\leq$ 1.3, a mean whole mouth MGI $\geq$ 1.75 to $\leq$ 2.30 and a mean overall TPI score $\geq$1.5 at the Baseline visit.
    f. A subject who habitually wears one conventional removable partial denture constructed of acrylic or cobalt chrome which is acceptable according to the well-made and well-fit assessments.

5.3 Exclusion Criteria

A subject with any of the following characteristics/conditions will not be included in the study:

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with an acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
4. A subject who is pregnant (self-reported) or intending to become pregnant over the duration of the study.
5. A subject who is breastfeeding.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject who smokes (defined as having smoked or used nicotine products (including e-cigarettes, chewing tobacco, gutkha, pan-containing tobacco, nicotine replacement therapies) during the previous 12 months).
8. A subject who is unwilling or unable to comply with the Lifestyle guidelines described in this protocol.
9. A subject with a recent history (within the last year) of alcohol or other substance (e.g. illicit drug) abuse.
10. A subject who has previously been enrolled in this study.
11. A subject who, in the opinion of the investigator, should not participate in the study.
12. Medication Exclusions:
    a. A subject who has taken or is currently taking antibiotics at the Screening visit or in the 14-day period prior to the Baseline visit or requiring antibiotic use prior to dental prophylaxis or other dental procedure.
    b. A subject who is currently taking, on a regular daily basis, an anti-inflammatory, anti-coagulant or any other systemic medication (e.g. calcium channel blockers, aspirin therapy, ibuprofen, warfarin) or has a medical condition which, in the opinion of the Investigator, could affect the gingival condition.
    c. A subject who has used an antibacterial mouth rinse (e.g. chlorhexidine, Listerine), dentifrice (e.g. stannous fluoride) or use of any oral care product that, in the opinion of the investigator, could interfere with plaque accumulation or clinical measures within 28 days preceding the baseline visit.
13. Oral and Dental Exclusions
    a. A subject with a condition or who is taking medication which, in the opinion of the investigator is causing xerostomia.
    b. A subject who, in the opinion of the investigator, has a periodontal condition that could be adversely affected by lack of immediate periodontal intervention.
    c. A subject who has received treatment for periodontal disease within 12 months of Screening and/or scaling or root surface debridement within 3 months of Screening,

which, in the opinion of the Investigator, could compromise study outcomes or the oral health of the subject if they were to participate in the study.

d. A subject who has numerous restorations in a poor state of repair.
e. A subject with a severe oral condition (e.g. acute necrotizing ulcerative gingivitis, severe active caries) that could, in the opinion of the investigator, compromise study outcomes or the oral health of the subject if they were to participate in the study.
f. A subject who has had tooth bleaching treatment or a dental prophylaxis within 4 weeks of screening.
g. A subject who frequently use commercially-available denture cleansers, e.g. denture cleanser tablets, denture cleaning pastes (defined as those subjects who use a commercially available cleanser more frequently than once per month).
h. A subject who currently use denture adhesives (defined as those subjects who have used an adhesive in the 28 day period prior to baseline).
i. A subject who displays evidence of dental fluorosis that might interfere with clinical assessments, as determined by the investigator.
j. A subject with gingivitis which, in the opinion of the investigator, is not expected to respond to treatment with an over-the-counter dentifrice.
k. A subject who has an overdenture or orthodontic appliance.

5.4 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria. Eligible subjects will be stratified based on denture material type (acrylic or cobalt chrome) and baseline mean overall MGI score (low: $\leq$2.0; high >2.0) to ensure a balance in treatments across the strata, and then randomized into one of two treatment groups (intervention /no intervention).

There will be four strata according to denture material type (acrylic or cobalt/chrome) and baseline mean overall MGI score (Low$\leq$2.0/High>2.0):

- Stratum 1: Denture material is acrylic, Baseline MGI $\leq$2.0
- Stratum 2: Denture material is acrylic, Baseline MGI >2.0
- Stratum 3: Denture material is cobalt chrome, Baseline MGI $\leq$2.0
- Stratum 4: Denture material is cobalt chrome, Baseline MGI >2.0

Subjects will be allocated to one of the four strata and within each stratum, randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

5.5 Lifestyle Considerations

5.5.1 During the entire study (screening – subject's last study visit):

- Subjects will abstain from chewing gum and consuming confectionery containing xylitol (e.g. mints).
- Subjects should abstain from interproximal cleaning (use of dental floss, waterpick and toothpicks). Use of toothpicks is permitted to remove impacted food only.

- Subjects will abstain from use of antimicrobial mouthrinses or dentifrices and any over-the-counter dental whiteners during the course of the study except those products supplied.
- Subjects will be requested to not have any elective dental /denture procedures (including dental prophylaxis and tooth whitening) other than those performed within the study (excluding emergency dental treatment).
- Subjects randomized to the intervention group should only use the dentifrice, mouth rinse, denture cleanser and toothbrushes provided and must abstain from use of all other oral hygiene products from the baseline visit. They should abstain from interproximal cleaning (as defined above).
- Subjects randomized to the no intervention group will be instructed to continue with their current dental/denture cleaning habits at baseline (excluding interproximal cleaning as defined above). These subjects should endeavor to maintain their current oral/denture hygiene practice and not introduce any change throughout the entire study. Any changes to a subject's oral hygiene practices/products used that, in the opinion of the investigator or designee, are significant and consistent should be documented in the CRF as deviations.

5.5.2 Prior to Visits 2, 3 and 4:

- Subjects must abstain from undergoing any oral hygiene (including denture cleansing) for a minimum of 12 hours (maximum of 18 hours) i.e. overnight immediately before an assessment visit (Visits 2, 3 and 4) until the visit is complete.
- Subjects must abstain from eating for at least 4 hours, and from drinking for at least 1 hour prior to all clinical assessments and until all assessments are complete. Small sips of water to aid in the taking of permitted medications and to relieve thirst are allowable.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, and any adverse events or incidents as applicable.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

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 located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the investigational site and the study team 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 card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information

for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

The assessor(s) performing the MGI, TPI and BI, OST, OHT, PDCI, OHI well-made and well-fit assessments and who perform the dental prophylaxis will be a suitably qualified dental professional. The assessor(s) performing the MGI, TPI and BI assessments should have a demonstrable history of use of these indices in clinical trials. The assessor(s) performing the well-made and well-fit assessments will have expert knowledge of prosthodontics.

6 INVESTIGATIONAL/STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and GSK policy, investigational product is defined as a pharmaceutical form of an active ingredient, a non-medicinal product (marketed or investigational), or a placebo, being tested or used as a reference (positive or negative control), in a clinical trial. This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Intervention Group	No Intervention Group
Product Description	Range of Dental/Denture Products	N/A Subjects will continue with their existing oral hygiene
Product Names (Formulation Codes)	Experimental Dentifrice containing 0.454% stannous fluoride (CCI [redacted]) COREGA Purfrisch Reinigungsschaum Denture Foaming Cleanser – German Marketplace (CCI [redacted]) Experimental Mouthrinse containing 90ppm sodium fluoride (CCI [redacted])	N/A
Dose	A strip of dentifrice (full brush head) brushed for 2 timed minutes, 2 pumps of denture cleanser foam brushed onto RPD for 90 timed seconds and 10 ml of mouthrinse for swished around the mouth for 1 timed minute.	N/A
Route of Administration	Dentifrice and mouthrinse applied topically orally. Denture cleanser applied to denture external to the mouth prior to rinse off.	N/A
Dosing Instructions	As per the Product Usage Instructions	N/A

The dose and frequency (twice per day, morning and evening) of application of the individual products in the interventional group is consistent with label instructions (denture cleanser foam), the intended label instructions (dentifrice and mouthrinse) and the tentative FDA anti-gingivitis monograph (FDA, 2003) for the dentifrice and the anti-caries monograph for the mouthrinse (FDA, 1995).

Subjects randomized to the no intervention group will not be supplied any products and will continue with their existing dental/denture hygiene practices and should endeavor not make changes to either their established habits nor to the products they use following screening. Any changes to their oral hygiene practices should be recorded by the participant in their diary card, and those deemed significant and consistent by the investigator or their designee should be detailed in the CRF as deviations.

The Sundry Items to be supplied are detailed in Table 6-2.

Table 6-2 Sundry Items

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples

Wisdom Denture Brush	GSK CH	Commercial packaging	To clean dentures (for use at the study site and by the subjects randomized to the intervention range of products to clean dentures at home).	Destroyed at site according to site disposal procedures.	Return
Countdown Timer	GSK CH	Individual commercial pack – 1 per subject	To accurately measure toothbrushing, mouth rinsing and denture cleansing activities. To be used by subjects randomized to the intervention range of products only.	Subject to keep or destroyed at site using site disposal procedures.	Return
Dentu Creme Denture cleansing paste	GSK CH	Individual commercial pack	To clean dentures at the study site only by the dental professional	Return.	Return
Aquafresh Clean Control toothbrushes	GSK CH	Individual commercial pack – 2 per subject	To apply dentifrice to the teeth and facilitate toothbrushing. To be used by subjects randomized to the intervention range of products only.	Destroyed at site according to site disposal procedures.	Return
Dosing cups	GSK CH	N/A	For dosing of mouthrinse. To be used by subjects randomized to the intervention range of products only.	Destroyed at site following site procedures.	Return
Trace plaque disclosing solution	GSK CH	Individual commercial pack	To disclose the presence of dental plaque at the study site only	To be destroyed at site according to site procedures.	Return

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.

6.1.1 Dosage Form and Packaging

The experimental dentifrice will be supplied in individual tubes. The experimental mouthrinse will be supplied in individual bottles. The denture foam will be supplied in individual

dispensers with the commercial labels either removed or overwrapped to hide the identity of the product.

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, directions for use and storage requirements.

Care should be taken 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. Subjects should be instructed to not remove or deface any part of the study label.

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

6.1.2 Preparation and Dispensing

Subjects will be assigned to products in accordance with the randomization schedule generated by an approved GSK CH vendor, prior to the start of the study, using validated software.

Study product will be dispensed by qualified unblinded site personnel per the dosage/administration instructions. These staff members will not be involved in any safety, efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional member of the clinical site staff should ensure the dispensing procedures are completed accurately. Initial dispensing of study products should occur at Visit 2 with additional re-dispensing at Visit 3. The dispensing should be performed in a room away from other subjects and blinded study staff (especially the examiner performing the efficacy and safety assessments, who will be prevented from viewing subjects once they have their study products). The study site will be provided with opaque bags in which the study products, diaries and product usage instructions will be placed in the bag prior to the subject leaving the dispensing area. Subjects randomized to the no intervention group will have just their diaries in the opaque bag.

Subjects should be advised as to correct product usage in accordance with the Product Usage Instructions at each visit. All randomized subjects should receive standard oral care advice at Visit 2 (section 8.2.1).

6.2 Administration

Subjects randomized to the intervention group will undertake first usage of the range of dental/denture products under supervision at the clinical site. These subjects will be instructed to self-administer their assigned range of products twice per day (morning and evening) per the Product Usage Instructions provided to the subject and will use their products under supervision again at Visit 3 to ensure adherence to the product usage instructions.

6.2.1 Medication/Dosing Errors

Medication/dosing errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,

- or at the wrong dosage.

Such medication/dosing errors occurring to a study subject are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

Medication/dosing errors are reportable irrespective of the presence of an associated AE, including:

- Medication/dosing errors involving subject exposure to any of the study products;
- Potential medication/dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated adverse event(s) are to be captured in the CRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose per se is not an AE. However, any clinical sequelae of an overdose should be reported as an AE (and serious adverse event (SAE), if appropriate). For reporting, follow the AE and SAE reporting instructions.

6.3 Investigational/Study Product Storage

The investigator, or designee, will ensure that all study products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of first product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported to appropriate site staff upon discovery and communicated to sponsor as soon as possible. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Excursions from the storage requirements, including any actions taken, must be documented as a protocol deviation and reported to the Sponsor.

Once an excursion is identified, the affected product (or products) must be quarantined and not used until the sponsor provides documentation of permission to use. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Site staff will instruct subjects on the proper storage requirements for all take-home products.

6.4 Investigational/Study Product Accountability

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

All study products must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study products should be stored according to the instructions specified on the product labels. Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by authorized site staff.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of all the product supplies. All study products will be accounted for using the investigational/study product accountability form/record. The investigator is responsible for study product accountability, reconciliation, and record maintenance.

The accountability records must be available for inspection by the study monitor during the study. Monitoring of product accountability will be performed by the monitor during site visits and at the completion of the study.

All unused product should be returned to the study site by the subjects at each visit.

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. Please see table of sundry items for return or destruction details. 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.

6.5 Blinding and Allocation/Randomization

All subjects will be centrally randomized to one of the study arms using an Interactive Response Technology (IRT). Before the study is initiated, training, login information and directions for the IRT will be provided. Study products will be dispensed according to the instruction received through the IRT at the appropriate study visits.

Returned study products should not be re-dispensed to any subject.

The investigator's knowledge of the product allocation should not influence the decision to enroll a subject or affect the order in which subjects are enrolled.

This study is described as single-blind (to the examiner(s) performing the plaque and gingivitis assessments).

To ensure the examiner remains blinded throughout the study, staff involved in the dispensing of study products will work in a separate area. The examiner is not permitted in any area where study product is stored, dispensed, or in use.

Subjects will be instructed not to remove study products from the opaque bags provided, outside of the dispensing room, while at the study site. Subjects randomized to the interventional group will have the study products, sundry items and their diary and usage instructions contained

within the bag, whilst the subjects randomized to the no intervention group will have their diary in the bag.

Dispensing staff will not be involved in any efficacy/safety assessment procedures during the study.

6.6 Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process.

The electronic system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's product assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

Any AE or incident associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required to inform the Institutional Review Board / Ethics Committee (IRB/EC) if the blind is broken.

6.7 Compliance

A diary will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects randomized to the no intervention group should record their dental/denture cleansing events in the diary. All subjects should also record, in the diary, additional information such as AEs or changes in medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects and transcribed to the CRF as appropriate. Additionally, all subjects currently active in the study will receive an SMS (text message) reminder from the study site prior to a scheduled visit (Visits 2-4) to remind them of the requirement for no oral hygiene on the morning prior to their visit.

During study site visits (Visits 2&3) subjects randomised to use of the interventional range of products will have correct product usage demonstrated to them by the study site staff. Subjects will then undergo supervised product usage which will be witnessed by the study site staff and incorrect application will be corrected.

Subjects randomised to the interventional range of products will be supplied with a dosing cup to ensure accurate dosing of the mouthrinse. These subjects will also be asked to bring their assigned study products at each visit, so that the compliance assessments can be made based upon observation of the amount of product used and so they can undergo supervised product application at Visit 3.

The number of any missed or additional applications or doses for subjects in the intervention group will be captured as protocol deviations and transcribed from the diary into the CRF. Subjects will be re-instructed in the correct usage requirements and diary completion as needed.

For subjects in the non-intervention group, changes to their oral hygiene behavior compared to their behavior as recorded at screening which are deemed significant and consistent by the investigator or their designee will be captured as protocol deviations in the CRF.

Subjects randomized to use of the interventional range of products will be instructed in/reminded of the correct usage of the product at visits 2 and 3 by the dispensing staff with subsequent supervised product usage at these visits.

Failure of any subject to follow the oral care advice given at Visit 2 (see section 8.2.1) will not be considered as a deviation except where this failure is covered by other inclusion/exclusion criteria, lifestyle considerations or product usage instructions detailed within this protocol.

6.8 Concomitant Medication/Treatment(s)

Any medications, treatments or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken during the study, from signing the informed consent, must be recorded in the CRF with indication, reason for use, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medication/treatments at each site visit.

Details of any relevant dental, medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded in the CRF. The use of concomitant medications is permitted in this study except for the use of anti-biotics, anti-inflammatory or anti-coagulants drugs as per the exclusion criteria, and any medications that in the opinion of the investigator would interfere with the conduct of this study per the inclusion/ exclusion criteria. Occasional use of anti-inflammatory drugs (e.g. ibuprofen) is allowable, if in the opinion of the investigator, the use would not affect the gingival condition.

Medication/treatments taken within 28 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken on and after Visit 2 will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the CRF.

7.2 Lost to Follow up

If a subject fails to return to the site for a required study visit the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented. If contact is made with the subject, the investigator should inquire about the reason for withdrawal, request that the subject return all products that they had been dispensed and if appropriate request that the subject return for a final visit and follow-up with the subject regarding any unresolved adverse events (AEs) or incidents.

Final safety assessments may be carried out when the subject returns to the study site, at the investigator's discretion and subject's consent, which could include an OST and OHT examination.

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

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

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

8 STUDY PROCEDURES

This section lists the procedures to be completed at each planned study visit. The timing of each procedure is listed in the Schedule of Activities section.

Adherence to the study design requirements, including all procedures are essential and required for study conduct.

8.1 Visit 1/Screening

Screening procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will be screened within 1-28 days prior to randomization to confirm that they meet the subject selection criteria for the study.

The following Screening procedures will be completed, in the following order (wherever possible), and the findings recorded in the CRF:

1. Informed Consent
2. Demographics
3. Review of medical history (including smoking/tobacco use status) and prior medication/treatment
4. Review of current/concomitant medication
5. Review of dental history
6. Well-fit assessment of the RPD
7. Subject removes RPD
8. Well-made assessment of the RPD
9. Full OST and OHT examinations
10. Gross gingival assessment
11. Review of the inclusion/exclusion criteria
12. Subject eligibility
13. RPD is returned to subject
14. AEs and Incidents recorded

8.1.1 Screening Procedures

8.1.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

The investigator, or designee, must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time. Appropriate forms for documenting a signed and dated consent will be provided by either the investigator or by GSK CH.

The investigator, or designee, should sign and date each copy of the ICF to confirm that the consent process was completed correctly after the subject has signed.

The time the subject signed the informed consent form will also be captured on the Informed Consent Form as this is the point at which all Adverse Events and incidents will be captured from. The date and time of consent will be transcribed to the CRF.

If, during a subject's participation in the study, any new information becomes available that may affect the subject's willingness to participate in the study, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form. The date of re-consent will be recorded on the CRF.

After signing the ICF, subjects will undergo the screening assessments to confirm that they meet all the inclusion criteria and none of the exclusion criteria. If the subject is confirmed eligible by the investigator (or designee) to participate in the study the subject is considered enrolled in the study.

8.1.1.2 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender and race. Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.1.3 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last year), including allergies or drug sensitivity, will be documented in the CRF.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 28 days and prior to signing the informed consent form, will be documented in the CRF.

The smoking/tobacco usage status of the subject should be recorded.

8.1.1.4 Dental History

The dental history of the subjects should be taken. Examples of the questions that should be solicited are given in Appendix 15.3.

8.1.1.5 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF. The OST, OHT, gross gingival assessment, well-made and well-fit assessments should be performed by suitably qualified examiners as described in Section 5.8.

8.1.1.6 Subject Eligibility

The investigator and/or medically qualified designee will review inclusion/exclusion criteria, medical history, prior medications to confirm subject eligibility to participate in the clinical trial. This will be documented in the CRF.

To prepare for study participation, subjects will be instructed in the Lifestyle Guidelines and any Concomitant Medication/Treatment(s) requirements of the protocol.

8.2 Study Period

8.2.1 Visit 2/Day 0 – Baseline

Procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will undergo, in the following order (wherever possible), and findings documented in the CRF:

1. Changes in health, medication and non-drug treatments/procedures will be documented in the CRF.
2. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as “How do you feel?” will be assessed.
3. Subject completes the questionnaire.
4. Subject removes RPD.
5. RPD is assessed for PDCI.

6. For a subset of subjects, photographic images of their RPD will be taken.
7. Subject undergoes a full OST examination.
8. Subject undergoes MGI assessment including a repeat assessment if required.
9. Subject undergoes a CI assessment.
10. Subject undergoes plaque disclosure and TPI including a repeat assessment if required.
11. Subject undergoes ODI assessment.
12. Subject undergoes BI assessment.
13. Review of the inclusion/exclusion criteria.
14. Subject eligibility assessed.
15. Subjects will be stratified and randomized to treatment group.
16. Subject's RPD will be cleaned by the study site and the subject will undergo a full sub and supra-gingival prophylaxis with confirmation of a TPI score of zero by a second suitably qualified member of site staff.
17. The subject's RPD will be returned.
18. Intervention group only - study products will be dispensed, including sundry items, product usage instructions and diary. Subject to perform supervised product usage and study staff to review instructions on correct product use with the subject for at home use.
19. No intervention group only – subject to receive only the diary.
20. All randomized subjects will receive standard oral care advice to brush their teeth twice per day with a fluoridated toothpaste, to remove their partial denture while sleeping, to clean their denture and to visit their dentist regularly.
21. AEs and incidents recorded.

8.2.2 Visit 3/Day 42 ±3

Procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will undergo, in the following order (wherever possible), and findings documented in the CRF:

1. Changes in health, medication and non-drug treatments/procedures will be documented in the CRF.
2. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed.
3. Study products and diaries collected from subjects. Staff will complete visual checks of the returned lead-in toothbrush/toothpaste and review the completed diary. Any suspected over or under use and the number of any missed or additional product usage will be documented in the CRF.
4. Subjects compliance with treatment and denture cleaning assessed through examination of subject diary and product usage.
5. Subject completes the questionnaire.
6. Subject removes RPD.
7. RPD is assessed for PDCI.
8. For a subset of subjects an image(s) of their RPD will be taken. This is only to be performed at this visit should insufficient images of acceptable quality not have been obtained at Visit 2.

9. Subject undergoes a full OST examination.
10. Subject continuance assessed.
11. Subject undergoes MGI assessment including a repeat assessment if required.
12. Subject undergoes CI assessment.
13. Subject undergoes plaque disclosure and TPI assessment including a repeat assessment if required.
14. Subject undergoes ODI assessment.
15. Subject undergoes BI assessment.
16. The subject's RPD will be returned.
17. Intervention group only - study products will be dispensed, including sundry items, product usage instructions and their diary returned to subject. Subject to perform supervised product usage and study staff to review instructions on correct product use with the subject for at home use.
18. No intervention group only – subject to receive only their returned diary.
19. AEs and incidents recorded.

8.2.3 Visit 4 /Day 84 ±3

Procedures will be conducted by the Investigator, or suitably qualified designee.

Subjects will undergo, in the following order (wherever possible), and findings documented in the CRF:

1. Changes in health, medication and non-drug treatments/procedures will be documented in the CRF.
2. Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed.
3. Study products and diaries collected from subjects.
4. Subjects compliance to treatment and denture cleaning assessed through examination of subject diary and product usage.
5. Subject completes the questionnaire.
6. Subject removes RPD.
7. RPD is assessed for PDCI.
8. For a subset of samples an image(s) of their RPD will be taken. This is only to be performed at this visit should insufficient images of acceptable quality not have been obtained at Visit 2/3.
9. Subject undergoes a full OST examination.
10. Subject undergoes a full OHT examination.
11. Subject continuance assessed.
12. Subject undergoes MGI assessment including a repeat assessment if required.
13. Subject undergoes CI assessment.
14. Subject undergoes plaque disclosure and TPI assessment including a repeat assessment if required.
15. Subject undergoes ODI assessment.
16. Subject undergoes BI assessment.

17. Subject undergoes an optional dental prophylaxis and RPD cleanse.
18. The subject's RPD will be returned
19. AEs and incidents recorded.
20. Study conclusion.

8.2.4 Study Procedures

8.2.4.1 Diary Review

The diary should be reviewed for treatment compliance at every visit by the investigator, or suitably qualified designee. Any subject comment captured in the diary which is considered an adverse event will be assessed and reported as per the defined procedure in this protocol. Adverse event reporting procedures are summarized in Section 10.

Any comments relating to medications/treatments provided in the diary will be reviewed by the investigator or medically qualified designee with the subject prior to the subject leaving the site and entered into the CRF as appropriate.

Additional and missed product applications will be considered deviations from the protocol and will be recorded on the Deviations Log.

The number of toothbrushing, mouthrinsing and denture cleaning occasions for all subjects since their previous visit should be recorded in the CRF.

8.2.5 Photography of RPD – subset of subjects only

At Visit 2-4, photographs of the RPDs from a subset of subjects (chosen at the examiner's discretion) are to be taken to demonstrate the range of scores of the PDCI. The photographs are to assist study site staff with consistent evaluation of the PDCI over the duration of the study, to assist with future studies that might use this scale, and to aid interpretation of results (including publication/dissemination of the study outcomes).

Extra oral digital photographs will be taken of the occlusal, fit and side views of each RPD immediately after the PDCI assessment. No plaque disclosing agent should be used.

This procedure should be performed by appropriately trained/experienced staff. It is expected that approximately 3 separate RPDs be photographed per score of the PDCI index (0-4) wherever possible. RPDs for photography should be chosen at the examiner's discretion with the aim of ensuring clear photographs demonstrating the visual state of the RPD for each scale score of the PDCI. For the zero PDCI score only it is acceptable to photograph RPDs that have undergone the denture cleansing procedure at Visit 2 (i.e. the photographs will be obtained immediately prior to return of the RPD to the subject). It is expected that sufficient numbers of photographs will be obtained at Visit 2, however should insufficient photographs for all scores be taken at this visit (e.g. insufficient RPDs available that demonstrate a specific score) then it is acceptable to take additional photographs at Visits 3 and 4. Photographs may be obtained from subjects randomized to either treatment groups. It is accepted that there may be insufficient RPDs available for each of the PDCI scores.

Photographs will be obtained using a digital camera with sufficient resolution and adequate lighting to convey the denture cleanliness. Photographs should be taken with a black background and the image should contain a prominent numeral depicting the PDCI score at the

periphery of the photograph. Images should be obtained as soon as possible after the PDCI grading.

Digital photographs and their filenames will not contain any personally identifiable information. The digital file should be appropriately named to identify the subject screening number and the associated PDCI score. The only photographs that will be taken will be of dentures outside of the mouth. No images of subjects will be obtained. No analysis of any kind will be performed on these images.

8.2.6 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF. The MGI, TPI, CI, ODI, BI, OST, OHT and PDCI assessments and the prophylaxis should be performed by suitably qualified examiners as described in Section 5.8.

8.2.7 Supervised Product Application

Subjects randomized to the interventional group will be instructed on how to use the study products at Visits 2&3. Written product usage instructions will also be provided, and these should be read by the subject immediately prior to undergoing supervised use of the products. A member of the study site staff should observe this supervised application and advise/correct any incorrect product usage.

8.2.8 Dental Prophylaxis and RPD Cleansing

A suitably qualified member of clinical staff will provide professional dental prophylaxis for each subject using a standard prophylaxis polishing paste followed by flossing to ensure teeth are free of all supra and gingival calculus and plaque, both visually and by tactile assessment using a dental explorer. A second suitably qualified examiner will then visually check that all plaque has been removed following plaque disclosure. Subjects will have their plaque disclosed and any residual plaque remaining will be removed by the second clinician by dental polishing with a standard prophylaxis polishing paste to bring the subject to zero plaque (TPI=0).

Each RPD will be cleaned by a suitably qualified member of the clinical staff to zero plaque state, assessed by visual examination, by using the supplied denture brush and denture cleansing paste followed by rinsing thoroughly with tap water before returning to the subject. No disclosing agent will be used whilst cleaning the RPD.

In addition, at the final study visit, subjects will be offered a dental prophylaxis and RPD cleaning by a suitably qualified member of the clinical staff if determined appropriate in the opinion of the investigator or suitably clinically qualified designee.

8.2.9 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. 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 a subject has any clinically significant, study-related abnormalities, AEs or incidents at the end of the study, the GSK CH medical monitor (or designated representative) should be notified

and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.2.10 Follow-up Visit / Phone Call

The study site may contact a subject to follow up an AE or incident post-study completion/withdrawal and, in some circumstances, request they return to the site for additional follow-up visits (final safety assessments). If needed, additional examinations may be carried out at such visits.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to complete an assessment. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments in a timely manner.

9.1 Screening Assessments

Screening assessments will be performed by appropriately trained staff/clinical examiners at the times, and in the order, defined in the Study Procedures section of this protocol.

9.1.1 OST Examination

The screening clinician will perform an initial oral soft tissue examination in agreement with Section 9.3.1 in order to record any abnormalities and assess the subject's eligibility for enrollment into the study.

9.1.2 OHT Examination

The screening clinician will perform a visual examination of the oral hard tissues in agreement with Section 9.3.2 in order to record any abnormalities and assess the subject's eligibility for enrollment into the study.

9.1.3 Gross Gingival Health Assessment

The screening dentist will determine gingival health by visual examination of the subject's oral soft tissue. Subjects considered to have generalized mild-moderate gingivitis will continue in the study.

9.1.4 Evaluation of Well Fit Partial Denture

The clinical assessment of denture fit will be made by an examiner with expert knowledge of removable prosthodontics. Higher values indicate a more favorable prosthesis.

Retention Criteria

0= Inadequate retention that cannot be adjusted. Prosthesis displaces and rocks when torque forces are applied.

1=Inadequate retention that can be adjusted by laboratory clasp adjustment.

2=Retention is adequate but there is slight displacement when torque forces are applied. It can be adjusted.

3=Retention is adequate and does not displace when torque forces are applied.

Stability Criteria

0=Poor stability due to inadequate saddle area extension and appliance fit that cannot be adjusted.

1=Partial denture is not stable due to inadequate saddle area that can be corrected by laboratory reline.

2=Partial denture is slightly unstable but can be adjusted.

3=Saddle area is properly covered, and partial denture has adequate stability.

Fit and Function

0=Prosthesis has poor fit and causes tissue irritation. Occlusion is worn out and appliance induces tooth movement.

1=Prosthesis does not have adequate fit and function that might lead to future tooth and tissue damage.

2=The fit and function of the appliance is of acceptable quality.

3=Prosthesis is satisfactory in function, design and fit.

Sum score 0-5= Clinically unacceptable retention and stability

Sum score 6-9= Clinically acceptable retention and stability

9.1.5 Criteria for a Well Made Removable Partial Denture

The clinical assessment of the suitability of the RPD will be made by an examiner with expert knowledge of removable prosthodontics. The investigator will evaluate each partial denture to see if there is adequate occlusal relationship with opposing dentition, missing teeth and/or clasps and quality of the denture itself, such as finish, porosity, tissue surface, polish, quality of occlusal surface.

Overall Rating will be rated as:

Acceptable: All factors rated “Acceptable”

Unacceptable: Any factor is rated “Unacceptable”

9.2 Efficacy Assessments

The following efficacy assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.2.1 Subject Questionnaire

On assessment days (visits 2-4), the subject will complete a questionnaire that aims to assess the subject's perceptions of dental/denture cleaning. The study staff should be mindful that whilst the questionnaire does not solicit safety information, any information on safety outcomes recorded by subjects on a questionnaire should be evaluated by the investigator to ensure all AEs and incidents are recorded. To ensure that the examiner who performs the gingival and plaque assessments is blinded to the assignment of treatment, the examiner will not have access to these questionnaires.

The questionnaire should be completed by the subject prior to any clinical assessments being performed.

A member of site staff will provide verbal instructions to subjects on correct completion prior to administration of the questionnaire and should part of the questionnaire not be completed, or ambiguous response be given (i.e. more than one answer is given for a question) these be clarified with the subject before they leave the study site. All subject responses should be entered into the CRF.

9.2.2 Partial Denture Cleanliness Index (PDCI)

The cleanliness of the partial denture should be evaluated by the clinical examiner using the PDCI at Visits 2-4 based on the modification of the Clinical Categorization of Denture Cleanliness Index, (Blair et al, 1995). The RPD should have been removed from the subjects' mouth prior to the assessment. This assessment should be performed as soon as possible after removal of the RPD from the mouth and prior to RPD photography (if performed). No plaque disclosing agent should be used. A suitable dental probe will be used to gently scrape the surfaces of the RPD and the PDCI scored using the descriptors detailed in Table 9-1. All surfaces of the RPD should be assessed and the highest score applicable recorded.

Table 9-1 The Partial Denture Cleanliness Index (PDCI) from (Blair et al, 1995).

PDCI Score	Description
0	No visible plaque; no matter adherent to the dental probe on light scraping
1	No visible plaque; matter adherent to the dental probe on light scraping
2	Deposits of plaque just visible on careful examination without need to confirm by scraping
3	Deposits of plaque clearly visible
4	Gross plaque deposits ("velvet appearance")

9.2.3 Modified Gingival Index (MGI)

The MGI is a non-invasive modification of the original GI (Loe and Silness, 1963) which focuses on the visual symptoms of gingivitis (redness, texture, edema) (Lobene, 1986). The MGI will be assessed for the facial and lingual/palatal gingiva of all evaluable teeth, four sites per tooth (facial surface - papilla and margin; lingual/palatal surface - papilla and margin). Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not to be assessed unless, as a result tooth loss, they are functioning as second molars

whereby they can be assessed. The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity.

The MGI scoring system will be as described in Table 9-2.

Table 9-2 The Modified Gingival Index (MGI)

Score	Description
0	Absence of inflammation
1	Mild inflammation: slight change in color, little change in texture of any portion of the marginal or papillary gingival unit
2	Mild inflammation: criteria as [1] but involving the entire marginal or papillary gingival unit
3	Moderate inflammation: glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit
4	Severe inflammation: marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration

The MGI will be assessed by the same examiner on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4.

9.2.4 Bleeding Index (BI)

The BI (Saxton and Ouderaa, 1989) assesses the number of bleeding points elicited on probing as a measure of gingival condition. The gingivae will be air dried and then the examiner will use an Oulix color coded periodontal PCPII 5B Hufreidy or blunt-ended Community Periodontal Index (CPI) probe to assess bleeding. The probe will be gently inserted into the gingival crevice to a depth of approximately 1 millimeter (mm) and then run around the tooth (at angle of ~ 60º to the long axis of the tooth), gently stretching the epithelium while sweeping from interproximal to interproximal along the sulcular epithelium. Minimum force should be used to avoid damage to the gingival tissue. The BI will be assessed on the facial and lingual gingival surfaces of each scorable tooth. Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not to be assessed unless, as a result tooth loss, they are functioning as second molars whereby they can be assessed. The scoring of the MGI will be performed under dental office conditions using a standard dental light for illuminating the oral cavity.

Three scores (according to the scale below) should be recorded bucally/labially (distal, body, mesial sites) and three scores lingually/palatally (distal, body, mesial sites). All scorable teeth in one quadrant should be probed first (approximately 30 seconds) before recording the number of gingival units which bleed. The scoring system is described in Table 9-3.

Table 9-3 The Bleeding Index (BI)

Score	**Description**
0	Absence of bleeding on probing
1	Bleeding observed within 30 seconds of probing
2	Bleeding observed immediately on probing

Sites with a score of 1 or 2 will be classified as 'bleeding' sites. The BI will be assessed by the same examiner on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4.

A repeatability exercise will not be performed for BI. Due to the invasive nature of the BI assessment it is not feasible to conduct a repeatability exercise.

9.2.5 Turesky Plaque Index (TPI)

Supra-gingival plaque will be assessed for the facial and lingual/palatal surfaces of all scorable teeth, six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual/palatal, lingual/palatal and distolingual/palatal), using the six site modification of the Turesky Modification of the Quigley Hein Plaque Index (TPI) (Lobene et al, 1982), which is weighted towards plaque accumulation in the gingival area of the tooth.

To perform the assessment, the dental plaque will first be disclosed with a plaque disclosing solution, rinse with water and expectorate in accordance with the manufacturer's instructions. The same disclosure procedure should be adopted as closely as possible throughout the study.

Only natural teeth can be assessed. This means no crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not to be assessed unless, as a result tooth loss, they are functioning as second molars whereby they can be assessed. The TPI will be assessed on the facial and lingual surfaces of each scorable tooth. Three scores should be recorded bucally/ labially (distal, body, mesial sites) and three scores lingually/ palatally (distal, body, mesial sites). Disclosed plaque will be scored as described in Table 9-4. The TPI will be assessed by the same examiner on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4.

Table 9-4 Turesky Plaque Index

Score	Description
0	No plaque
1	Separate flecks of plaque at the cervical margin
2	Thin continuous band of plaque (up to 1 mm) at the cervical margin
3	Band of plaque wider than 1 mm but covering < 1/3 of the tooth surface
4	Plaque covering ≥ 1/3 but < 2/3 of the tooth surface
5	Plaque covering ≥ 2/3 of the tooth surface

9.2.6 Oral Hygiene Index

The Oral Hygiene Index (Greene and Vermillion, 1960) is a composite index based upon a calculus and an oral debris assessment. The Calculus Index (CI) should be performed after the MGI and prior to plaque disclosure, whilst the Oral Debris Index (ODI) should be performed after the TPI assessment. Due to the invasive nature of the ODI assessment it is not feasible to conduct a repeatability exercise.

As originally utilized this assessment was performed on a segment basis (6 segments per mouth). However, in this study the assessments will be performed on a per tooth surface basis. This is required since the presence of RPDs in the mouth may mean that entire segments are not scorable.

The OHI for each subject will be calculated as the sum score of the mean CI and the mean ODI and thus the range of the OHI is 0-6.

Each natural tooth will be assessed for ODI and CI. No crowns, bridges, and teeth with fillings (surface that has 50% of the surface gradable or no more than 50% of the surface filled) which, in the examiner's judgment, would prevent an accurate grading should be assessed. Third molars should not to be assessed unless, as a result tooth loss, they are functioning as second molars whereby they can be assessed.

9.2.6.1 Calculus Index

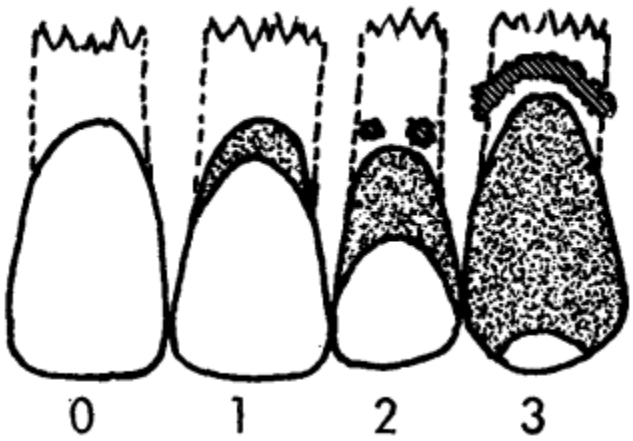
The extent of calculus on each tooth surface (buccal and lingual) will be determined by visual examination. Only definite deposits of hard calculus will be recorded. The CI will be assessed on the facial and lingual surfaces of each scorable tooth.

The CI will be assessed by the same examiner for all subjects throughout the study on all evaluable teeth at Baseline/Visit 2, Visit 3 and Visit 4. The CI will be scored as described in Table 9-5 and Figure 9-1. The CI for each subject will be calculated as the mean score of all tooth surfaces (facial/lingual).

Table 9-5 The calculus index – from (Greene and Vermillion, 1960)

Score	Description
0	No calculus present
1	Supragingival calculus covering not more than one third of the exposed tooth surface
2	Supragingival calculus covering more than one third but not more than two thirds of the exposed tooth surface or the presence of individual flecks of subgingival calculus around the cervical portion of the tooth or both
3	Supragingival calculus covering more than two thirds of the exposed tooth surface or a continuous band of subgingival calculus around the cervical portion of the tooth or both

Figure 9-1 Diagram demonstrating the calculus index – from (Greene and Vermillion, 1960). Copyright obtained, no further reproduction is permitted.



9.2.6.2 Oral Debris Index

The extent of oral debris (defined as soft foreign matter on the surface of teeth) on each tooth surface (buccal and lingual) will be determined by running the side of a number 5 explorer (Shephard's crook) or similar probe along the buccal, labial and lingual surfaces and noting the

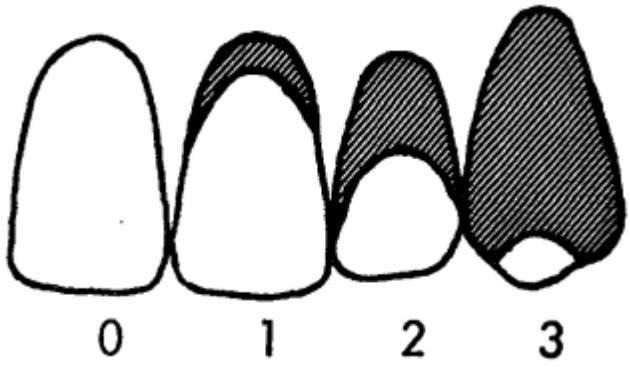
occlusal or incisal extent of the debris as it is removed from the tooth surface. The ODI will be scored in accordance with Table 9-6 and Figure 9-2.

The ODI will be assessed on the facial and lingual surfaces of each scorable tooth. The ODI will be assessed by the same examiner for all subjects throughout the study. The ODI for each subject shall be calculated as the mean score of all tooth surfaces (facial/lingual).

Table 9-6 The oral debris index – from (Greene and Vermillion, 1960)

Score	Description
0	No debris or stain present
1	Soft debris covering not more than one third of the tooth surface, or the presence of extrinsic stains without other debris regardless of surface area covered
2	Soft debris covering more than one third, but not more than two thirds, of the exposed tooth surface
3	Soft debris covering more than two thirds of the exposed tooth surface

Figure 9-2 Diagram demonstrating the oral debris index – from (Greene and Vermillion, 1960). Copyright obtained, no further reproduction is permitted.



9.3 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

9.3.1 Oral Soft Tissue Examination (OST)

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee. The OST examination will be accomplished throughout the study by direct observation and palpation with retraction aids as appropriate. The examiner will include examination of the oral labial mucosa (including lips), buccal mucosa, mucogingival folds, gingival mucosa, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands.

The results of the examination will be recorded in the CRF as either normal or abnormal, with details of any abnormalities. Any soft tissue abnormality, or worsening of a pre-existing condition, observed by the examiner or reported by the subject will be recorded on the CRF.

Any abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening will be recorded as an AE.

Findings from the examination performed at screening will be used to determine subject eligibility.

9.3.2 Oral Hard Tissue Examination (OHT)

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects. The OHT examination will be accomplished by direct observation, using retraction aids as appropriate and will identify any grossly carious lesions or signs of erosive wear, enamel irregularities, tooth fracture, gross decay, decalcification and faulty restorations. The presence of any implants, fixed or removable dentures, fixed or removable orthodontic braces/bands, fixed orthodontic retainers, full crowns or veneers will be recorded. Observations will be listed as either absent or present, and conditions noted as present will be described in the CRF. Any change observed by the clinical examiner or reported by the subject from the OHT examination carried out at Screening will be recorded as an AE.

Findings from this examination at Screening will be used to determine subject eligibility.

9.3.3 Repeatability Assessments – subset of subjects only

The clinical examiner selected for this study will have demonstrated their ability to replicate their own scores (intra-examiner repeatability) on a tooth site-by-tooth site basis in previous studies and/or calibration exercises. Given both the MGI and the TPI allow accurate repeat assessment, repeat assessments will be performed for both clinical measures throughout the treatment period (Visits 2-4) to monitor consistency of scoring.

Depending on subject visit scheduling, every effort will be made to perform at least 2 repeat assessments for each index on each clinical assessment day (≥1 in the morning; ≥1 in the afternoon). 'Repeat' subjects will be selected at random from those in attendance. Different subjects can be used for repeat MGI and TPI assessments.

There should be a delay of at least 10 minutes (maximum 60 minutes) between original and repeat assessments for a given subject. No other procedure should be carried out on that subject between the first and the repeat assessment.

Scores from the first assessment must not be visible to the examiner/scribe when the repeat assessment is carried out.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

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 Reporting of Adverse Events

10.3.1 Reporting Period

All AEs, and therefore all SAEs will be collected immediately after a subject consents to participate in the study by the completion (signature) of the ICF and until 5 days following last administration of the study product (or last procedure).

Medical occurrences that began before obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the CRF not the AE section.

Details recorded by the subject on a diary or similar document that meet the definition of an AE must also be discussed with the subjects and transcribed in the AE section of the CRF.

10.4 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study, or a study procedure, or that caused the subject to discontinue the study product or study.

The investigator (or medically qualified designee) is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

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

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE in the CRF and all details relating to an SAE in the paper SAE Form provided.

It is **not** acceptable for the investigator (or medically qualified designee) to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE CRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator (or medically qualified designee) in a standard manner at the study visits should also be recorded in the AE section of the CRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

All AEs will be reported on the AE page of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the AE CRF page and the SAE form must be completed in a consistent manner. For example, the same AE term should be used on both. AEs should be

reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

10.4.2 Reporting of a Serious Adverse Event

In addition to recording the details of each AE on the AE CRF page, an SAE form should be completed, as fully as possible. Hard copies of the 'paper' SAE form will be provided in the investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken in relation to the study product
- Outcome if known

The SAE form, completed as fully as possible, must be scanned and e-mailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed** 24 hours of it being available. The GSK CH Study Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

The investigator or medically qualified designee will make an assessment of intensity for each AE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

10.5.2 Assessment of Causality

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE (serious and non-serious), the investigator (or medically qualified designee) **must** provide an assessment of causality on the AE CRF page and the SAE form (subject to the classification of the AE). The investigator will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK CH to elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE CRF page and on the SAE form (subject to the classification of the AE).

The investigator will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH 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 Clinical Safety and Pharmacovigilance group mailbox at GSK PPD

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

10.7 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 CRF page.

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

10.7.1 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the sponsor will review and then file it along with the Investigator's Brochure in the investigator study master file, and will notify the IRB/IEC, if appropriate according to local requirements.

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 5 days after last administration of study product.

10.8.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan 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 Clinical Safety and Pharmacovigilance mailbox PPD. Original pregnancy information forms will be retained in the investigator study master file.

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 the investigator 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 Clinical Safety and Pharmacovigilance 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.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

10.9 Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSK CH for use in this study; the medical devices in this study are the denture brushes and the denture cleansing foam.

10.9.1 Definition of an Incident

A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.

Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

An **incident** associated with a device happened and

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.
- A serious deterioration in state of health can include any of the following:
- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

10.9.2 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH **immediately and under no circumstance should this exceed 24 hours** of the investigator or designee becoming aware of the situation.

Any medical device incident occurring during the study will be documented in the subject's medical records, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE (serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

The Incident Report Form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK CH. It is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

The completed Incident Report Form should be scanned and emailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

The GSK CH Study Manager should be notified of the situation by telephone or email.

Email the Incident Report Forms to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox PPD), responsible for the study and other GSK CH personnel as appropriate.

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

The investigator will follow the following directions regarding the reporting of a device failure (malfunction):

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- Return the failed device to the sponsor as soon as possible, including documentation of the details of the failure

All communications regarding a medical device incident should be directed towards the GSK CH study manager. The study manager will assess if follow up action is required.

10.9.3 Follow-up of Medical Device Incidents

Medical device incidents involving an AE will be followed and reported in the same manner as other AEs. This applies to all subjects, including those who discontinue study product or are withdrawn from the study.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed Incident Report form with all changes signed and dated by the investigator.

10.9.4 Regulatory and Ethics Reporting Requirements for Incidents

To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during all periods of the study in which the medical device is used.

The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (e.g. the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

11 DATA MANAGEMENT

As used in this protocol, the term CRF is understood to refer to either a paper form or an electronic data record or both, depending on the data collection method.

For this study, subject data will be entered into an electronic CRF (eCRF), using a validated system. Data relating to SAEs, pregnancy and incidents will also be collected on paper forms.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified. The CRF and Diary can be used as a source document at the discretion of data management.

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/assent the CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Management of clinical data will be performed in accordance with Third Party BDM Vendor 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 Personal Information (PI) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs 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, 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 the Investigator.

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

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. 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.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Patient Reported Outcomes

Paper based patient reported outcome (PRO) data may be collected from a diary, questionnaire, or other specified document, etc. and entered into the data management system (DMS).

Electronic Patient reported outcome (ePRO) data may be collected using electronic devices and transferred electronically to GSKCH or Third-party DM vendor.

All PRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the CRF and/or DMS. PROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or GSK CH as required.

To protect the privacy of subjects, no Personal Information (PI) (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 Third-Party Vendor.

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format

agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed quality control process will be performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

A sufficient number of subjects will be screened to randomize at least 150 (maximum 175) subjects to ensure approximately 128 evaluable subjects complete the entire study

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12.2 Statistical Methods and Analytical Plan

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 the database lock and study unblinding. The RAP creation and statistical analysis will be performed by Syneos Health.

12.2.1 Definition of Analysis Populations

The modified intent to treat (mITT) population is defined as those subjects who are randomized, receive at least one dose of study product and have at least one post-baseline efficacy measurement performed.

The Per Protocol (PP) population will be a subset of the mITT population. Subjects with a protocol violation that is deemed to affect efficacy for all efficacy assessments will be excluded from the PP population. Subjects with a protocol violation that is deemed to affect efficacy for only some (but not all) of the efficacy assessments will be part of the PP population, but their data will be excluded from the assessment at which the protocol violation occurred.

Efficacy analysis will be based on the mITT population. A PP analysis will be performed only if 10% or more mITT subjects are excluded from PP population.

The Safety population is defined as all subjects who are randomized and have received at least one dose of study products.

The repeatability population is defined as all subjects who have a repeat clinical assessment (MGI or TPI) at any visit.

12.2.2 Exclusion of Data from Analysis

Subjects who deviate from the protocol will be identified and excluded from analyses as agreed by the biostatistician and clinical scientist or designee. Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.2.3 Demographic and Baseline Characteristics

The Safety population will be used for demographic and baseline characteristics. Descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic, baseline characteristics and dental history. Medical history will be listed.

12.2.4 Study Drug/Product Compliance and Use of Other Therapies

12.2.4.1 Study Drug/Product Compliance

The number of subjects exposed to each treatment will be tabulated for the safety population.

Treatment deviations for individual subjects will be listed and summarized. The mean number of toothbrushing, mouth rinsing and denture cleaning occasions will be summarized by visit and treatment group for the safety population.

12.2.4.2 Prior and Concomitant Medications

Prior medications, concomitant medications, and other concomitant non-drug therapies will be listed for the safety population.

12.2.5 Primary Analysis

The mITT population will be used for the primary analysis. The primary efficacy endpoint will be the Bleeding Index (BI) score after 12 weeks of study treatments. The BI score will be calculated as the average index values over all tooth sites. An ANCOVA model will be used for the primary analysis with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline BI score as a covariate. The adjusted means of the two treatments, the proportionate reduction for each treatment group, and the treatment difference will be provided together with 95% CI and P-values.

The null and alternative hypotheses to be tested in the primary analyses are;

H_0: There is no treatment difference in mean BI score after 12 weeks

H_1: There is a treatment difference in mean BI score after 12 weeks

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated and if violated, data transformations will be investigated. If suitable transformations cannot be found, non-parametric tests will be performed, and results will be compared with the ANCOVA results. If the inferences from the two analyses are similar, then both sets of results will be reported and emphasis will be made on the ANCOVA results. In case of discrepancies between inferences of the ANCOVA and non-parametric analysis, results will be drawn from the non-parametric analysis.

A PP analysis will be performed on the primary analysis only if 10% or more mITT subjects are excluded from the PP population.

12.2.6 Secondary Analyses

The mITT population will be used for all secondary analyses. For all of the secondary analyses, Normality assumptions in ANCOVA models will be checked and accounted for in the same way as for the primary variable.

12.2.6.1 Number of bleeding sites at Week 6 and Week 12

Number of bleeding sites will be calculated as the average number of sites with a BI score of 1 or 2. At each post-baseline visit, the average number of bleeding sites will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline score as a covariate. The adjusted means of the two treatments, the proportionate reduction for each treatment group, and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.2 MGI score at Week 6 and Week 12

The MGI score will be calculated as the average index value over all tooth sites. At each post-baseline visit, the MGI score will be analyzed using an ANCOVA model with treatment, gender, and denture material type (acrylic or cobalt chrome) as factors and the baseline MGI score as a covariate. Since the baseline MGI score is included as a covariate, the baseline mean overall MGI score (low, high) is not required. The adjusted means of the two treatments, the proportionate reduction for each treatment group, and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.3 Overall TPI at Week 6 and Week 12

The overall TPI score will be calculated as the average index value over all tooth sites. At each post-baseline visit, the overall TPI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and baseline overall TPI score as a covariate. The adjusted means of the two treatments and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.4 Interproximal TPI at Week 6 and Week 12

The Interproximal TPI score will be calculated as the average index value over all interproximal tooth sites. The Interproximal TPI score will be analyzed in a similar manner to the overall TPI score.

12.2.6.5 BI score at Week 6

The BI score at Week 6 will be analyzed using the same ANCOVA model as used for the primary analysis. The adjusted means of the two treatments, the proportionate reduction for each treatment group, and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.6 CI score at Week 6 and Week 12

The CI score will be calculated as the average index value over all tooth sites. At each post-baseline visit, the CI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline CI score as a covariate. The adjusted means of the two treatments and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.7 ODI score at Week 6 and Week 12

The ODI score will be calculated as the average index value over all tooth sites. At each post-baseline visit, the ODI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline ODI score as a covariate. The adjusted means of the two treatment, and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.8 OHI score at Week 6 and Week 12

The OHI for each subject will be calculated as the sum score of the CI and the ODI. At each post-baseline visit, the OHI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and the baseline OHI score as a covariate. The adjusted means of the two treatments and the treatment difference will be provided together with 95% CI and P-values.

12.2.6.9 PDCI score at Week 6 and Week 12

The PDCI score will be calculated as the average index values over all subjects. At each post-baseline visit, PDCI score will be analyzed using an ANCOVA model with treatment, gender, denture material type (acrylic or cobalt chrome), and baseline mean overall MGI score (low, high) as factors and baseline PDCI score as a covariate. The adjusted means of the two treatments and the treatment difference will be provided together with 95% CI and P-values.

12.2.7 Safety Analysis

All AEs will be coded using MedDRA. AEs will be categorized as oral and non-oral by the PI, or suitably qualified delegate, prior to database lock. Treatment-emergent adverse event (Oral AEs as well as all AEs) will be summarised. The number of AEs and number of subjects with AEs will be listed and tabulated by treatment group. The results of OST exams will be tabulated. Incidents will be listed. The safety analysis will be performed on the Safety population.

12.2.8 Exploratory Analyses

The following endpoints are all considered exploratory. The analysis of these endpoints will be performed in a similar manner to the primary or secondary analysis described above.

Unless indicated otherwise, the following endpoints will be analyzed using the same ANCOVA model with mITT population as used for the primary or secondary analysis.

- BI associated with abutment teeth at 6 and 12 weeks.
- Number of bleeding sites associated with abutment teeth at 6 and 12 weeks.
- TPI associated with abutment teeth (overall and interproximal) at 6 and 12 weeks.

- CI associated with abutment teeth at 6 and 12 weeks.
- ODI associated with abutment teeth at 6 and 12 weeks.
- OHI associated with abutment teeth at 6 and 12 weeks.
- MGI associated with abutment teeth at 6 and 12 weeks. MGI score will be calculated as the average index associated with the abutment teeth only. At each post-baseline visit, the MGI score will be analyzed using an ANCOVA model with treatment, gender and denture material type (acrylic or cobalt chrome) as factors and baseline MGI score as a covariate. As baseline MGI score is included as a covariate, baseline mean overall MGI score (low, high) is not required. Adjusted means of the two treatments, the proportionate reduction for each treatment group, and the treatment difference will be provided together with 95% CI and P-values.
- Cleaning Perceptions Questionnaire at 6 and 12 weeks will be summarized and listed. Additional details of the proposed statistical analysis will be documented in the RAP.
- RPD photographs - No analysis will be performed on these photographic images. These will be incorporated into the clinical study report for illustration of the PDCI scale only.

12.2.9 Other Analyses

The Kappa coefficients for MGI & TPI Repeatability Analysis will be performed using the repeatability population. The repeat assessments will be compared to the original assessments. The repeat assessments will not be used in any efficacy analysis. The first and second assessments on each analyzed site at a given visit will be cross-tabulated and a weighted Kappa coefficient (κ) will be calculated, along with the 95% confidence interval, to assess the intra-examiner repeatability. Repeatability will be deemed:

- Excellent, if $\kappa > 0.75$
- Fair to good, if $0.4 \leq \kappa \geq 0.75$
- Poor, if $\kappa < 0.4$

All subjects who have repeatability data will be included in this analysis.

12.2.10 Handling of Dropouts and Missing Data

Subjects who withdraw from the study early will be included in the study analysis up to the point of withdrawal. Subjects who withdraw will not be replaced. No data will be imputed in the case of dropouts or missing data.

12.2.11 Interim Analysis

No interim analysis is planned for this study.

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

In accordance with applicable regulations including GCP, and GSK CH procedures, GSK CH or designee (i.e. third-party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK CH requirements.

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

GSK CH or designee will monitor the study and site activity to verify that the:

- 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.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

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 site 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, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff 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.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) 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 investigator file. 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. As per the Regulatory Determination for this study, the denture foam cleanser is categorized as a medical device and therefore a Non-significant Risk (NSR) application will be required as part of the IRB submission to conduct this study in the US.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with 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 (ICH, Nov 2016), 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.

The study site 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 informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent 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.

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

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This

generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

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 the investigator 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, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator 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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK CH site or other mutually-agreeable location.

GSK CH will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK CH Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g. for a GSK CH audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years 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, 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 the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or 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. In addition, GSK CH retains the right to discontinue development of the products in the range of products under investigation at any time. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator 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, the investigator 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 monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

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15 Appendix

15.1 Abbreviations

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

Table 15-1 Abbreviation

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
ANCOVA	analysis of covariance
BDR	Blinded data review
BI	Bleeding Index
CI	confidence interval, calculus index
CPITN	community periodontal index of treatment needs
CRF	case report form
CSA	clinical study agreement
EC	ethics committee
EDC	Electronic data capture
eCRF	electronic case report form
ePRO	Electronic patient recorded outcome
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FRP	Females of Reproduction Potential
GSKCH	GlaxoSmithKline consumer healthcare
GCP	Good Clinical Practice
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRB	institutional review board
IRT	Interactive Response Technology
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities

Abbreviation	Term
mITT	Modified intent to treat
MGI	Modified gingival index
N/A	not applicable
NSR	Non-significant risk
OHI	Oral hygiene index
ODI	Oral debris index
PDCI	Partial Denture Cleanliness Index
PI	principal investigator
PI	Personal information
PP	Per protocol
PRO	Patient reported outcome
QC	quality control
RAP	Reporting and analysis plan
RPD	Removable partial denture
RTM	reduced transport medium
SAE	serious adverse event
SOP	standard operating procedure
SRSD	single reference study document
SS	safety statement
TPI	Turesky plaque index
UK	United Kingdom
US	United States

15.2 Product Usage Instructions

Please remove your partial denture prior to brushing your teeth and rinsing your mouth.

Twice per day (morning and evening), you should clean your teeth, then clean your denture, then rinse with mouthrinse in that order.

Toothbrushing – Helps remove plaque to keep gums healthy and helps protect teeth from decay

1. Wet your supplied toothbrush with running tap water.
2. Apply the supplied toothpaste along the full length of the brush head.
3. Brush all of your teeth with the toothbrush for 2 (two) timed minutes in your usual way.
4. Spit out the toothpaste.

Denture Cleanser Foam – Helps to clean bacteria and stain from your denture

1. Hold partial denture firmly.
2. Shake bottle.
3. Apply 2 (two) full pumps of foam wash onto partial denture, adjust amount if needed.
4. Brush for 90 seconds using the supplied denture cleaning brush.
5. Rinse partial denture thoroughly with running water before inserting in the mouth.

Keep the denture foam out of the sight and reach of children. Do not use on natural teeth or in mouth. Do not touch mouth or eyes after use. Wash hands thoroughly after handling. May cause an allergic skin reaction, or irritation to the eyes and mucous membranes. If on skin, wash off with plenty of water. If skin or eye irritation occurs, or skin rash occurs: discontinue use, wash with plenty of water and get medical advice/attention and advise the study site. In case of an allergic reaction, stop using the product and contact your doctor immediately and advise the study site. Avoid breathing mist or vapour.

Mouthrinse - Helps protect you from tooth decay

1. Pour out 10ml of the supplied mouthrinse.
2. Rinse your mouth with the mouthrinse for 1 timed minute, swishing the rinse vigorously around your mouth.
3. Spit out the mouthrinse.
4. Reinsert your partial denture.

15.3 Dental History

The Investigator, or medically qualified designee, will take a dental history from each subject and document in the CRF. The dental history will solicit detail on the subject's RPD, missing teeth and the subject's current oral hygiene routine. Examples of the type of questions that will be asked include:-

- the age of the subjects current RPD
- the location of the RPD, recorded as the tooth numbers the RPD has replaced
- whether the subject normally sleeps with the RPD in place
- the type of the RPD based upon the Kennedy classification
- the material of the RPD framework (cobalt chrome or acrylic)
- the subject's overall satisfaction with their RPD
- the cause of tooth loss leading to the RPD (e.g. caries, periodontal disease, trauma, other, unknown)
- documentation of missing natural teeth, recorded using tooth numbers
- identification of abutment teeth, recorded using tooth numbers
- the toothpaste and mouthrinse the subject currently uses including frequency of use
- current method of denture cleaning (including frequency, method and name of any products used (if any))

The Kennedy classification (Miller, 1970) describes the type of partial denture worn as:

- Class I (bilateral free ended saddle; partially edentulous)
- Class II (unilateral free ended saddle; partially edentulous)
- Class III (unilateral bounded saddle; partially edentulous)
- Class IV (bilateral bounded anterior saddle; partially edentulous)

Examples of the 4 Kennedy classes are shown in Figure 15-1. For complex RPDs described as e.g. Kennedy Class II with modification I, only the primary class will be recorded, i.e. as Kennedy Class II.

Figure 15-1 Examples of the 4 Kennedy classes of RPDs.