Clinical Protocol

205202

CONFIDENTIAL

SUMMARY INFORMATION

Title:	A Method Development Clinical Study to Investigate the Efficacy of the Different Frequencies of Use of a Denture Cleanser
Protocol Number:	205202
Sponsor:	GlaxoSmithKline Consumer Healthcare (GSKCH)
Product Name:	Corega® Tabs Dental Weiss für Raucher
Development Phase:	N/A

Expert Advice Outside of Normal Working Hours:	Tel: PPD
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PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current 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:	Douglas Robertson
Investigator Qualifications:	BDS (Hons), PhD, MFDS, RCS-Ed, ISFE, FHEA
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

Table of Content

PROCESS FOR AMENDING THE PROTOCOL

Protocol modifications to ongoing studies which could potentially adversely affect the safety of subjects or which alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or subject selection criteria are considered major/substantial amendments and must be made only after appropriate consultation between an appropriate representative of GSKCH and the investigator.

Details of amendments to the protocols should be recorded on the following page. Protocol modifications must be prepared by a representative of GSKCH. All changes must be justified in the Reason for Amendment section of the following Protocol Amendment Page. Approval of amendments will be made by the original protocol signatories or their appropriate designees.

All major/substantial protocol modifications must be reviewed and approved by the appropriate IEC in accordance with local requirements, before the revised edition can be implemented.

All non-substantial/ minor/ administrative amendments should be submitted to the IEC as per country specific requirements. In some countries pre-approval of a minor amendment is not required and will just be held on file by the sponsor and investigator.

PROTOCOL AMENDMENT PAGE

Details of all amendments should be recorded in the table below. Affected sections should be listed in the table; the actual amendment/ change should be made in the relevant section of the main protocol.
To highlight the change, the following features will be used:
To **add** text: Use of **CAPITAL LETTERS, BOLD AND UNDERLINE**
To **delete** text: Use of Strikethrough e.g. ~~strikethrough~~

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 1	Non-Substantial/Minor ☒	• Ethics committee did not provide permission to use the University of Glasgow Dental database to recruit subjects for the clinical study. Hence, this information has been removed from the protocol.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	• 3.3, Type and Planned Number of Subjects	Signature: PPD
Protocol Version No.: 3	Substantial/ Major ☐				Date: PPD
Amendment No.: 2	Non-Substantial/Minor ☒	• To change the size of the filter discs for the microbiological sampling from 13 mm to 10 mm to accommodate two filter discs in each quadrant for sampling.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	• 6.1.12, Microbiology Samples – Disc Sampling and Denture Sonicate	Signature: PPD
Protocol Version No.: 4	Substantial/ Major ☐				Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 3	Non-Substantial/Minor ☒	• To remove Exclusion Criteria 8 b as it is already covered in Exclusion Criteria 8 a. This will prevent the confusion which the site is experiencing with regards to Exclusion Criteria 8 b about pre-existing oral irritations.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☒ Yes ☐ No	• 4.2, Exclusion Criteria	Signature: PPD
Protocol Version No.: 5	Substantial/ Major ☐				Date: PPD
Amendment No.: 4	Non-Substantial/Minor ☒	• To add two additional examiners and change Biostatistician in the clinical study.	Informed Consent ☐ Yes ☒ No Safety Statement ☐ Yes ☒ No CRF ☐ Yes ☒ No	• Summary Information	Signature: PPD
Protocol Version No.: 6	Substantial/ Major ☐				Date: PPD

Amendment No. & New Protocol Version No.	Type of Amendment	Reason for Amendment	Other Documents Requiring Amendment	Section(s) Amended	PI Amendment Agreement Signature & Date
Amendment No.: 5	Non-Substantial/Minor ☒	• As the subject dropout has been lower than expected, 17 evaluable subjects would be achieved without the need to randomize to the full maximum of 20 randomised subjects. Therefore, rewording the appropriate sections to reflect this.	Informed Consent ☐ Yes ☒ No Safety Statement ☒ Yes ☐ No CRF ☐ Yes ☒ No	• Synopsis: Type and Planned Number of Subjects • 3.3, Type and Planned Number of Subjects • 9.1, Sample Size Determination	Signature: PPD
Protocol Version No.: 7	Substantial/ Major ☐				Date: PPD

SCHEDULE OF EVENTS

Procedure/ Assessment	Treatment Period 1								Wash-out Period between Treatment Schedules (7 ± 3 Days)	Treatment Period 2							
	Visit 1 Screening		Visit 2		Visit 3		Visit 4			Visit 5		Visit 6		Visit 7		Visit 8	
	Day -1		Day 0		Day 3 (Day 0 + 3d) [±1d]		Day 7 (Day 0+ 7d) [±1d]			Day -1		Day 0		Day 3 (Day 0 + 3d) [±1d]		Day 7 (Day 0+ 7d) [±1d]	
	Pre prophy	Post prophy	Baseline (Pre-trt)	Post trt	Pre trt	Post trt	Pre trt	Post trt		Pre prophy	Post prophy	Baseline (Pre trt)	Post trt	Pre trt	Post trt	Pre trt	Post trt
Informed consent	X																
Demographics	X																
Medical History	X																
Dental History	X																
Current/Concomitant medication	X		X		X		X			X		X		X		X	
Criteria for well made dentures	X																
Oral Soft Tissue (OST) examination – edentulous	X[1]		X[2]		X[2]		X[2]			X[1]		X[2]		X[2]		X[2]	
Denture Bearing Tissue Score	X																
Denture Retention and Stability Assessment	X																
Inclusion /Exclusion Criteria	X																
Subject Eligibility	X																
Subject Adherence			X		X		X			X		X		X		X	
Subject Assessment Questionnaire (SAQ)	X						X	X		X						X	X
Stain Assessment	X	X	X		X		X	X		X	X	X		X		X	X
Plaque assessment	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

Procedure/ Assessment	Treatment Period 1								Wash-out Period between Treatment Schedules (7 ± 3 Days)	Treatment Period 2							
	Visit 1 Screening		Visit 2		Visit 3		Visit 4			Visit 5		Visit 6		Visit 7		Visit 8	
	Day -1		Day 0		Day 3 [±1d]		Day 7 [±1d]			Day -1		Day 0		Day 3 [±1d]		Day 7 [±1d]	
	Pre prophy	Post prophy	Baseline (Pre-trt)	Post trt	Pre trt	Post trt	Pre trt	Post trt		Pre prophy	Post prophy	Baseline (Pre trt)	Post trt	Pre trt	Post trt	Baseline (Pre-trt)	Post trt
Microbiology Sample (Disc Sampling)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Microbiology Sample (Denture Sonicate)	X							X		X							X
Denture Prophylaxis & Dental Prophylaxis (if applicable)	X							X[3]		X							X[3]
Dispense Diary Card		X									X						
Return Diary Card			X[4]		X[4]		X					X[4]		X[4]		X	
Compliance check					X		X							X		X	
Treatment Randomisation			X														
Dispense Treatment / Supplies[5]			X									X					
Return Treatment/ Supplies[5]					X[6]		X							X[6]		X	
Supervised Product Use[7]			X		X		X					X		X		X	
Adverse Events		X[8]	X		X		X			X		X		X		X	
Incidents			X		X		X			X		X		X		X	
Study Conclusion/ Medical Sign-off																	X

[1] OST is performed pre-prophylaxis.
[2] OST is performed pre-treatment.
[3] Final Prophylaxis/cleaning of dentures and teeth (if applicable) to remove stains and build up, post all assessments and questionnaire.
[4] Diary card brought back to the site for compliance check.
[5] Study treatment/ supplies will include the assigned treatment product ,denture brush, measuring cylinder and timer.
[6] Study treatment/ supplies brought to the site for compliance check and supervised product use.
[7] For treatment period where subject is randomised to a weekly use, the supervised product use on Day 0 and Day 3 will be using water. The denture cleanser will only be used on Day 7.
[8] Adverse events will be collected from prophylaxis at the Screening visit.

PROTOCOL SYNOPSIS FOR STUDY 205202

Brief Summary

The study will investigate the changes in levels of plaque, stain, microbial counts and composition on the maxillary dentures after daily denture cleaning versus weekly cleaning.

This study will be conducted at the University of Glasgow Dental School, Glasgow, UK under the direction of the Principal Investigator Douglas Robertson and funded by GlaxoSmithKline Consumer Healthcare (GSK CH).

Objectives and Endpoints

Primary Objective	**Endpoint**
• To evaluate and compare the microbial count from Denture Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 7.	• Change from baseline (Day 0 pre-treatment) in Microbial count on Day 7 (post-treatment) from disc samples
Secondary Objective	**Endpoint**
• To evaluate and compare the microbial count from the Denture Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 3.	• Change from baseline (pre-treatment) in Microbial count on Day 3 (post-treatment) from disc samples
Exploratory Objectives	**Endpoints**
• To evaluate and compare the microbial count from the Denture Sonicate following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 7.	• Microbial count on Day 7 (post-treatment) from Denture Sonicate
• To evaluate and compare plaque levels following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from baseline (Day 0 pre-treatment) in plaque levels on Day 7 (post-treatment) • Change from baseline (Day 0 pre-treatment) in plaque levels on Day 3 (post-treatment)

• To evaluate and compare the microbial composition from the Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from Baseline (Day 0 pre-treatment) in Microbial composition on Day 7 (post-treatment) • Change from Baseline (Day 0 pre-treatment) in Microbial composition on Day 3 (post-treatment)
• To evaluate and compare stain levels on the maxillary denture following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from Baseline (Day 0 pre-treatment) in stain levels on Day 7 (post-treatment) • Change from Baseline (Day 0 pre-treatment) in stain levels on Day 3 (post-treatment)
• To evaluate and compare the subject assessment questionnaire following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from pre-prophylaxis (Day -1) in Subject assessment questionnaire on Day 7 (post-treatment)

Study Design

Overall Design
This is a single-center, 2 treatment period, examiner-blind, randomised, 7 day crossover study in adult volunteers with a complete maxillary denture. This is a method development study to investigate the changes in the level of denture plaque, microbial counts, microbial composition and stain on the maxillary dentures after daily denture cleanser use versus dentures that are cleaned weekly.
Screening (Visit 1):
The following assessments will be conducted: • Written informed consent • Demographics • Medical history • Dental History • Current and concomitant medications • Criteria for well made dentures • Oral Soft Tissue (OST) Examination – Edentulous • Denture Bearing Tissue Score • Denture Retention and Stability Assessment • Inclusion/ Exclusion Criteria

- Subject Eligibility
- Pre-prophylaxis measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
  - Microbiology Sample (Denture Sonicate)
- Denture Prophylaxis & Dental Prophylaxis (if applicable)
- Post-prophylaxis measures
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event Check
- Dispense Diary Card

Treatment Period 1 (Visit 2) & Treatment Period 2 (Visit 6): Day 0

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Pre-treatment measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Treatment Randomisation (Visit 2 Only)
- Dispense Treatment Product/ Supplies
- Supervised Product Use
- Post-treatment measures:
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event and Incident Check

Treatment Period 1 (Visit 3) & Treatment Period 2 (Visit 7): Day 3

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Return Treatment Product/ Supplies
- Compliance Check including Diary Card
- Pre-treatment measures:

- Stain Assessment
- Plaque Assessment
- Microbiology Sample (Disc Sampling)

- Supervised Product Use
- Post-treatment measures:
  - Plaque Assessment Post-Treatment
  - Microbiology Sample (Disc Sampling) Post-Treatment
- Adverse Event and Incident Check
- Re-dispense Treatment Product/ Supplies and Diary Card

Treatment Period 1 (Visit 4) & Treatment Period 2 (Visit 8): Day 7 and LSLV

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Return Treatment Product/ Supplies
- Compliance Check including Diary Card
- Pre-treatment measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Supervised Product Use
- Post-treatment measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
  - Microbiology Sample (Denture Sonicate)
- Adverse Event and Incident Check
- Denture Prophylaxis & Dental Prophylaxis (if applicable)

LSLV:

- Study Conclusion/ Medical Sign-off

Treatment Period 2 (Visit 5): Day -1

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence

- OST examination – Edentulous
- Pre-prophylaxis measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
  - Microbiology Sample (Denture Sonicate)
- Denture Prophylaxis & Dental Prophylaxis (if applicable)
- Post-prophylaxis measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event and Incident Check
- Dispense Diary Card

Type and Planned Number of Subjects

Approximately 30 healthy subjects will be screened to randomise ~~at least~~ **APPROXIMATELY** 20 subjects to ensure 17 evaluable subjects complete the entire study. This will ensure approximately 17 evaluable subjects per treatment arm with the cross over design.

Diagnosis and Main Criteria for Inclusion

Healthy male and female subjects between 18 years and 84 years of age. Subjects must have a completely edentulous maxilla restored with well to moderately well fitting and well made conventional full maxillary denture.

Product Information

	Test Product 1 Daily use period Treatment Regimen 1	Test Product 2 Weekly use period Treatment Regimen 2
Product Name	Corega® Tabs Dental Weiss für Raucher German Marketed Product	Corega® Tabs Dental Weiss für Raucher German Marketed Product
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]
Dose	1 tablet per day.	1 tablet on Day 7 at the clinic.
Route of Administration	N/A	N/A
Dosing Instructions	**Supervised product use at site:** Soak dentures in cup of very warm water (150 millilitre [ml]) with 1 tablet for 15 minutes (mins). Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. **Home use:** *In the evening*: ○ **Upper arch:** Soak dentures in cup of very warm water (150 ml) with 1 tablet for 15 mins. Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. Overnight soak in 150 ml of water.	**Supervised product use at site:** Soak dentures in cup of very warm water (150 ml) with 1 tablet for 15 mins. Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. **Home use:** *In the evening*: ○ **Upper arch:** Soak dentures in cup of very warm water (150 ml) for 15 mins. Brush dentures for 30 seconds using the water, rinse under running water for 10 seconds in the evening. Overnight soak in 150 ml of water.

	○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted). If the subjects have lower removable partial or complete dentures, the soaking of these dentures should be done in a separate cup from the cup provided for soaking the upper denture. *In the morning*: ○ **Upper arch:** Cleaning of the upper denture is not permitted. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted).	○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted). If the subjects have lower removable partial or complete dentures, the soaking of these dentures should be done in a separate cup from the cup provided for soaking the upper denture. *In the morning*: ○ **Upper arch:** Cleaning of the upper denture is not permitted. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted).

Other items to be supplied by the Clinical Supplies Department, GSKCH:

Name of Item	Purpose
Denture bath	Cleaning dentures
Denture brush	Cleaning dentures
Measuring cylinder	Measure water for soaking dentures
Countdown timer	Timing soaking dentures and brushing dentures

Statistical Methods

Summary statistics of number of subjects, mean, standard deviation, median, minimum and maximum will be displayed where the variable is continuous and counts and percentages where the variable is categorical. Summaries will be split by study visit and treatment procedure.

Though this study is not powered to detect any treatment differences an analysis of covariance (ANCOVA) model will be used to check whether there is any difference between the two treatment procedures. Changes from baseline (pre-treatment assessment on Day 0) in stain, plaque and microbial count (from disc sampling and disc sonication) assessments will be calculated and analysed using an ANCOVA model with treatment and period as factors and subject-level and period-level pre-treatment (on Day 0) baseline scores as covariates. To allow model estimates to be representative of the studied population, subject will be included into the model as a random effect. Microbial count will be log transformed (log 10 scale) before analysis.

Post treatment denture sonication samples will be analysed using an analysis of variance model with post-treatment values on day 7 as response variable and treatment, period and subject (random effect) as factors.

All analyses described above will be carried out separately at Day 0, 4 and 7, apart from denture sonication sample analysis that will be carried out only at day 7. Model assumptions will be investigated and if violated then the non-parametric Wilcoxon Signed rank test will be used to investigate any treatment differences.

Repeatability assessments will be performed on all subjects for plaque and stain. A kappa statistics will be calculated to assess intra-examiner repeatability.

Simple summary statistics of number of subjects, mean, standard deviation, minimum and maximum by treatment procedure will be provided for the most important 10 molecular species. Counts and percentages by treatment will be used to summarize the subject assessment questionnaire data.

1. INTRODUCTION

Prosthetic rehabilitation using removable full dentures is a treatment option for the fully edentulous patients. Dentures are removable prosthetic devices constructed with materials such as acrylic, porcelain or various types of metals. They are constructed to fit over the remaining edentulous arch to replace missing teeth.

It is known that some Dental health professionals (DHPs) do not recommend daily use of denture cleansers ([redacted], however only a small body of evidence exists to promote the use of denture cleansing using specialized products (Axe *et al*., 2016). Without regular cleaning, denture biofilms can build up and can lead to bad breath and oral candidiasis. There has also been research published where this has also been associated with other serious health conditions such as pneumonia (Azarpazhooh and Leak, 2006).

This method development study will be a two treatment arm, randomised, cross over study in a population with edentulous upper arch restored with a maxillary complete denture. The lower may be a partial or fully edentulous mandibular arch that may be restored with a stable complete, partial or implant supported denture. All assessments will be made on the upper complete denture.

The denture cleansing product to be used in this study will be the Germany marketed product Corega® Dental Weiss für Raucher (Corega® Denture Whitening for Smoker). Subjects will be randomised to a daily or a weekly denture cleansing treatment regimen.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoint
• To evaluate and compare the microbial count from Denture Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 7.	• Change from baseline (Day 0 pre-treatment) in Microbial count on Day 7 (post-treatment) from disc samples
Secondary Objective	**Endpoint**
• To evaluate and compare the microbial count from the Denture Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 3.	• Change from baseline (pre-treatment) in Microbial count on Day 3 (post-treatment) from disc samples
Exploratory Objectives	**Endpoints**
• To evaluate and compare the microbial count from the Denture Sonicate following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 7.	• Microbial count on Day 7 (post-treatment) from Denture Sonicate
• To evaluate and compare plaque levels following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from baseline (Day 0 pre-treatment) in plaque levels on Day 7 (post-treatment) • Change from baseline (Day 0 pre-treatment) in plaque levels on Day 3 (post-treatment)
• To evaluate and compare the microbial composition from the Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from Baseline (Day 0 pre-treatment) in Microbial composition on Day 7 (post-treatment) • Change from Baseline (Day 0 pre-treatment) in Microbial composition on Day 3 (post-treatment)
• To evaluate and compare stain levels on the maxillary denture following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from Baseline (Day 0 pre-treatment) in stain levels on Day 7 (post-treatment) • Change from Baseline (Day 0 pre-treatment) in stain levels on Day 3 (post-treatment)

• To evaluate and compare the subject assessment questionnaire following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from pre-prophylaxis (Day -1) in Subject assessment questionnaire on Day 7 (post-treatment)

3. STUDY PLAN

3.1. Study Design

Overall Design
This is a single-center, 2 treatment period, examiner-blind, randomised, 7 day crossover study in adult volunteers with a complete maxillary denture. This is a method development study to investigate the changes in the level of denture plaque, microbial counts, microbial composition and stain on the maxillary dentures after daily denture cleanser use versus dentures that are cleaned weekly.
Screening (Visit 1):

The following assessments will be conducted:
• Written informed consent
• Demographics
• Medical history
• Dental History
• Current and concomitant medications
• Criteria for well made dentures
• Oral Soft Tissue (OST) Examination – Edentulous
• Denture Bearing Tissue Score
• Denture Retention and Stability Assessment
• Inclusion/ Exclusion Criteria
• Subject Eligibility
• Pre-prophylaxis measures:
  ○ Subject Assessment Questionnaire (SAQ)
  ○ Stain Assessment
  ○ Plaque Assessment
  ○ Microbiology Sample (Disc Sampling)
  ○ Microbiology Sample (Denture Sonicate)
• Denture Prophylaxis & Dental Prophylaxis (if applicable)
• Post-prophylaxis measures
  ○ Stain Assessment
  ○ Plaque Assessment

- Microbiology Sample (Disc Sampling)
- Adverse Event Check
- Dispense Diary Card

Treatment Period 1 (Visit 2) & Treatment Period 2 (Visit 6): Day 0

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Pre-treatment measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Treatment Randomisation (Visit 2 Only)
- Dispense Treatment Product/ Supplies
- Supervised Product Use
- Post-treatment measures:
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event and Incident Check

Treatment Period 1 (Visit 3) & Treatment Period 2 (Visit 7): Day 3

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Return Treatment Product/ Supplies
- Compliance Check including Diary Card
- Pre-treatment measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Supervised Product Use
- Post-treatment measures:
  - Plaque Assessment Post-Treatment
  - Microbiology Sample (Disc Sampling) Post-Treatment
- Adverse Event and Incident Check
- Re-dispense Treatment Product/ Supplies and Diary Card

Treatment Period 1 (Visit 4) & Treatment Period 2 (Visit 8): Day 7 and LSLV

The following assessments will be conducted:
• Current and Concomitant Medications
• Subject Adherence
• OST examination – Edentulous
• Return Treatment Product/ Supplies
• Compliance Check including Diary Card
• Pre-treatment measures:
  ○ Subject Assessment Questionnaire (SAQ)
  ○ Stain Assessment
  ○ Plaque Assessment
  ○ Microbiology Sample (Disc Sampling)
• Supervised Product Use
• Post-treatment measures:
  ○ Subject Assessment Questionnaire (SAQ)
  ○ Stain Assessment
  ○ Plaque Assessment
  ○ Microbiology Sample (Disc Sampling)
  ○ Microbiology Sample (Denture Sonicate)
• Adverse Event and Incident Check
• Denture Prophylaxis & Dental Prophylaxis (if applicable)
 	
LSLV:
• Study Conclusion/ Medical Sign-off

Treatment Period 2 (Visit 5): Day -1

The following assessments will be conducted:
• Current and Concomitant Medications
• Subject Adherence
• OST examination – Edentulous
• Pre-prophylaxis measures:
  ○ Subject Assessment Questionnaire (SAQ)
  ○ Stain Assessment
  ○ Plaque Assessment
  ○ Microbiology Sample (Disc Sampling)
  ○ Microbiology Sample (Denture Sonicate)
• Denture Prophylaxis & Dental Prophylaxis (if applicable)
• Post-prophylaxis measures:
  ○ Stain Assessment

- Plaque Assessment
- Microbiology Sample (Disc Sampling)

- Adverse Event and Incident Check
- Dispense Diary Card

3.2. Subject Restrictions

Lifestyle/ Dietary
During the entire study (Screening – LSLV): • Subjects should not use any denture adhesive products during the course of the study. • Subjects must refrain from denture hygiene with the exception of the allocated treatment and instructions for use. • Subjects will only be allowed to use the study products provided to clean their dentures. Other normal oral hygiene routine can continue during the study eg. brushing the natural teeth if present. • Subjects must refrain from using any mouthwash. • Refrain from use of xylitol containing, or 'oral care' type chewing gums or confectionary.
Medications and Treatments
During the entire study (Screening – LSLV): • Subjects should not use any medication described in Exclusion Criteria. • Current concomitant medications will be recorded and are allowed, if judged to be non-interfering by the Investigator. If, for unforeseen reasons, a subject begins therapy with excluded medications during the treatment phase of the study, the medication, dosage and duration of therapy will be recorded in the case report form (CRF). The investigator and sponsor will confer as to the subject's continued eligibility based on the expected clinical course of the condition being treated.

3.3. Type and Planned Number of Subjects

Due to lack of appropriate data it was not possible to perform a formal sample size calculation. A total of 17 subjects was considered sufficient to assess the efficacy and safety of the treatments under investigation. Confidence intervals will be provided to aid precision of treatment estimate.

Approximately 30 healthy subjects will be screened to randomise ~~at least~~ **APPROXIMATELY** 20 subjects to ensure 17 evaluable subjects complete the entire

study. This will ensure approximately 17 evaluable subjects per treatment arm with the cross over design.

~~Subjects will be recruited from the University of Glasgow Dental School database.~~

3.4. Study Design and Dose Justification

This is a single-center, 2 period, examiner-blind, randomised, 7 day crossover study in adult volunteers with a complete maxillary denture. This is a method development study to investigate the changes in the level of denture plaque, microbial counts, microbial composition and stain on the maxillary dentures after daily denture cleanser use versus dentures that are cleaned weekly.

Complete upper denture wearers were chosen because of the large area required for taking microbiology samples.

At Visit 1 Screening, subjects will provide written informed consent and establish eligibility. The quality of the maxillary dentures including denture retention and stability will be assessed. Subjects should have a well made and moderately well-fitting maxillary complete denture to be included in the study. The denture bearing tissue surface will also be assessed to ascertain if the subjects are eligible for the study. Subjects with lower partial or fully edentulous mandibular arch that has been restored with a stable complete, partial or implant supported denture can be included in the study but only maxillary dentures will be assessed in the study.

All subjects will have a pre-baseline microbiology samples, plaque and stain assessments done prior to denture prophylaxis. This will give information about the condition of the dentures generally. Baseline microbiology samples, plaque and stain assessments will be done on prior to treatment on Day 0. The prophylaxis performed will give a more level baseline for all subjects, to allow treatment comparisons. The schedule of assessments and samples are provided in the Schedule of Events table. Denture prophylaxis of the maxillary complete denture is performed at the Screening Visit, Visit 4, Visit 5 and Visit 8. Denture prophylaxis is performed to remove all the denture plaque, food particles and stain on the maxillary dentures and mandibular dentures (if present) according to the standard denture prophylaxis procedure used at the site to ensure zero plaque and stain. Zero plaque and stain will be confirmed by the post-prophylaxis stain and plaque assessments. If residual plaque or stain is present, then this will be removed by the investigator or examiner until zero plaque or stain is achieved.

Denture prophylaxis of the mandibular complete or partial dentures, if present, will be performed at the Screening Visit, Visit 4, Visit 5 and Visit 8 according to the standard denture prophylaxis procedure used at the site. Dental prophylaxis of the mandibular

teeth, if present, will also be performed at the Screening Visit, Visit 4, Visit 5 and Visit 8 according to the standard dental prophylaxis procedure used at the site.

Subjects will return for sampling and assessments on Day 0 (Visit 2 & Visit 6), Day 3 (Visit 3 & Visit 7) and Day 7 (Visit 4 & Visit 8) as indicated in Schedule of Events table.

Within each treatment period, first treatment will occur on Day 0 (Visit 2 and Visit 6). Pre-Treatment and Post-Treatment samples and assessments will be performed as per Schedule of Events table to understand the build-up of the microbiota, plaque and stain before treatment and the removal of the microbiota, plaque and stain after the treatment.

An OST Examination is performed at the beginning of study Visits 1, 2, 3, 4, 5, 6, 7 and 8.

Microbiology samples (Disc sampling [rough and smooth surfaces of the tissue fitting surface of the maxillary denture] and Denture Sonicate) will be taken immediately prior to treatment and after treatment, to achieve data on the increase in bacterial and/or fungal loads between cleaning and the effect of the treatment and to compare the two treatment arms. Subjects will cleanse their dentures in the same way, on each day as instructed in the Product Information section. The tissue fitting surface will be used for taking microbiology samples (Blair *et al*., 1995). This is the more critical surface with regards to microbial load and its effect on the tissues. Microbiology samples will be analyzed by standard plate counting, Miles and Misra, 1938; to evaluate the microbial load before and after use of the denture cleanser treatment regimens. The microbiology samples will also be used to analyze the microbial composition using Microbiome analysis (Caporaso *et al.,* 2011).

Two disc samples each from both the rough and smooth surfaces of the tissue fitting surface of the maxillary denture will be taken pre-prophylaxis/ post-prophylaxis and pre-treatment/ post-treatment as described in the study assessment/ procedure section.

Dentures can accumulate plaque and stain over time. Stain on the surfaces of the denture including the teeth will be assessed by modification of the Denture Cleanser Index (Mylonas *et al.,* 2014) before and after use of the denture cleanser treatment regimens. The plaque on the denture will be measured by assessing the surfaces of the denture including the teeth using the modification of the Clinical Categorization of Denture Cleanliness Index (Blair *et al.,* 1995).

The subjects will also complete a consumer perception questionnaire (Subject Assessment Questionnaire [SAQ]) to check for themselves what they feel about their

maxillary dentures with respect to freshness, cleanliness etc. before and after they have cleaned their dentures as per the two treatment regimens. Subjects will be asked the questionnaire pre-baseline, before denture prophylaxis on Day -1 (Visit 1 & Visit 5) to understand the condition of the denture generally from the subjects' perspective. The questionnaire will also be done before supervised product use on Day 7 (Visit 4 & Visit 8) to understand the consumer perception of their dentures after they cleaned their dentures daily with the denture cleanser or water. The questionnaire will be done after supervised product use on Day 7 (Visit 4 & Visit 8) to evaluate the consumer perception of their dentures after the denture has been cleaned daily with a denture cleanser for a week or cleaned once a week with a denture cleanser (Day 7 supervised product use).

The study is a crossover design which allows each subject to act as their own control. There will be a 7 day wash-out period between the treatment schedules to minimise any carry over effects from the previous treatment. During the wash-out period, subjects are allowed to revert back to their normal denture and oral hygiene procedures.

A single centre study has been chosen. In line with the International Conference on Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, for a study to be classed as truly double blind, not only does the examiner (and any appropriate member of staff who may be involved in treatment dispensing, analysis of data etc.) need to be blinded as to the treatment the subject receives, but the treatments under investigation must be identical in every way (color, flavor, appearance, packaging). The level of blindness by GSKCH for this study is described as 'examiner blind'. The study will be blinded with respect to the dental examiner to ensure there is no bias in the assessments. Subjects will be instructed not to discuss their treatment with the examiner.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Safety Statement.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or

subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. CONSENT
Demonstrates understanding of the study procedures, restrictions and willingness to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the informed consent form.

2. AGE
Aged between 18 and 84 years inclusive.

3. GENERAL HEALTH
Good general and mental health with, in the opinion of the investigator or medically qualified designee: a) No clinically significant and relevant abnormalities in medical history or upon oral examination. b) Absence of any condition that could affect the subject's safety or wellbeing or their ability to understand and follow study procedures and requirements.

4. DENTAL HEALTH
a) Maxillary Arch: Completely edentulous maxillary arch restored with a conventional full acrylic based upper complete denture. b) Mandibular Arch: Dentate, partial or full edentulous mandibular arch. Partial or full edentulous arch may be restored with a stable complete, partial or implant supported denture. (Mandibular dentures are not used for assessments or measures). c) Maxillary dentures must be considered to be moderately well-fitting at the screening visit. (Kapur Index, Olshan Modification: retention score $\geq$2, stability score $\geq$2). d) Maxillary dentures must be considered to be well-made based on design and construction criteria specified in the protocol.

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. PREGNANCY
Women who are known to be pregnant or who are intending to become pregnant over the duration of the study.

2. BREAST-FEEDING
Women who are breast-feeding

3. ALLERGY/ INTOLERANCE
Known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.

4. CLINICAL STUDY/ EXPERMENTAL PRODUCT
a) Participation in another clinical study (including cosmetic studies) or receipt of an investigational drug within 30 days of the screening visit. b) Previous participation in this study.

5. SUBSTANCE ABUSE
Recent history (within the last year) of alcohol or other substance abuse.

6. PERSONNEL
a) An employee of the sponsor or the study site or members of their immediate family. b) An employee of any toothpaste manufacturer or their immediate family.

7. CONCURRENT MEDICATION/ MEDICAL HISTORY
Medical History a) Current or relevant history of any serious, severe or unstable physical or psychiatric illness or any other medical condition (e.g. Diabetes Mellitus) that would make the subject unlikely to fully complete the study or any that increases the risk to the subject or undermines the data validity. b) Implanted with a cardiac pacemaker. c) Daily doses of medication (E.g. Antibiotics, Inhaled steroids etc.) that might interfere with ability to perform the study according to protocol or might affect the efficacy assessments (as determined by the Investigator/ Examiner).

8. DENTAL HEALTH
a) Any clinically significant or relevant oral abnormality that, in the opinion of the investigator, could affect the subject's participation in the study. ~~b) Any pre-existing oral irritations.~~ c) Any recent (within 30 days) gingival /oral surgery.

9. TOBACCO USERS INCLUDING E-CIGARETTES
Subjects who are unwilling to refrain from smoking, including e-cigarettes and the use of chewing tobacco or other tobacco products for the duration of the study.

4.3. Screening/ Baseline Failures

Screen failures are defined as subjects who consent to participate in the study but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events. Re-screening of subjects will not be allowed in this study.

4.4. Withdrawal/ Stopping Criteria

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws or is withdrawn from the study, all human biological samples collected before they left will be analyzed and reported unless the subject requests otherwise. A subject may request for their human biological samples to be destroyed. In these cases, the investigator/ examiner must document this in the site study records and the samples should not be used for any further research.

If the reason for removal of a subject from the study is an Adverse Event (AE) or an abnormal laboratory test result, the principal specific event or test will be recorded on the electronic case report form (eCRF). If a subject is withdrawn from the study because of a product limiting AE, thorough efforts should be clearly made to document the outcome. Any AEs ongoing at the final visit will be followed up until resolved, the condition stabilizes, is otherwise explained, or the subject is lost to follow-up.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, up to 2 telephone calls). The contact attempt should be documented in the subject's record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

4.5. Subject Replacement

Subjects who withdraw from the study post-randomisation will not be replaced.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study.

The end of the study is defined as the date of the last data in house (with the sponsor).

5. PRODUCT INFORMATION

5.1. Study Product

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

	Test Product 1 Daily use period Treatment Regimen 1	Test Product 2 Weekly use period Treatment Regimen 2
Product Name	Corega® Tabs Dental Weiss für Raucher German Marketed Product	Corega® Tabs Dental Weiss für Raucher German Marketed Product
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]
Dose	1 tablet per day.	1 tablet on Day 7 at the clinic.
Route of Administration	N/A	N/A
Dosing Instructions	**Supervised product use at site:** Soak dentures in cup of very warm water (150 millilitre [ml]) with 1 tablet for 15 minutes (mins). Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. **Home use:** *In the evening*: ○ **Upper arch:** Soak dentures in cup of very warm water (150 ml) with 1 tablet for 15 mins. Brush	**Supervised product use at site:** Soak dentures in cup of very warm water (150 ml) with 1 tablet for 15 mins. Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. **Home use:** *In the evening*: ○ **Upper arch:** Soak dentures in cup of very warm water (150 ml) for 15 mins. Brush dentures for 30

	dentures for 30 seconds using the solution, rinse under running water for 10 seconds. Overnight soak in 150 ml of water. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted). If the subjects have lower removable partial or complete dentures, the soaking of these dentures should be done in a separate cup from the cup provided for soaking the upper denture. *In the morning*: ○ **Upper arch:** Cleaning of the upper denture is not permitted. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted).	seconds using the water, rinse under running water for 10 seconds in the evening. Overnight soak in 150 ml of water. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted). If the subjects have lower removable partial or complete dentures, the soaking of these dentures should be done in a separate cup from the cup provided for soaking the upper denture. *In the morning*: ○ **Upper arch:** Cleaning of the upper denture is not permitted. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted).

Other items to be supplied by the Clinical Supplies Department, GSKCH:

Name of Item	Purpose
Denture bath	Cleaning dentures
Denture brush	Cleaning dentures
Measuring cylinder	Measure water for soaking dentures
Countdown timer	Timing soaking dentures and brushing dentures

5.2. Dose Schedule

Subjects will use their assigned treatment regimens three times at the site under study staff supervision – once each on Day 0, Day 3 and Day 7. Refer to Dosing Instructions in Table 5.1 for more detail.

Product use at home

Subjects will be instructed to clean their dentures using their assigned treatment regimen once in the evening. On Treatment Days 0 and 3, subjects will be instructed not to use their treatment regimen again that evening. Refer to Dosing Instructions in Table 5.1 for more detail.

5.3. Dose Modification

No dose modification is permitted in this study.

5.4. Product Compliance

First study product use will be supervised by the site staff at the baseline visit (Day 0) to facilitate compliance and understand how to use the product. Subjects will record each product use in the diary provided.

Completed diaries and the denture cleanser tablets provided to the subjects will be reviewed at Visits 3 and 7 (Day 3); and Visits 4 and 8 (Day 7) at the study site. Refer to Dosing Instructions in Table 5.1 for more detail. Any missed and additional denture cleansing will be recorded in the CRF. Changes in the medical/dental history and medications will be documented.

5.5. Precautions

No special precautions are necessary provided the study is carried out in accordance with this protocol. Study products will be labelled “Exclusively for Clinical Investigation”.

5.6. Overdose

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

Overdose is not likely to occur in this study. Limited quantities of the product will be supplied, and closely monitored by the site for each subject.

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.

5.7. Rescue Therapy

No rescue therapy is required in this study.

5.8. Product Assignment

Subjects will be assigned to one of the study procedures (daily or weekly cleaning) in accordance with the randomisation schedule generated by the Biostatistics Department, GSKCH, prior to the start of the study, using validated internal software.

5.8.1 Randomisation

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomised according to the randomisation schedule. Randomisation numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible.

5.8.2 Blinding

The study statistician and other employees of the Sponsor who may influence study outcomes are blinded to the product allocation of subjects.

The examiner will be blinded to the treatment received. To ensure the examiner remains blinded throughout the study, the examiner will not be permitted in the room where the test products are stored or dispensed. The product dispensing area will be separate from the subjects' examination area. The dispensing staff will not be involved in any study efficacy assessments.

5.8.3 Code Breaks

The blind must only be broken in an emergency where it is essential to know which product a subject received in order to give the appropriate medical care. Wherever possible the Investigator (or designee) must contact the Sponsor prior to breaking the blind. The investigator must document the reason for breaking the code and sign and date the appropriate document.

The study blind must be returned to GSKCH at the end of the study.

5.9. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements and will be the responsibility of the Clinical Supplies Department, GSKCH.

The denture cleansing tablets will be supplied in their commercial blister packaging with a study label affixed. All sundry items will be supplied in their commercial packaging. Each subject will receive a labelled subject kit containing all the required items for the specific treatment period (except for measuring cylinders which will be supplied separately).

Each study label will contain, but not be limited to, protocol number, product code letter, directions for storage, emergency contact telephone number and a statement "Exclusively for Clinical Investigation".

All sundry items will be provided in their commercial packaging for dispensing by the study staff as and when required.

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.

5.9.1. Accountability of Product

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

The investigator or designee will maintain a full record of study product accountability. A Product Dispensing Log must be kept current and will contain the following information:

- The identification of the subject to whom the study product was dispensed.
- The date(s) and quantity of the study product dispensed to the subject.
- The date(s) and quantity of the study product returned by the subject (if applicable).

The inventory must be available for inspection by the study monitor during the study. At the end of the study, study product supplies will be verified by the monitor. Study product supplies will then be either collected by the study monitor or returned by the investigator or designee to the GSKCH Clinical Supplies Department or designated vendor.

5.9.2. Storage of Product

Study product supplies must be stored in compliance with the label requirements in a secure place with limited or controlled access.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. Each assessment is listed in the Schedule of Events section.

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

6.1. Visit 1 - Screening Visit

6.1.1 Screening

Prior to the screening visit, telephone screening of interested subjects will be conducted using a telephone script. This will be conducted by the site recruitment staff or designee.

6.1.2. Informed Consent

The investigator, or designee, must obtain written (signed and dated by the subject) informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

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 written consent will be provided by the investigator or by GSKCH. The investigator, or designee, should sign and date the consent form to confirm that the consent process was completed correctly. The subject, will be provided with a copy of their signed and dated consent form and any other written information which they should be instructed to retain.

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. Subjects or be provided with a copy of the signed and dated amended consent form. The date of consent will be recorded on the CRF.

6.1.3. Demographics

The following demographic parameters will be captured by the Investigator or designee and recorded on the CRF: year of birth, gender and race.

6.1.4. Medical History and Concomitant Medication

Medical history will be assessed as related to the inclusion/exclusion criteria by the Investigator or medically qualified designee. Details of any relevant medical or surgical history (within the last year), including allergies or drug sensitivity, will be recorded on the CRF. Any concomitant therapy taken in the 30 days prior to the Screening Visit and throughout the study will also be recorded.

6.1.5. Dental History

The Investigator, or medically qualified designee, will take a dental history from each subject and record it in the eCRF. Dental history will include information of all prostheses in the mouth, maxillary and mandibular, as well as information regarding the age of the dentures, and how long the subject has worn the dentures. Documentation of prosthetic teeth material will also be recorded by the Investigator in the eCRF.

6.1.6. Criteria for a Well-Made Denture

The examiner will examine each subject's maxillary complete denture to determine whether this is well made i.e.:

- Denture(s) has adequate vertical dimension, freeway space, horizontal occlusal relationships and border extension
- Denture(s) has acceptable contour and finish
- Denture(s) has acceptable porosity, tissue surfaces, polished surfaces, color and thickness.

For each maxillary complete denture, the examiner will identify from what material it is made and indicate acceptable or unacceptable on the eCRF.

6.1.7. Denture Bearing Tissue Score

The denture bearing tissue score (Kapur 1967) will be recorded for the maxillary arch only.

* Note, for completeness, the entire index (for maxillary and mandibular arches) is presented below. Due to an inconsistency observed in the original printed publication, the two descriptors below marked by an asterisk (*) have been modified (by inverting their order) to better reflect the authors intent and align with the grading scale.

Ridge Shape (for both Maxillary and Mandibular)

1= Flat
2= V-shaped
3= Shaped between U and V
4= U shaped

Tissue Resiliency (for both Maxillary and Mandibular)

1= Flabby
2= Resilient
3= Firm

Location of Border Tissue Attachment

Maxillary Arch		Mandibular Arch	
1=	Low	1=	High
2=	Medium	2=	Medium *
3=	High	3=	Low *

6.1.8. Kapur (Olshan Modification) Denture Retention and Stability Assessment

At the screening visit, the examiner will determine the subject's denture retention and stability score and recorded.

Retention Criteria

With gloved hands, the examiner will attempt to unseat the maxillary complete denture by applying an opposing vertical force at the canine/lateral incisor region of the denture. The examiner will score **retention** as 0 - 5 using the following criteria:

5= Excellent- denture offers excellent resistance to vertical pull and lateral force

4= Very Good- denture offers very good resistance to vertical pull and lateral force

3= Good- denture offers moderate resistance to vertical pull and lateral force

2= Fair- denture offers moderate resistance to vertical pull and little or no resistance to lateral forces

1= Poor- denture offers slight resistance to vertical pull and little or no resistance to lateral force

0= No retention- when the denture is seated in place, it displaces itself

Stability Criteria

With gloved hands, the examiner will attempt to rock the seated dentures by placing alternate horizontal force at the cuspid and contralateral molar regions of the maxillary complete dentures. The examiner will score denture stability as 0 – 4 using the following criteria:

4= Excellent- when denture base offers no rocking on its supporting structures under pressure

3= Good- when denture base has very slight rocking on its supporting structures under pressure

2= Fair- when denture base has slight rocking on its supporting structures under pressure

1= Poor- when denture base has moderate rocking on its supporting structures under pressure

0= No stability- when denture base has extreme rocking under pressure

6.1.9. Oral Soft Tissue Examination - Edentulous

The OST Exam-Edentulous will include the maxillary mucogingival fold, maxillary edentulous gingival mucosa, maxillary hard palate, mandibular mucogingival fold, mandibular edentulous gingival mucosa (if applicable), gingival mucosa (if applicable), labial mucosa (including lips), buccal mucosa, tongue, sublingual area, soft palate, submandibular area, salivary glands, tonsilar and pharyngeal areas. Observations will be made of any erythema, desquamation and ulcerations, and other relevant clinical observations. The results of the examination will be recorded in the CRF as either normal or abnormal. The location and brief description of any abnormalities will also be recorded.

A single examiner should complete this assessment for all the subjects. If this is not possible, then the same examiner should perform this procedure for the same subject for all the visits.

6.1.10. Denture Prophylaxis and Dental Prophylaxis

Denture prophylaxis of the maxillary complete denture will be performed according to the standard denture prophylaxis procedure used at the site to ensure zero plaque and stain. Zero plaque and stain will be confirmed by the post-prophylaxis stain and plaque assessments. If residual plaque or stain is present, then this will be removed by the investigator or examiner until zero plaque or stain is achieved. Denture prophylaxis is performed at the Screening Visit, Visit 4, Visit 5 and Visit 8.

The denture prophylaxis will be performed on the maxillary complete dentures and if present, the partial or complete mandibular dentures.

Dental prophylaxis of the mandibular teeth, if present, will also be performed at the Screening Visit, Visit 4, Visit 5 and Visit 8 according to the standard dental prophylaxis procedure used at the site.

6.1.11. Subject Assessment Questionnaire (SAQ)

The Subject Assessment Questionnaire (SAQ) will be completed by the subject on Day -1 (Visit 1 & Visit 5) before prophylaxis. The SAQ will also be done on Day 7 (Visit 4 & Visit 8), before and after supervised product use. The SAQ will be done as described in Appendix 2.

6.1.12. Microbiology Samples – Disc Sampling and Denture Sonicate

Disc Sampling: The quadrants of the fitting surface of the maxillary denture will be sampled as described below. The selected areas will be lateral to the midline and corresponding to the palatal rugae. Where a relief chamber was present on the denture, it will be avoided during specimen collection.

Figure 1a.

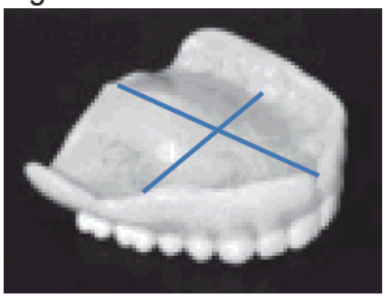
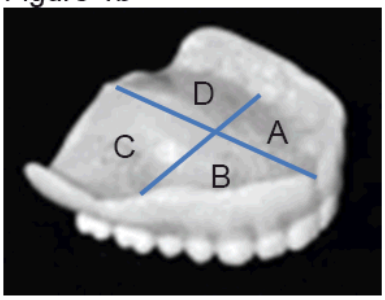


Figure 1b



The maxillary denture will be marked by the dental examiner using a denture marker (Fig 1a). The selected areas will be lateral to the midline and corresponding to the palatal rugae. Where a relief chamber was present on the denture, it will be avoided during specimen collection. Pre-prophylaxis and Pre-treatment samples will be taken from the left rough (A) and left smooth (D) denture surface (Fig 1b). Post-prophylaxis and post-treatment samples will be taken from the right rough (B) and right smooth (C) denture surface (Fig 1b).

A pre-sterilised **10**~~13~~mm filter paper disc (Whatman Grade 1, **SIGMA-ALDRICH COMPANY LTD., DORSET**~~Whatman Laboratory Division, Maidstone~~, England) is to be lightly pressed against the allocated quadrant, leaving enough space to place two discs without overlap. Microbiological sampling will be carried out from one standardised site on the fitting surface of the denture for standard culture (Miles and Misra, 1938). The disc will be left for 20 sec prior to aseptic removal using sterile tweezers, with one of the discs added to a bijoux tube containing 5 mL of saline solution and the other disc to a cryotube containing 1.5 mL of RNAlater®. At Visit 1 and Visit 5, the subjects will have pre- and post-prophylaxis samples taken. At Visits 2, 3, 4, 6, 7 and 8, the subjects will have pre- and post-treatment samples taken.

Denture Sonicate: On Day -1 (pre-prophylaxis) and Day 7 (post-treatment) for Treatment Schedules 1 and 2, following disc sampling, the maxillary denture will be placed in a sterile bag containing 50 mL saline solution. The bag will be placed in an ultrasonic bath and adherent organisms removed by mild sonication (35 Kilo Hz). The contents of the bag will then be poured into a 50mL tube. All biological samples will be placed in a sealed plastic container then transported to the category 2 microbiology laboratories of the dental school. All tubes will be anonymised and coded accordingly.

The samples will be taken and handled following the relevant laws or guidelines covering the collection, use, storage, transportation and disposal of human tissue and protection of data privacy [Human Tissue (Scotland) Act].

6.1.13. Denture Plaque Assessment

The denture plaque will be assessed on the fitting surface of the maxillary denture; the polished surfaces of the denture; and the teeth (Facial/ Buccal and Palatal) based on the modification of the Clinical Categorization of Denture Cleanliness Index, Blair *et al.,* 1995.

0	No visible plaque; no matter adherent to the side of the dental probe on light scraping
1	No visible plaque; matter adherent to the side of 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”)

6.1.14. Denture Stain Assessment

The subject’s maxillary denture will be assessed for stain on the fitting surface of the denture; the polished surfaces of the denture; and the teeth (Facial/ Buccal and Palatal) based on the modification of the Denture Cleanser Index, Mylonas *et al.,* 2014.

0	No staining detectable
1	Little staining (<25% of surface stained)
2	Moderate staining of surface (25-50% of surface stained)
3	Severe staining of surface (>50% of surface stained)

6.1.15. Examiner Repeatability Assessments

Data for Plaque assessments and Stain assessments will be taken from replicate examinations performed by the Examiners during the study. Depending on subject visit scheduling, every effort will be made to do repeatability examinations once during each treatment period for each subject, that is, one in Treatment Period 1 and one in Treatment Period 2. Repeatability examinations will have a minimum of 10 minutes between repeat of the same subject. In addition, every effort should be made to ensure that the examiner does not refer to the results of the prior assessment before conducting the repeat assessment. Intra-examiner repeatability will be assessed using a weighted kappa coefficient.

6.2. Treatment Period 1 (Visit 2) & Treatment Period 2 (Visit 6) - Baseline Visit Day 0

6.2.1. Oral Soft Tissue Examination - Edentulous

See Section 6.1.9.

6.2.2. Microbiology Samples – Disc Sampling

See Section 6.1.12 for Disc Sampling.

6.2.3. Denture Plaque Assessment

See Section 6.1.13.

6.2.4. Denture Stain Assessment

See Section 6.1.14.

6.3. Treatment Period 1(Visit 3) & Treatment Period 2 (Visit 6) – Day 3

6.3.1. Oral Soft Tissue Examination - Edentulous

See Section 6.1.9.

6.3.2. Microbiology Samples – Disc Sampling

See Section 6.1.12 for Disc Sampling.

6.3.3. Denture Plaque Assessment

See Section 6.1.13.

6.3.4. Denture Stain Assessment

See Section 6.1.14.

6.4. Treatment Period 1(Visit 4) & Treatment Period 2 (Visit 8) – Day 7 - Last Subject Last Visit (LSLV)

6.4.1. Oral Soft Tissue Examination - Edentulous

See Section 6.1.9.

6.4.2. Subject Assessment Questionnaire (SAQ)

See Section 6.1.11.

6.4.3. Microbiology Samples – Disc Sampling and Denture Sonicate

See Section 6.1.12 for Disc Sampling and Denture Sonicate.

6.4.4. Denture Plaque Assessment

See Section 6.1.13.

6.4.5. Denture Stain Assessment

See Section 6.1.14.

6.4.6. Denture Prophylaxis and Dental Prophylaxis

See Section 6.1.10.

6.4.6. Study Conclusion

Subjects will be evaluated to determine if they completed all study procedures or if they were discontinued from the study early. If the subject discontinued at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page of the CRF by selecting one of the options below.

1. Subject did not meet study criteria
2. Adverse Event
3. Lost to Follow Up
4. Protocol Violation
5. Withdrawal of Consent
6. Other

6.5. Treatment Period 2 (Visit 5) – Day -1

6.5.1. Oral Soft Tissue Examination - Edentulous

See Section 6.1.9.

6.5.2. Subject Assessment Questionnaire (SAQ)

See Section 6.1.11.

6.5.3. Microbiology Samples – Disc Sampling and Denture Sonicate

See Section 6.1.12 for Disc Sampling and Denture Sonicate.

6.5.4. Denture Plaque Assessment

See Section 6.1.13.

6.5.5. Denture Stain Assessment

See Section 6.1.14.

6.5.6. Denture Prophylaxis and Dental Prophylaxis

See Section 6.1.10.

6.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, must be conducted in accordance with the Laboratory Manual or according to the laboratory section of the Protocol, and Protocol Schedule of Events. Samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant or abnormal by the investigator (e.g., SAE or AE or dose modification or protocol deviations) the results must be recorded in the CRF. If the clinically significant abnormal lab is associated with a diagnosis, the diagnosis should be recorded on the CRF.

6.6.1. Microbiological Analysis

The disc bijoux samples will be immediately prepared for microbiological processing. The microbiological processing will be performed according to manuals and specifications at the University of Glasgow Dental School Oral Science Labs.

After the colonies have been counted and verified, the plates will be disposed of following the University of Glasgow Dental School Local Rules and Procedures for Safety.

6.6.2. Molecular Analysis

For molecular analysis, a targeted approach will be taken, looking at 8 important oral species: *Candida albicans, Streptococcus species, Actinomyces naeslundii, Veillonella dispar, Lactobacillus casei, Lactobacillus zeae, Rothia denticariosa, Fusobacterium nucleatum*. The molecular processing will be performed according to manuals and specifications at the University of Glasgow Dental School Oral Science Labs. The retention and destruction of all the samples upon completion of the study will be done following the University of Glasgow Dental School Local Rules and Procedures for Safety.

6.6.3. Microbiome Analysis

The microbiome analysis will be performed by Academisch Centrum Tanndheelkunde Amsterdam (ACTA), Amsterdam, Netherlands according to manuals and specifications at ACTA.

The retention and destruction of all the samples upon completion of the study will be done following the ACTA Local Rules and Procedures for Safety.

7. SAFETY ASSESSMENTS

7.1. Definitions of an Adverse Event and Serious Adverse Event

7.1.1. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the start of the denture and dental prophylaxis at the Screening Visit, whether or not considered related to the procedure. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated from the start of the denture and dental prophylaxis at the Screening Visit.

Events meeting AE definition include:
• Any abnormal laboratory test results (if applicable) or other safety

assessments, including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition(s) detected or diagnosed after study product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected 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).

Events NOT meeting definition of an AE include:

- 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/ condition 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): the condition that leads to the procedure is an AE.
- 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.

7.1.2. Serious Adverse Events

Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

A. Results in death

B. Is life-threatening
NOTE: 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.

C. Requires hospitalization or prolongation of existing hospitalization
NOTE: 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 out-patient 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.
D. Results in disability/incapacity NOTE: 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 or prevent everyday life functions but do not constitute a substantial disruption.
E. Is a congenital anomaly/birth defect
F. Other Situations • Medical or scientific judgment should be exercised in deciding whether 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 should also be considered serious. • Examples of such events are 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 or reports of spontaneous abortion.

7.2. Recording Adverse Events and Serious Adverse Events

Recording of adverse events and serious adverse events:
• The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. • The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on

signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

- AEs will be collected from the start of the denture and dental prophylaxis at the Screening Visit; and until 5 days following last administration of the study product.
- SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

7.3. Evaluating Adverse Events and Serious Adverse Events

Assessment of Intensity:

The investigator or designee will make an assessment of intensity for each AE and SAE 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. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality:

- The investigator is obligated to assess the relationship between study product and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes (source document) or CRF that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

7.4. Reporting Adverse Events and Serious Adverse Events

AE Reporting to GSKCH:

- AEs will be recorded in the AE section of the CRF.
- Medical conditions recorded by the subject on a diary card or similar document that meet the definition of an AE must also be recorded in the AE section of the CRF, if not previously well-characterized by the investigator in the subject's medical history.
- AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. The investigator or designee must ask the subject the following question during each visit including any follow-up visits: ***"Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since the last session)?"***
- The medically qualified investigator should review adverse events in a timely manner; this review should be documented in writing in the source document or in the CRF.
- After the study is completed at a given site, and the site has received their study data on Compact Discs (CDs), the electronic data collection tool will be removed from the internet to prevent the entry of new data or changes to existing data.

SAE Reporting to GSKCH:

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.
It is essential to enter the following information:

- Protocol and subject identifiers

- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (see section 8.3)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSKCH 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 on study product
- Outcome if known

The SAE form, completed as fully as possible, and SAE fax cover sheet must be faxed or e-mailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax Serious Adverse Events to:
UK: PPD

The GSKCH Study Manager will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Phamacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate via email.

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

7.5. Follow-up of Adverse Events and Serious Adverse Events

Follow-up of AEs and SAEs:

- 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/SAEs 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 to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any

time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSKCH.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

Regulatory and ethics reporting requirements for SAEs:

- The investigator will promptly report all SAEs to GSKCH within the designated reporting timeframes (within 24 hours of learning of the event). GSKCH 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 GSKCH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.
- GSKCH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IEC and investigators.
- Investigator safety reports are prepared according to GSKCH policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation.
- An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary of listing of SAEs) from GSKCH will file it with the Investigator Brochure (or safety statement) and will notify the IEC, if appropriate according to local requirements.

7.6. Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSKCH for use in this study; the medical device in this study is the denture cleanser (Corega® Tabs). GSKCH medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator on the CRF throughout the study.

7.6.1. Definition of an Incident

Definition of an Incident:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have lead to the death of a patient or user or of other persons or to a serious deterioration in their state of health.

7.6.2. Reporting of Incidents and Malfunctions

Incident Reporting to GSKCH:

- **All incidents must be reported to GSKCH within 24 hours (or sooner if possible) 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, 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 or an SAE, the appropriate AE CRF page or 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 GSKCH. 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 faxed or emailed to the appropriate GSKCH Study Manager as soon as possible, **but not later than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE pages 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 remain with the subject's records.
- The GSKCH Study Manager should be notified of the situation by telephone or email.

Fax the Incident Report Forms to:
UK: PPD

- The GSKCH Study Manager will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance, the Medical Director responsible for the study and other GSKCH personnel as appropriate.

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

Reporting of Malfunctions to GSKCH:

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

- Notify GSKCH immediately.
- 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.

7.6.3. Follow-up of Incidents

Follow-up of Incidents:

During the study:

- All incidents will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up. This applies to all subjects, including those withdrawn prematurely. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

After the study:

- Investigators are not obligated to actively seek reports of incidents in former subjects. However, if the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSKCH medical device provided for the study, the investigator will promptly notify GSKCH.

Regulatory and Ethics Reporting Requirements for Incidents:

- The investigator will promptly report all incidents occurring with any GSKCH medical device provided for use in the study within 24 hours. GSKCH has a legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies. Prompt notification of incidents by the investigator to GSKCH is essential in order to meet legal obligations and ethical responsibility towards the safety of subjects.
- The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IEC.

7.7. Collection of Pregnancy Information

7.7.1. Time Period for Collecting of Pregnancy Information

Collection of Pregnancy Information:

- Pregnancy information will be collected on all pregnancies reported following administration of any investigational product (or washout product). Information on pregnancy identified during the screening phase and prior to

investigational product (or washout product) administration does not need to be collected.

7.7.2. Action to be Taken if Pregnancy Occurs

Action to be Taken:
• The investigator will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product (or washout product). The investigator will record pregnancy information on the appropriate form and submit it to GSKCH within 2 weeks of learning of the subject becoming pregnant. 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 to GSKCH. 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, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE. • A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK. • While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting. • If the subject becomes pregnant during the study they should be withdrawn from the study and this should be recorded in the appropriate section of the CRF.

8. DATA MANAGEMENT

For this study subject data will be entered into an electronic case report form, using a GSKCH validated data system.

8.1. Source Documents/ Data

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or 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 in the Source Document Designation Form. In some cases the CRF can be used as a source document.

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

8.2. Electronic Case Report Form

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

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable GSKCH standards and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

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

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

Subject data will be entered into GSKCH defined CRFs and transmitted electronically to GSKCH in a validated (21 CFR Part 11 compliant) web-based electronic data capture system (InForm^{TM}).

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.

The CRFs (including queries, query responses and audit trails) will be retained by GSKCH. Site data archived compact discs (CD(s)) prepared by a third party will be sent to the investigator to maintain as the investigator copy following the decommissioning of the study.

8.3. 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.

8.3.1. Data Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, 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 (Adverse Events and Drugs) are reported appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and 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. Monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction

8.4. Processing Patient Reported Outcomes

Patient reported outcome (PRO) data are collected directly from the subject PRO measures e.g. diary cards, questionnaires etc, and entered into the sponsor's clinical data management system (DMS) by the study site representative. In instances where the PRO data is entered into the DMS by GSKCH, the PROs will be anonymised, and forwarded to GSKCH for entry, as agreed and documented ahead of the study starting. PROs that are source will be retained by the investigator and certified copies will be sent to GSKCH.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on all PRO's that will be forwarded to GSKCH.

8.5. 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 GSKCH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is 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 GSKCH via secured web portal or CD/DVD via mail carrier with tracking capabilities.

Proper 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.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Sample Size Determination

Due to lack of appropriate data it was not possible to perform a formal sample size calculation. A total of 17 subjects was considered sufficient to assess the efficacy and safety of the treatments under investigation. Confidence intervals will be provided to aid precision of treatment estimate.

Approximately 30 healthy subjects will be screened to randomise ~~at least~~ **APPROXIMATELY** 20 subjects. This will ensure that approximately 17 evaluable subjects will complete the entire study.

9.2. General Considerations

9.2.1. Definition of Analysis Populations

All assessments of safety will be based on the safety population, defined as all subjects who are randomised and receive at least one dose of study treatment during the study. Safety population summaries will be presented by treatment received.

The primary population for efficacy assessment will be the intent-to-treat (ITT) population, defined as all subjects who are randomised, receive at least one dose of the study treatment and provide at least one post-baseline assessment of microbial count from disc sampling. All ITT population summaries and analyses will be presented by treatment randomised.

The per protocol (PP) population is defined as all subjects in the ITT population who have at least one assessment of efficacy considered unaffected by protocol violations.

PP analysis will be performed only on those data considered unaffected by protocol violations. Efficacy analysis on the PP population will be performed only if there is more than 10% difference in the number of subjects between PP and ITT populations. A decision on whether a PP analysis will be performed will be made prior to study unblinding.

9.2.2. Exclusion of Data from Analysis

Any of the following will be considered a protocol violation which may warrant exclusion of data or the subject from efficacy analysis:

- Violation of inclusion or exclusion criteria that are deemed to affect efficacy.
- Medical history which is deemed to affect efficacy.
- Use of prohibited treatment or medication before or during the study, which is felt to affect the assessment of efficacy.
- Not receiving randomised treatment.
- Treatment non-compliance
- Assessments outside the scheduled time windows
- Protocol deviations captured in CRF.
- Any other reason identified likely to affect efficacy

Protocol violations which warrant exclusion from efficacy analysis will be identified between the statistician and medical director or designee ahead of database lock and breaking the study blind and will be documented in the population definitions document.
The repeatability population will comprise subjects who will have initial and repeat assessments for plaque or stain data. The repeat data will not be used in the plaque or stain data analysis.

9.2.3. Criteria for Evaluation

All measures captured in the study will be used to investigate the effect of daily denture cleanser use versus the effect of denture cleanser use weekly (on the 7th day from entering the study). OST abnormalities, incidents and AEs reported in the study will be used for safety evaluations of the study treatments.

9.2.4. Criteria for Assessing Efficacy

Not Applicable.

9.2.5. Criteria for Assessing Tolerability

The assessment for safety will be based on OST abnormalities, incidents and AEs reported following dosing with study treatment.

9.2.6. Criteria for Assessing Bioequivalence

Not Applicable.

9.2.7. 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.

9.2.8. Other Issues

Not Applicable.

9.3. Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate).

9.3.1. Demographic and Baseline Characteristics

Descriptive statistics (percentages, means and standard deviations) of demographic and baseline characteristics data will be tabulated.

9.3.2. Primary Analysis

Microbial Count – Denture Disc Samples at Day 7

Microbial count will be log transformed (log 10 scale) before any summary or statistical analysis will be performed. Changes from baseline (pre-treatment assessment on Day 0) in microbial count from denture disc sampling will be calculated on Day 7. These will be analysed using an ANCOVA model with treatment and period as factors and subject-level and period-level pre-treatment (on day 0) baseline scores as covariates. To allow model estimates to be representative of the studied population, subject will be included into the model as a random effect.

9.3.3. Secondary Analyses

Microbial Count – Denture Disc Samples at Days 0 and 3 and Stain and Plaque at Days 0, 3, and 7

Changes from baseline in microbial count on Day 3 (from disc sampling), stain and plaque will be calculated and analysed using an ANCOVA model as described for the primary endpoint analysis. All analyses will be carried out separately at Day 0, 3 and 7.

Microbial Count – Denture Sonication Samples at Day 7

Post treatment denture sonication samples will be analysed using an analyses of variance model with post-treatment values on day 7 as response variable and treatment procedure, period and subject (random effect) as factors.

Model assumptions will be investigated and if violated then the non-parametric Wilcoxon Signed rank test will be used to investigate any treatment procedure differences.

Molecular Species Analysis

Simple summary statistics of number of subjects, mean, standard deviation, minimum and maximum by treatment procedure will be provided for the most important 10 molecular species.

Subject Questionnaire Data

Counts and percentages by treatment procedure will be used to summarize the subject assessment questionnaire data.

9.3.4. Safety Analysis

For the assessment of safety/tolerability, incidents and AEs will be listed. AEs will be summarised by treatment group. AEs will be regarded as treatment emergent if they occur on or after the first treatment application at the baseline visit.

9.3.5. Other Analysis

Repeatability will be performed for plaque and stain assessments. Each repeat assessment will be compared to the original assessment.

A weighted kappa coefficient (κ) will be calculated, along with the 95% confidence interval to assess the intra-examiner repeatability. Repeatability will be deemed (Fleiss):

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

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

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trials Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IEC for the trial protocol (including amendments), written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), investigator brochure/ safety statement (including any updates) and any other written information to be provided to subjects. A letter or certificate of approval will be sent by the investigator to the sponsor prior to initiation of the study, and also when subsequent amendments to the protocol are made.
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK 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 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 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 GSKCH. 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.

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK 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 sponsor will be available to help investigators prepare for an inspection.

10.5. Conditions for Terminating the Study

Upon completion or premature discontinuation of the study, the GSKCH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSKCH Standard Operating Procedures.

Both GSKCH and the Investigator reserve the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies (if applicable), this can occur at one or more or at all sites.

If the trial is prematurely terminated or suspended for any reason, the investigator site should promptly inform the trial subjects and should assure appropriate therapy/ follow-up for the subjects. Where required by the applicable regulatory requirements, GSKCH should inform the regulatory authority(ies).
In addition:

- If the investigator terminates or suspends a trial without prior agreement of GSKCH, the investigator site should promptly inform the sponsor and the IEC, and should provide the sponsor and the IEC a detailed written explanation of the termination or suspension.
- If the GSKCH terminates or suspends a trial, the investigator should promptly inform the IEC and provide the IEC a detailed written explanation of the termination or suspension.
- If the IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSKCH and provide GSKCH with a detailed written explanation of the termination or suspension.

10.6. 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 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 GSKCH, 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 GSKCH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements (GSKCH recommends that documents be kept for 10 years). The investigator is also required to keep subject identification codes on file for at least 15 years after completion or discontinuation of the study. 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 standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH and the investigator. The investigator must notify GSK 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.

10.7. Provision of Study Results to Investigators, posting of Information on Publicly Available Clinical Trials Registers and Publication

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 site or other mutually-agreeable location.

GSK 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 Policy.

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

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1 - Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
C	Centigrade
CD	Compact Disc
CRF	Case Report Form
Ct	Cycle Threshold
EDC	Electronic Data Capture
g	Gravitational Acceleration
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
H	Hours
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention to Treat
µM	Micrometer
mm	Millimeter
MINS	Minutes
ng	Nanograms
OST	Oral Soft Tissue
PII	Personally Identifiable Information
PP	Per Protocol
SAE	Serious Adverse Event
SAQ	Subject Assessment Questionnaire
PRO	Patient Reported Outcome

Trademark Information

Trademarks of the GlaxoSmithKline group of companies:
COREGA

12.2. Appendix 2 – Subject Assessment Questionnaire (SAQ)

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SIGNATURE PAGE

205202 Protocol

Date	Signed By
07-Nov-2016 04:43:29	PPD
Justification	Biostatistics Approval

Date	Signed By
07-Nov-2016 07:38:50	PPD
Justification	Approved

Date	Signed By
07-Nov-2016 15:21:17	PPD
Justification	Approved

Date	Signed By
09-Nov-2016 12:46:10	PPD
Justification	Clinical Operations Approval

Date	Signed By
Justification	

Date	Signed By
Justification	