Clinical Protocol

209649

A Randomized, Single-Blind, Clinical Study to Assess Food Occlusion Efficacy of a Marketed Denture Adhesive in Healthy, Edentulous Subjects
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GlaxoSmithKline Consumer Healthcare

184 Liberty Corner Road, Warren, NJ,

07059, USA

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CLINICAL PROTOCOL

A Randomized, Single-Blind, Clinical Study to Assess Food Occlusion Efficacy of a Marketed Denture Adhesive in Healthy, Edentulous Subjects.

Protocol Number:	209649
Compound/Product Name:	Sodium-calcium mixed partial salt of poly(methylvinylether/maleic acid) and carboxymethylcellulose
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	Not applicable
Other Regulatory Agency Identified Number:	Not applicable
Phase:	IV

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Research & Development Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	1. Name of product change throughout protocol from SuperPoligrip Max Seal (SPMS) to COREGA Máximo Sellado/Selamento. 2. Subscript “e” added as footnote to Section 1.1 Schedule of Activities, Table 1.1 to align with Section 8.1. 3. Section 5.4- change of duration for Lifestyle Considerations from Visits 2-4 to Visits 2-3. 4. Section 9.1.3- modification that the denture bearing tissue score will be recorded for both maxillary and mandibular dentures rather than just the mandibular denture.
Amendment 2	3.0	1. Section 12.2.6- clarification of success criteria to align with the formal study success criteria stated in Section 3.

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

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines and ISO 14155:2011 (E).
- 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:	
Investigator Qualifications:	
Investigator Signature:	PPD
Date of Signature/Agreement:	DD-Mmm-YYYY

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1 PROTOCOL SUMMARY

Background and Rationale

This study is designed to investigate the effectiveness of a marketed denture adhesive, dispensed through a precision nozzle to prevent the ingress of peanut particles under dentures, in a food occlusion model. The study will compare COREGA Máximo Sellado/Selamento with a precision nozzle versus no adhesive using the methodology that was developed under study 208397.

Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To assess the performance of a marketed denture adhesive (COREGA Máximo Sellado/Selamento compared to no adhesive in a model for food occlusion.	Mass of peanuts under combined maxillary and mandibular dentures.
Secondary	
To compare the ability of a marketed denture adhesive (COREGA Máximo Sellado/Selamento) to prevent food particle ingress under upper and lower dentures versus no adhesive.	Mass of peanuts under maxillary dentures. Mass of peanuts under mandibular dentures.
To evaluate and compare subject-reported denture dislodgments during a food occlusion methodology when marketed denture adhesive (COREGA Máximo Sellado/Selamento) is used compared to no adhesive.	The number of subject reported denture dislodgements during chewing.
To evaluate and compare subject responses to a questionnaire administered after eating peanuts when using a marketed denture adhesive (COREGA Máximo Sellado/Selamento) compared to no adhesive.	Mean scores from Subject-completed questionnaire.
Safety	
To assess the tolerability of marketed denture adhesive (COREGA Máximo Sellado/Selamento).	Treatment emergent adverse events.

Study Design

This will be a single center, controlled, single blind (with respect to the technician weighing the peanut particles that have migrated under the denture), randomized, two-treatment, two-period cross-over design, in subjects with well fitting (as defined by the well-made and well fit assessment) full upper and lower dentures (maxillary and mandibular). This study design is based on study 208397, where the ingress of peanut particles was compared when using adhesive (applied by two different methods) versus no adhesive. Whilst the objective measure of peanut mass is the primary endpoint of interest in this study, subject perceived efficacy will also be investigated by means of a subject-completed questionnaire. The number of denture dislodgments reported by the subjects during the chewing of the peanuts will also be collected and analyzed and this, and the questionnaire data, will be used to support the findings of the peanuts mass measure.

Study Products

COREGA Máximo Sellado/Selamento will be compared to no adhesive. The adhesive will be applied by the clinical site dispensing staff and 1.0 g (±0.1g) will be weighed and applied to the maxillary denture and 0.6g (±0.1g) will be weighed and applied to the mandibular denture. No washout products will be required for this study and there will be a 2-7 day period between each visit.

Type and Planned Number of Subjects

A sufficient number of subjects will be screened to randomize 52 subjects to ensure 48 evaluable subjects complete the entire study. Healthy edentulous subjects, between 18 and 85 years of age with both upper and lower dentures will be recruited.

1.1 Schedule of Activities

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

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

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening	Study Period			
	Visit 1	Between 2 and 7 days	Visit 2 Treatment Period 1	Between 2 and 7 days	Visit 3 Treatment Period 2
Informed consent	X				
Review Inclusion/Exclusion criteria	X		X		X
Medical history	X				
Demographics	X				
Current/Concomitant treatments	X		X		X
Dental history	X				
OST examination edentulous	X[e]		X[b]		X[b]
Denture bearing tissue score	X				
Clean Dentures[c]	X		X		X
Criteria for well-made and fitting dentures (retention, stability, clinical acceptability and denture finish)	X				
Food migration adequacy	X				
Subject eligibility	X				
Randomization			X		
Subject continuance			X		X
Treatment application and denture insertion[a]			X		X
Efficacy assessment- Food occlusion testing			X		X
Efficacy assessment- Number of denture dislodgements			X		X
Photograph of dentures (subset of subjects' dentures will be selected.)			X		X
Subject completed questionnaire			X		X
Adverse events[d]	X		X		X
Incidents[d]	X		X		X
Study conclusion					X

[a] There will be a 60±5 minute wait after dentures are inserted and the commencement of the food occlusion testing.
[b] At visits 2 and 3 the OST examination will be performed before product application and also after the denture removal and peanut recovery.
[c] Dentures will be cleaned both prior to and after the food migratory adequacy (V1) or food occlusion testing assessment (V2 and V3)
[d] Any adverse event, serious adverse event or incident assessed as related to study participation that occurs subsequent to the signing of informed consent.
[e] At screening visit, the OST examination will be performed before and after the food migration adequacy determination as per Section 8.1.

2 INTRODUCTION

Denture adhesives are recommended to denture wearers, not only to increase the retentive hold of dentures to the oral mucosa, but also to reduce the ingress of food particles under the denture. Such particles are often a cause of irritation to the mucosa. Current understanding suggests that restriction of food particle ingress is achieved through a tighter denture fit provided by the denture adhesive through its ability to both adhere the denture to the mucosa and to occlude gaps between the denture and the mucosa which might otherwise be susceptible to food particle ingress (Ozcan et al, 2005). The increased adherence to the mucosa leads to reduced movement of the denture whilst chewing, leading to a reduction in particle migration under the denture (Tarbet et al, 1980). Additionally, the hydration of denture adhesives through contact with saliva leads to expansion of the adhesive, occluding gaps between the denture and the underlying mucosa (Ozcan et al, 2005). The adhesive can therefore be thought of as forming a seal along the denture borders which prevents ingress of small food particles.

Published methodologies for evaluating the performance of a denture adhesive at reducing the ingress of food particles under the denture are rather limited in numbers. Tarbet et al (Tarbet et al, 1980) had subjects subjectively rate (on a ten-point scale) whether they experienced less food particles under their dentures after eating foods including celery, steak, taffy apples and sandwiches when using a denture adhesive compared to no adhesive. This study showed a statistically significant difference ($p<0.01$) in subjective score in favour of the use of adhesive compared to no adhesive use. Ahmad et al (Ahmad et al, 2009; Ahmad et al, 2010) described a quantitative methodology based upon having fully edentulous subjects chew a prescribed amount of peanuts whilst wearing both their maxillary and mandibular dentures. After chewing the peanuts, the subjects brushed their dentures whilst still wearing them, rinsed with water then removed their dentures. Study staff then removed the peanut particles from the fit surfaces of the dentures and any adhesive from the dentures and the denture bearing tissues, washed and sieved the peanut particles and dried the particles prior to weighing them. This study was able to show statistically significant lower mass of peanuts collected between subjects using an adhesive compared to no adhesive use. The mass of peanut particles recovered was not reported in full, however, a mean mass of 51mg and 35mg was found for maxillary dentures for the no-adhesive and adhesive treatments respectively.

A GSK CH method development study, similar to that described above was conducted (Study 208397) and was able to show that more peanut particles were recovered from dentures without any adhesive than those that had adhesive applied. This methodology will be employed for this study, and will be designed to evaluate the ability of COREGA Máximo Sellado/Selamento to reduce food ingress under dentures.

2.1 Study Rationale

The study will compare COREGA Máximo Sellado/Selamento with a precision nozzle versus no adhesive using the methodology based on that developed under Study 208397. The aim of the study is to evaluate if the use of denture adhesive can minimize the ingress of food particles under dentures.

This study will compare the efficacy of a marketed denture adhesive against use of no adhesive. No adhesive has been chosen as a control group to provide a continual reference point to allow interpretation of the results and to facilitate comparison of the results from this study with

previous work, and is representative of a significant number of denture wearers who currently do not use an adhesive.

The application of the adhesive will be controlled by mass, where 1.0g (±0.1g) will be weighed and applied to the maxillary denture and 0.6g (±0.1g) will be weighed and applied to the mandibular denture (in line with previous GSK CH studies CCI and 208397).

The technician who will weigh the peanuts recovered from the dentures will be different to the technician that will wash, sieve and dry the peanuts, and will therefore be blinded to the treatments, hence this is a single blind study.

Denture adhesive achieves its function by physical means and once completely removed from the denture does not have any residual carry-over effects. Therefore the 2-7 day period between each visit is considered adequate rest for the oral soft tissue from the stresses of mastication encountered in this study. Subjects will be permitted to continue using their normal oral hygiene products, including denture adhesive, between study visits. The study will also not exclude current denture adhesive users as the test adhesive is intended to be suitable for both current adhesive users as well as those not currently using adhesive. The safety and efficacy outcomes of this study design are considered independent of whether or not a subject has used adhesive between study periods.

This is a Phase IV study that is planned to be performed by a clinical site with experience in this methodology. COREGA Máximo Sellado/Selamento, whilst marketed in many countries is currently not commercially available in the USA, and therefore the study product will be imported to the USA for the study. The product is considered a non-significant risk device in the USA and therefore the IRB will be required to ratify (i.e. IRB review of the protocol) this before importing the study products to the USA. No health authority regulatory approval will be required to conduct the proposed study.

Complete information for the COREGA Máximo Sellado/Selamento may be found in the single reference safety document (SRSD), which for this study is the Safety Statement.

2.2 Background

This study is designed to investigate the effectiveness of a marketed denture adhesive, dispensed through a precision nozzle in a food occlusion model. The study will compare COREGA Máximo Sellado/Selamento packaged with a precision nozzle versus no adhesive using the methodology based on that developed during GSKCH study 208397.

Clinical study 205915 aimed to evaluate the relative efficacy of an experimental denture adhesive to reduce food ingress under dentures compared to a standard marketed adhesive (COREGA Máximo Sellado/Selamento Denture Adhesive Cream), and no adhesive. Briefly, subjects with both full upper and lower dentures were assigned to either the test denture adhesive (COREGA Máximo Sellado/Selamento), a positive control adhesive (SPF) or the negative control (no adhesive group) in this three- treatment, three-period, cross-over study. One hour after the application of the denture adhesive to both upper and lower dentures by the examiner, subjects were instructed to chew a defined mass of peanuts in a controlled manner. After a rinsing procedure with water, the dentures were then removed, and any peanuts that had migrated under each denture were collected and weighed after a drying process.

The results showed that there was no significant difference in the mass (g) of peanuts recovered from the subjects using the positive control or the no adhesive (negative control) groups and it was therefore concluded that the study failed to demonstrate assay sensitivity.

One major learning from the 205915 study concerned the way in which the denture adhesive was applied to the dentures. The adhesives were applied directly from the tubes by the study staff, following the package usage instructions without weighing. Although this was intended to replicate typical consumer usage, it resulted in the mass of adhesive being uncontrolled. The mean mass of the positive-control adhesive used for the upper and lower dentures combined was 0.63g (range 0.3–1.0g; SD 0.16g). This dose was considerably lower, with much greater variability, than that used in previous studies (standardized and controlled at 1.6g), which may have contributed to the lack of differentiation in mass of peanut particles retrieved between the adhesives compared to no adhesive. A further point to consider for any future studies was to optimize the rinsing procedure and collection of peanut particles following chewing.

Based on these results and findings, a method development study was conducted (study 208397). This study was a three-treatment, three-period, cross-over design study with the main aim of this study to validate a food occlusion methodology. The study results showed that there were more peanut particles recovered under dentures when using no-adhesive compared to using adhesive. This updated methodology will now be used for the basis of the study design for the proposed study outlined in this protocol.

2.3 Mechanism of Action/Indication

Sodium-calcium mixed partial salt of poly (methylvinylether/maleic acid) and carboxymethylcellulose is currently included in a denture adhesive marketed by GSK CH. Denture adhesives work through their ability to both adhere the denture to the mucosa and to occlude gaps between the denture and the mucosa which might otherwise be susceptible to food particle ingress (Özcan, 2005). The increased adherence to the mucosa leads to reduced movement of the denture whilst chewing, leading to a reduction in particle migration under the denture (Tarbet, 1980). Additionally, the hydration of denture adhesives through contact with saliva leads to expansion of the adhesive, occluding gaps between the denture and the underlying mucosa (Özcan, 2005). The adhesive can therefore be thought of as forming a seal along the denture borders which prevents ingress of small food particles.

COREGA Máximo Sellado/Selamento is a medical device that is currently being investigated in fully edentulous subjects with both maxillary and mandibular full dentures.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To assess the performance of a marketed denture adhesive (COREGA Máximo Sellado/Selamento) compared to no adhesive in a model for food occlusion.	Mass of peanuts under combined maxillary and mandibular dentures.
Secondary	
To compare the ability of a marketed denture adhesive (COREGA Máximo Sellado/Selamento) to prevent food particle ingress under upper and lower dentures versus no adhesive.	Mass of peanuts under maxillary dentures. Mass of peanuts under mandibular dentures.

To evaluate and compare subject-reported denture dislodgments during a food occlusion methodology when marketed denture adhesive (COREGA Máximo Sellado/Selamento) is used compared to no adhesive.	The number of subject reported denture dislodgements during chewing.
To evaluate and compare subject responses to a questionnaire administered after eating peanuts when using a marketed denture adhesive (COREGA Máximo Sellado/Selamento) compared to no adhesive.	Mean scores from Subject-completed questionnaire.
Safety	
To assess the tolerability of marketed denture adhesive (COREGA Máximo Sellado/Selamento).	Treatment emergent adverse events.

This study will be considered successful if there is a statistically significant difference between the mass of peanuts under dentures of subjects using denture adhesive versus when using no adhesive.

4 STUDY DESIGN

4.1 Overall Design

This Phase IV study will be a single center, controlled, single blind (with respect to the technician weighing the peanut particles that have migrated under the denture), randomized, two-treatment, two-period, cross-over design, in subjects with full upper and lower dentures. Each treatment period will consist of one day of testing with at least two days between adjacent treatment visits.

A sufficient number of subjects will be screened to randomize 52 subjects to ensure 48 evaluable subjects complete the entire study. Healthy edentulous subjects, between 18 and 85 years of age with both upper and lower dentures will be recruited.

At the screening visit, following an oral soft tissue (OST) examination, each subject's denture (maxillary and mandibular) will be cleaned and assessed for retention and stability using the Kapur Index (Olshan Modification) [Kapur, 1967; Olshan, 1992] and whether they are well made. Only those subjects with dentures (both maxillary and mandibular) that satisfy both of these criteria will then undergo the food migration adequacy assessment, where the peanuts under the dentures will be visually assessed after the subject chews a portion of peanuts. A visual observation and rating of location and extent of peanut particle migration adequacy must indicate > 0 on a 0-3 scale. Subjects meeting all the inclusion criteria with no exclusions will then be randomized at Visit 2.

On each test day (Visit 2 and 3), subjects will undergo an OST examination (edentulous) and have their dentures cleaned using denture cleanser as per the denture cleansing procedure. Treatment (or no treatment as per randomization schedule) will then be applied as per the application instructions (Appendix 15.3) and the dentures worn by the subject. Then, 60±5 minutes after inserting their dentures, each subject will be given a standardized portion of peanuts to consume, following a prescribed chewing and swallowing method. Whilst chewing the peanuts, subjects will record the number of denture dislodgements that occur during the chewing procedure. After this, subjects will rinse their mouths with water for up to 10 seconds to remove peanut particles that have not migrated under the dentures. The rinsing step may be

repeated as required, if necessary, in the opinion of the examiner, to ensure peanut particles that have not migrated under the dentures are cleared from the oral cavity. The examiner will then remove the mandibular denture and any peanut particles or adhesive remaining on the mandibular edentulous ridge will be removed using gauze. The examiner will then remove the maxillary denture and any peanut particles or adhesive remaining on the maxillary edentulous ridge will be removed using new gauze. Each gauze (including peanut particles) will be retained separately. Once all peanuts particles have been collected from the dentures, they will be retained for cleaning. The subject will then complete a questionnaire on efficacy and a further OST examination will then be performed, before the cleaned dentures are returned to the subject.

Peanut particles will then be collected from the fit surface of the dentures using gauzes and then weighed to evaluate the mass of food particles that had migrated under the denture (keeping the particles associated with the upper and lower dentures separate).

For the first 5 randomized subjects in the study, the fit surface of their dentures will be photographed before peanuts are collected from the dentures (no photographs of the subjects themselves will be taken). It is expected that where possible, consistency of subjects between treatments is maintained (i.e. a subject will be identified at visit 2) as being suitable for denture imaging and have their dentures photographed at visits 2 and 3.

These subjects will be repeated in a cross-over manner. There will be 2-7 days between treatment visits to allow for recovery from the mastication procedures.

Safety will be assessed by examination of the oral soft tissues at the Screening Visit and before and after each treatment assessment has been completed at each of the treatment visits. Abnormalities reported after informed consent will be considered as adverse events (AEs). Incidents will be recorded from informed consent. In addition, subject reported outcome/AEs will also be recorded.

4.2 Rationale for Study Design

This study will be a controlled study in order to show the benefit of food occlusion from the use of denture adhesive versus no adhesive (negative control). A positive control has not been included in this study since there is insufficient evidence to support a denture adhesive being considered as a “gold-standard” in this model.

Whilst the objective measure of peanuts is the primary endpoint of interest in this study, subject derived opinion of efficacy will also be measured by means of a subject-completed questionnaire. The number of denture dislodgements reported by the subjects during the chewing of the peanuts will also be collected and analysed and this, and the questionnaire data, will be used to better understand the findings of the peanut mass measure.

An oral soft tissue (OST) examination will be conducted at each treatment visit before treatment is applied to ensure the subject’s oral health is sufficient to allow the subject to complete the assessments at that visit. A further OST exam will be performed at each treatment visit after the completion of assessments in order to screen for abnormalities.

This study will be single blind, with respect to the technician who will be carrying out the final weighing of peanut particles recovered from dentures and the edentulous ridges. This technician will be separate from the personnel that will be washing, sieving and drying the peanuts after removal from subjects’ mouths and will therefore remain blinded to treatment used.

Denture adhesive achieves its function by physical means and once completely removed from the denture is not expected to have any residual carry-over effects. Therefore the 2-7 day period between each visit is considered adequate rest for the oral soft tissue from the stresses of mastication encountered in this study. Subjects will be permitted to continue using their normal oral hygiene products, including denture adhesive as it is believed that the objective measure will not be affected if subjects are current adhesive users or not. We will also not be excluding current adhesive users from the study as this product is intended for both current and non-users of adhesives.

In this study, denture adhesive will be applied using a continuous strip pattern as per label instructions on the marketed COREGA Máximo Sellado/Selamento product. The application will be controlled by mass (1.0g on the maxillary denture and 0.6g on the mandibular denture) in line with previous GSK CH studies ([redacted] and 208397) and as described in the product application instructions (Appendix 15.4).

Dentures are unique to each individual. Therefore, the most efficient approach to evaluating their performance with different adhesives or 'no adhesive' is a within subject comparison (i.e. a crossover design).

Peanuts were chosen as the model food in this methodology because they are a brittle food that, when masticated, break into small particles that can be recovered. Peanuts have therefore been retained as a model food for this study and to allow comparison with previous data.

In order for subjects to be eligible they must report that they get food trapped under their dentures and this must be evident following the standardised peanut migration adequacy testing at screening (Visit 1). This is to ensure that measurable amounts of peanut particles migrate under the denture when no denture adhesive is being used. Whilst peanut allergy is specific, peanuts supplied for this study may themselves be contaminated with other nuts owing to the manufacturing process. Therefore, subjects with any nut allergy are excluded from this study. Should however, a subject suffer an adverse reaction to the peanuts consumed in this study then the study staff will administer appropriate first aid including the use of adrenaline in the case of anaphylaxis. Subjects with temporomandibular joint disorders are excluded should the investigator believe that this could affect the subject's participation, principally regarding the ability for the subject to adequately chew the peanuts. Subjects who use or have ever used bisphosphonate medications are specifically excluded from this study owing to the enhanced risk of bisphosphonate-related osteochemonecrosis of the jaw (BRONJ) that is associated with reduced tissue tolerance to function with removable prostheses (Saldanha et al, 2012). Subjects in this study must be habitual wearers of full dentures to ensure that they are familiar with chewing with their dentures in place. Subjects who are xerostomic are excluded since the proper function of denture adhesives requires adequate hydration from saliva.

During this study, photographs of dentures with peanut particles attached will be taken. The purpose of this is to gather representative photographs of the dentures to aid in the dissemination and interpretation of the results, e.g. in manuscript preparation. No personally identifiable information will be included in these photographs.

Demographic information will be recorded as part of this study, including age, race and gender. In accordance with the United States Food and Drug Administration (US FDA) guidelines (FDA, 2005) the ethnicity of subjects will also be captured.

The Kapur-Olshan index is a composite score based upon stability and retention ratings for the maxillary and mandibular dentures (Kapur, 1967; Olshan et al, 1992). Subjects presenting with

a very low Kapur-Olshan score at Screening (<6), defined as "Clinically Poor" (Olshan et al, 1992), will be excluded from this study.

Denture adhesive achieves its function by physical means and once completely removed from the denture does not have any residual effects. Therefore, the 2-7 day period between each test day is considered adequate rest for the oral soft tissues from the stresses of mastication encountered in this study.

4.3 Justification for Dose

The COREGA Máximo Sellado/Selamento adhesive will be applied directly from the primary product packaging, with 1.0g (±0.1g) being weighed and applied to the maxillary denture and 0.6g (±0.1g) being weighed and applied to the mandibular denture. This dosing is in line with previous GSK CH studies (CCI and 208397), and eliminates variability associated with not controlling the mass of the adhesive.

4.4 End of Study Definition

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

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

This study will recruit healthy volunteers, of either gender aged 18-85 years who are completely edentulous and wear full maxillary and mandibular dentures. The test denture adhesive is indicated for the general population who wear dentures and therefore the inclusion criteria allows for investigation of typical denture users.

A sufficient number of subjects will be screened to randomize 52 to ensure 48 evaluable subjects complete the entire study.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions will be taken into consideration when deciding whether a subject is suitable for this protocol.

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

5.2 Inclusion Criteria

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

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 and 85 years, inclusive.

3. A subject who is willing and able to comply with scheduled visits, treatment plan and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant/relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. Self-reports experience of getting food trapped under their denture.
6. Is a habitual wearer of both of their dentures defined as subjects who wear both of their dentures for the majority of their time whilst awake.
7. Have denture protheses that fulfil all of the following:
   a) A qualifying conventional acrylic full denture in both the upper and lower arch.
   b) Dentures are well fitting (Kapur (Olshan Modification) Retention and Stability Index Sum Score ≥6) (Olshan et al, 1992) with no individual stability or retention scores <1.
   c) Dentures are well made (according to the well-made assessment).
   d) Has a peanut particle migration rating >0 for each denture.

5.3 Exclusion Criteria

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

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GSK CH employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject who is a pregnant female (self-reported).
5. A subject who is a breastfeeding female.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
8. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
9. History of swallowing difficulties or choking.
10. Currently taking or have taken a bisphosphonate drug (i.e., Fosamax, Actonel, Boniva).

11. Any clinically significant or relevant oral abnormality (e.g. temporomandibular joint [TMJ] problems) that, in the opinion of the investigator, could affect the subject's participation in the study.
12. Known allergy to peanuts or any other nut.
13. Any condition or medication which, in the opinion of the investigator, is currently causing xerostomia.
14. Recent history (within the last year) of alcohol or other substance abuse.
15. OST examination findings such as stomatitis, open sores, lesions, redness or swelling which in the opinion of the investigator, would interfere with the conduct of the study or the safety of the subject.
16. Use of any medication that, in the opinion of the investigator, would interfere with the conduct of the study.
17. A serious chronic disease requiring intermittent hospital visits.
18. Having been previously enrolled in this study.
19. Any subject, in the opinion of the investigator, who should not participate in the study.

Subjects will be randomized into the study provided they have satisfied all subject selection criteria.

5.4 Lifestyle Considerations

During the entire study (screening – LSLV):

- Subjects will not be permitted to have any dental/denture work performed during the time they are in the study, unless discussed and permitted by the examiner. This is to assure that the denture fit will not be altered during the study.

During the treatment visits (Visits 2-3):

- Subjects will not be allowed to use tobacco or nicotine or nicotine-containing products following denture insertion until after their dentures are returned at completion of the food occlusion testing.
- Subjects will not be able to use any oral healthcare product other than those supplied by the investigator following denture insertion until after their dentures are returned at completion of the food occlusion testing.

5.4.1 Meals and Dietary Restrictions

Subjects will not be allowed to consume any food (including chewing gum) or drinks following denture insertion until after their dentures are returned at completion of food occlusion testing with the exception of small sips of water to alleviate thirst, to aid chewing the peanuts or to assist with medication.

5.4.2 Alcohol, Caffeine and Tobacco

Subjects will not be allowed to use tobacco or nicotine or nicotine-containing products following denture insertion until after their dentures are returned at completion of the food occlusion testing.

5.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. To ensure transparent reporting of screen failure subjects, a

minimal set of screen failure information will include demography, screen failure details (e.g. withdrawal of consent), eligibility criteria, and any adverse events or incidents as applicable.

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

5.6 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical/dental personnel for the study is documented in the Study Contact List located in the investigator study master file held at the study site.

The contact number is only to be used by investigational staff seeking advice on medical/ dental questions or problems in the event that the established communication pathways between the investigational site and the study team are not available.

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.7 Rater/Clinical Assessor Qualifications

Suitably-qualified dental professionals with expertise in prosthodontics will be required to perform the OST examination and the screening assessments relating to denture fit and condition for this study.

6 INVESTIGATIONAL/STUDY PRODUCTS

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Test Product	Control
Product Name	COREGA Máximo Sellado/Selamento	No Adhesive
Pack Design	Precision nozzle tube	N/A
Dispensing Details	N/A	N/A
Product Master Formulation Code (MFC)	CCI [redacted]	N/A
Dose/Application	1.6g of adhesive applied as 1.0g (±0.1g) for maxillary denture and 0.6g (±0.1g) for mandibular denture.	N/A
Route of Administration	Applied to upper and lower denture which is then placed in mouth	N/A
Usage Instructions	See usage instructions (Appendix 15.4)	N/A
Return Requirements	All used/unused samples to be returned to the sponsor	N/A

COREGA Máximo Sellado/Selamento, whilst marketed in many countries is currently not commercially available in the USA, and therefore the study product will be imported to the USA for the study. As per the Regulatory Determination for this study, the experimental adhesive is categorized as a medical device, and therefore a Nonsignificant Risk (NSR) application will be performed as part of the IRB submission to conduct this study in the USA.

Table 6-2 Sundry Items

Sundry Items to be supplied:

Item	Supplied By	Return/Disposal Details	
		Used Samples	Unused Samples
Oral B Denture brushes	GSK CH	Destroy at site using site disposal procedures	Return
Polydent Dentu Crème Denture cleansing paste (USA marketplace)	GSK CH	Destroyed at site using site disposal procedures	Return

Detailed instructions for the return of study product/study supplies for the accountability checks and subsequent destruction which will be provided by GSK CH during the course of the study in time for study close out visit.

6.1.1 Dosage Form and Packaging

The test product is intended for oral use, and will be administered to dentures externally to the mouth, with the dentures then replaced in the subject's mouth as detailed in the Product Application Instructions (Appendix 15.4). The test product will be supplied by GSK CH in commercially marketed tubes. The contents of the product label will be in accordance with all appliance regulatory requirements and will be the responsibility of the Global Clinical Supplies group.

All sundry items will be supplied in their commercial packaging for use by study staff as required.

All investigational study products will be overwrapped. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

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

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

6.1.2 Preparation and Dispensing

COREGA Máximo Sellado/Selamento will be applied to the dentures by qualified unblinded site personnel according to the Product Application Instructions instruction (Appendix 15.4).

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

These staff members will not be involved in any safety, efficacy assessments or other study aspects that could be influenced by the knowledge of product a subject has been assigned to use.

6.2 Administration

Subject's dentures will first be cleaned prior to application of adhesive. For subjects randomized to no adhesive, the cleaning will still be performed in order to standardize the cleanliness of the denture prior to commencement of the food occlusion testing. Using the supplied denture brush and cleansing paste, both the upper and lower dentures will be thoroughly cleaned to remove all traces of denture fixative, plaque and particulates/debris. Dentures should then be dried.

Adhesive will be applied from the primary product packaging onto the dentures as per the Product Application Instructions (Appendix 15.4). The dentures will then be returned to the subject who should reposition the dentures in their mouth and bite down to secure hold. For subjects on the "no adhesive" treatment visit, the dentures should be cleaned and dried as above, and refitted by the subject.

6.2.1 Medication/Dosing Errors

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

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

Such medication/dosing errors occurring to a study subject are to be captured in the CRF.

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

- Medication/dosing errors involving subject exposure to any of the study products;

- Potential medication/dosing errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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

6.3 Investigational/Study Product Storage

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

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

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

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

6.4 Investigational/Study Product Accountability

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

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

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

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

6.4.1 Destruction of Investigational/Study Product Supplies

At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH (study monitor) will inventory all used and unused study products and sundry items. The investigational/study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study (including empty containers), will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided.

6.5 Blinding and Allocation/Randomization

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

Open or used study products should not be re-dispensed to any subject.

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

This study is described as single blind (with respect to the technician weighing the peanut particles). The study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the Sponsor, who may influence study outcomes will also be blinded to the product allocation.

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

6.6 Breaking the Blind

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

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

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

Any AE associated with breaking the blind must be recorded and reported as specified in this protocol. The study site may also be required to inform the IRB/EC if the blind is broken.

6.7 Subject Compliance

Study products will be administered by site staff and this will be controlled by mass, and this will be documented in the CRF. The number of any missed or additional applications or doses will be captured as protocol deviations and transcribed into the CRF.

6.8 Concomitant Medication/Treatment(s)

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

Details of any relevant dental, medical or surgical history (within the last year), including allergies of drug sensitivity, will be recorded in the CRF. The use of concomitant medications is permitted in this study except for the use of bisphosphonate drugs (exclusion criteria 10) and any medications that in the opinion of the investigator would interfere with the conduct of this study (exclusion criteria 16).

Medication/treatment taken within 7 days of signing the informed consent form will be documented as a prior medication/treatment. Treatment taken after the first dose of study investigational product will be documented as concomitant treatment.

All concomitant treatments taken during the study must be recorded with indication, unit dose, daily dose, and start and stop dates on administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Subjects will be asked not to have any non-emergency dental/denture work performed during the times they are in the study, unless discussed and permitted by the examiner. This is to assure that the denture fit will not be altered during the study.

6.9 Rescue Medication

No specific rescue therapy is required in this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

A subject will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

If a subject fails to return to the site for a required study visit, the site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

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

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

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

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

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

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening

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

Subjects will be screened within 2–7 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures/assessments will be completed in the order listed below (where possible), and recorded in the CRF:

- Obtain written informed consent.
- Collect demography (year of birth, gender, race and ethnicity).
- Obtain medical history, including history of illegal drugs, alcohol and tobacco use.
- Obtain dental history.

- Obtain complete medication history of all prescription or non-prescription drugs, and dietary and herbal supplements taken within 7 days prior to planned first dose.
- Perform OST Examination-Edentulous.
- Perform the denture bearing tissue score assessment.
- Clean the subject's dentures using the supplied denture brush and cleansing paste, both the upper and lower dentures will be thoroughly cleaned to remove all visible traces of denture fixative, plaque and particulates/debris. Dentures should then be dried.
- Perform the Well-Made Assessment.
- Perform the Well-Fit Assessment.
- Perform the Food Migration Adequacy Assessment.
- Perform OST Examination-Edentulous.
- Review Inclusion and Exclusion criteria. Pregnancy status will be confirmed verbally by the subject.
- Assess subject eligibility.

To prepare for the study participation, subjects will be instructed on the use of the Lifestyle Considerations and Concomitant Treatment(s) sections of the protocol.

8.1.1 Visit 2

Subjects will be admitted to the clinical site 2-7 days after screening. The following procedures will be completed in the following order (wherever possible) and recorded in the CRF:

- Review Inclusion and Exclusion criteria. Pregnancy status will be confirmed verbally by the subject.
- Review changes in the subject's medical history including medication history since Screening. Any exacerbation of pre-existing medical history will be recorded as AEs.
- Perform OST Examination- Edentulous.
- Assess subject continuance.
- Randomize subject to a treatment sequence group.
- Clean the subject's dentures using the supplied brush and cleansing paste. Both upper and lower dentures will be thoroughly cleaned to remove all visible traces of denture fixative, plaque and particulates/debris. Dentures should then be dried.
- Apply the denture adhesive (or no adhesive per the randomization schedule) and insert dentures per the Product Application Instructions.
- 60±5 minutes after denture insertion, begin Food Occlusion Testing including Subject Denture Dislodgment Assessment. (This includes peanut chewing, and peanut retrieval from dentures and the oral cavity).
- Subjects report the number of denture dislodgments during peanut chewing.
- Subjects complete questionnaire (as per Appendix 15.3) once dentures have been removed.
- Photograph dentures of the first five randomized subjects.
- Perform OST Examination-Edentulous.
- Dentures will be cleaned and returned to subject.

- Record AEs and incidents. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

8.1.2 Visit 3

Subjects will be admitted to the clinical site between 2-7 days after Visit 2. The following procedures will be completed in the following order (wherever possible) and recorded in the CRF:

- Review Inclusion and Exclusion criteria. Pregnancy status will be confirmed verbally by the subject.
- Review changes in the subject's medical history since Screening. Any exacerbation of pre-existing medical history will be recorded as AEs.
- Perform OST Examination- Edentulous.
- Assess subject continuance.
- Clean the subject's dentures using the supplied denture brush and cleansing paste. Both upper and lower will be cleaned to remove all traces of denture fixative, plaque and particulates/debris. Dentures should then be dried.
- Apply denture adhesive (or no adhesive per the randomization schedule) and insert dentures per the Product Application Instructions.
- 60±5 minutes after denture insertion, begin Food Occlusion Testing including Subject Denture Dislodgment Assessment. (This includes peanut chewing, and peanut retrieval from dentures and the oral cavity).
- Subjects report the number of denture dislodgments during peanut chewing.
- Subjects complete questionnaire (as per Appendix 15.3) once dentures have been removed
- Photograph dentures of the first five randomized subjects at Visit 2.
- Perform OST Examination-Edentulous.
- Dentures will be cleaned and returned to subject.
- Records AEs and incidents. Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as (How do you feel?"
- Study Conclusion.

If a subject has any clinically significant, study-related abnormalities at the conclusion of scheduled inpatient portion of the study, the GSK CH monitor (or designated representative) should be notified and depending on the abnormality, the subject may be asked to remain at the clinical site until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain at the clinical site and /or when outpatient follow up is deemed appropriate, the GSK CH medical monitor (or designated representative) should be notified, and the investigator, should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

8.1.3 Informed Consent

The investigator, or designee, must obtain informed consent at the screening visit from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Two copies of the informed consent form (ICF) will be

signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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

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

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

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

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

e-Consent is a tool that assists in the consent process by using multimedia components delivered by an electronic system (e.g. IPad/tablet). The multimedia components consist of video, audio, knowledge review, dictionary and electronic signature.

The site staff can use the system to consent the subject with the benefit of helping the subject understand the research they are taking part in and to control the consent process.

The system will allow for a copy of the consent to be printed and given to the subject and for consent documents to be retained by the site in PDF format.

A GSK CH approved vendor will be used to provide the system and training and help desk will be provided as needed.

If the country and/or site does not have approval to use the e-Consent system, or the subject does not want to use the e-Consent system, then the conventional paper process will be followed. It is possible to use the e-Consent system to educate the subject while using paper to obtain signatures.

8.1.4 Demographics

The following demographic information will be recorded at the screening visit by the investigator or designee in the CRF: year of birth, gender, ethnicity and race.

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005. This is required for this study as the product is intended to be marketed in the US and allows for summary of data across different clinical studies, and different launch markets. This aids in a better understanding of potential differences across ethnicities.

8.1.5 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented at the screening visit in the CRF by the investigator or designee. The well-made assessment of dentures, denture bearing tissue assessment, denture retention and stability assessment, and OST examination should be performed by suitably qualified personal with expertise in prosthodontics.

8.1.6 Medical History and Prior Medication/Treatment

Details of relevant medical and surgical history (in the last 1 year), including allergies or drug sensitivity, will be documented in the CRF at the screening visit by the investigator or designee.

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 7 days and prior to signing the informed consent form, will be documented in the CRF.

8.1.6.1 Dental History

The Investigator, or medically qualified designee, will take a dental history from each subject at the screening visit. Dental history will include information of all prostheses in the mouth, maxillary and mandibular, as well as information regarding the age of the dentures, how long the subject has worn dentures, the prosthetic teeth material and whether the subject is a regular user of denture adhesives. This will be documented in the CRF.

8.1.7 Subject Eligibility

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

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

8.1.8 Clean Dentures

Denture cleansing will be performed by suitably qualified site staff. Enough denture cleansing paste will be applied to the supplied denture brush. All surfaces of the dentures will be thoroughly cleaned to remove all visible traces of denture fixative, plaque and particulates/debris. The dentures will then be rinsed thoroughly with running water.

Dentures should then be dried using clinical paper towels. Please note that the denture cleansing paste is to be used extra-orally and not for use in the mouth. Hands should be washed thoroughly following application and use of the denture cleansing paste. This procedure should be performed at all study visits.

8.1.9 Screening Procedures

The following assessments will be performed at times defined in the Study Procedure section of this protocol.

- Well-fit assessment, Kapur Olshan Modification Index
- Well-made assessment
- Denture bearing tissue assessment
- Food migration adequacy training

8.2 Study Period

The following efficacy and safety assessments will be performed at time defined in the Study Procedures section of this protocol.

- Oral soft tissue (OST) examination- edentulous
- Food occlusion testing incorporating denture dislodgment
- Subject questionnaire
- Denture photographs at treatment visits

Remind subject to inform the site if they experience any untoward medical occurrence or use any medications in the next visit. Changes in concomitant medication or non-drug treatments/procedures will be documented in the CRF.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to a non-leading question such as "How do you feel?" will be assessed and any AEs recorded in the CRF.

All procedures listed above will be carried out at Visit 2 and 3. As visit 3 is the last study visit, study close out procedures will also be carried out here.

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

8.3 Study Conclusion

The Study Conclusion page of the CRF will be completed for all subjects whether they completed all study procedures or if they were discontinued from the study early. If the subject discontinued early, at any point during the study, the primary reason for withdrawal should be recorded on the Study Conclusion page.

If a subject has any clinically significant, study-related abnormalities or AEs at the conclusion of the study, the GSK CH medical monitor (or designated representative) should be notified and, the subject may be asked to remain at the clinical site or be asked to return for a follow-up visit to ensure any issue is resolved or deemed not clinically significant.

8.4 Follow-up Visit

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

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

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

9.1.1 Well-Fit Assessment, Kapur (Olshan Modification) Index

At Screening, each denture (maxillary and mandibular) will be examined for retention and stability using the Kapur Index (Olshan Modification) (Kapur, 1967; Olshan, 1992) by an examiner with the expert knowledge of prosthodontics. The subject should not be using any denture adhesives during this examination. A sum score (maxillary and mandibular) of ≥6 is required for inclusion.

Retention:

With gloved hands, the examiner will attempt to unseat the maxillary and mandibular 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 and lateral force.

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

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

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

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

Stability

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 and mandibular 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 structure under pressure

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

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

Sum score (upper + lower denture) of <6 = dentures with poor retention and stability.
Sum score (upper + lower denture) 6-9 = dentures with fair retention and stability.
Sum score (upper + lower denture) 10-14 = dentures with good retention and stability.
Sum score (upper + lower denture) >14 = dentures with very good retention and stability.

9.1.2 Well Made Assessment

This assessment should be performed at screening.

Clinical Acceptability

Each denture (maxillary and mandibular) will be examined. Only having adequate (as judged by an examiner with expert knowledge of prosthodontics) vertical dimension, freeway space,

horizontal occlusal relationships and border extension will be considered clinically acceptable. For each denture (maxillary and mandibular), the examiner will indicate acceptable or unacceptable on the CRF.

Denture Finish and Contour

The contour and finish of each denture (maxillary and mandibular) will be examined. Only dentures with acceptable (as judged by an examiner with expert knowledge of prosthodontics) porosity, tissue surfaces, polished surfaces, color and thickness will be accepted. For each denture (maxillary and mandibular), the examiner will indicate acceptable or unacceptable on the CRF.

9.1.3 Denture Bearing Tissue Score

The denture bearing tissue score (Kapur, 1967) will be assessed at the screening visit by an examiner with the expert knowledge of prosthodontics and recorded for the maxillary and mandibular dentures on the appropriate CRF. There are no eligibility requirements associated with this measure in this clinical trial.

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 *

Due to an inconsistency observed in the original printed publication, the two descriptors above marked by an asterisk (*) have been modified (by inverting their order) to better reflect the authors intent and align with the grading scale.

9.1.4 Food Migration Adequacy Determination

Subjects must complete the food migration adequacy assessment at the screening visit by an appropriately trained/experienced staff whilst using no denture adhesives/fixatives. Dentures should have been cleaned and dried by the study staff and replaced in the subject's mouth. Subjects will be provided with 30-32 grams (accurately weighed) of non-salted peanuts, divided into smaller portions of approximately eight peanut halves. Each portion should be chewed for approximately 20 seconds, after which the subject will be instructed to swallow at any time they are comfortable. Subjects will be allowed small sips of water during the peanut consumption to aid chewing as appropriate. After completion of the peanut consumption, the subject will rinse their mouth with water for up to 10 seconds before removing their denture. The rinsing step

may be repeated as required, if necessary, in the opinion of the examiner, to ensure peanut particles that have not migrated under the dentures are cleared from the oral cavity, Subjects will be asked to remove their dentures (the examiner may assist in this if required) and place them into a labelled tray (with subject screening number) teeth side down, and may remove any residual peanut particles from their mouth with water and a gauze pad (not for collection). The amount of food particles on each denture will be visually assessed according to the scale below and recorded in the CRF to determine if there is evidence of peanut particle migration under the dentures. The following 0 – 3 assessment scale will be used. Subjects who present no evidence of peanut particles under either the upper or lower denture (i.e. if either denture scores as 0) will not be eligible.

The location and extent of peanut particle migration will be rated as follows:

0= None – No peanut migration under the denture.

1= Minimal – Slight migration of peanuts under the denture.

2= Moderate – Migration of peanuts over the internal walls of the denture.

3= Extensive – Peanuts migration on the crest of the denture.

Dentures should be cleaned thoroughly prior to returning to the subject.

9.2 Efficacy Assessments

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

9.2.1 Food Occlusion Testing Incorporating Dislodgment Assessment

Food Occlusion will be measured by a trained or experienced operator at Visits 2 and 3 using the method described below. 60±5 minutes after the dentures have been inserted:

1. The subject will be instructed to bite down firmly on their dentures. The subject will then rinse their mouth vigorously with water. The site staff will remove any adhesive that is oozing from the dentures. Note: The subject must not eat any food during the 60±5 minutes period with the exception of small sips of water.
2. The subjects will be given the denture dislodgement sheet to record the number of denture dislodgements experienced during the chewing of the peanuts. Subjects will also be instructed in this procedure using the standardized script.
3. The subject will be given 30-32g of non-salted, dry roasted peanuts to chew and swallow. The 32g portion of peanuts will be divided by the staff into smaller portions of approximately 8 peanut halves (approximately 4 g). The subject will be asked to chew each pre-measured portion of peanuts for at least 20 seconds, after which they may swallow at any time they are comfortable. The subject may sip water during peanut consumption to aid swallowing where required.
4. Whilst consuming the peanuts, the subject should tick a box (as per Appendix 15.2) every time they feel their denture dislodge. The total number of denture dislodgments for the subject should be recorded by the study site staff in the CRF.
5. Should a subject be unable to fully complete the chewing procedure above owing to excessive discomfort arising from peanut particles under their dentures or for any other reason, the chewing procedure should cease immediately and the subject's dentures

removed, cleaned and returned to them. The subject should undergo an OST examination per study schedule, but no efficacy measures (peanut mass, questionnaire responses, number of denture dislodgements) should be performed. The subject can continue for any remaining visits or be rescheduled to repeat the assessment. The reason for an absence of efficacy measures should be recorded in the eCRF. The examiner should assess whether the reason the subject was unable to complete the chewing procedure qualifies as an adverse event or incident and record in the eCRF as appropriate.

6. After consuming all of the peanuts, the subject will gently rinse their mouth with water whilst biting their dentures together for up to 10 seconds and then expectorate in order to remove any peanut particles not retained under the dentures. The rinsing step may be repeated as required, if necessary, in the opinion of the examiner, to ensure peanut particles that have not migrated under the dentures are cleared from the oral cavity
7. The examiner will clear the vestibular and sub-lingual areas (maxillary and mandibular) of any food particulates and then carefully remove the subject's mandibular denture and place it on a tray, teeth side down and remove any residual adhesive and/ or peanut particles from the lower edentulous ridge with a piece of gauze that will be placed in a separate beaker coded with the subject's screening number, treatment period (not treatment) and identifier to indicate mandibular denture.
8. The examiner will carefully remove the subject's maxillary denture and place it on a small tray, teeth side down and remove any residual adhesive and/ or peanut particles from the upper edentulous ridge/palate with a piece of gauze that will be placed in a separate beaker coded with the subject's screening number, treatment period (not treatment) and identifier to indicate maxillary denture.
9. All of the non-fitting surfaces of the dentures will be checked for residual peanuts. If any is found on any surface other than those in contact with oral soft tissue, it will be removed with a spatula and discarded.
10. For a subset of approximately 5 subjects at each treatment visit, a photograph of the fitting surface of the dentures will be taken as per section 9.2.3.
11. The maxillary and mandibular dentures of each subject will be placed in the coded beakers with the gauze (maxillary and mandibular separately).
12. Immediately following removal of the prostheses, the subject will complete the study questionnaire per section 9.2.2.
13. In the laboratory, approximately 100mls (or enough to cover the prostheses) of warm deionized water (approximately 50°C/122°F) will be added to each beaker. The beakers will be sonicated for at least 30 minutes to loosen any adhering peanut particles.
14. After sonication, any peanuts particles still remaining on the prosthesis or the gauze will be washed out into the beaker. The gauze pieces will be discarded and the dentures will be cleaned and returned to the subject.
15. The dentures should be cleaned thoroughly (section 8.1.8) before returning to the subject.
16. The solutions in the beakers (mixture of water, adhesive and saliva and peanut particles) will be heated to boiling with frequent stirring to dissolve any undissolved adhesive.
17. The hot solution in each beaker will be strained through a standard testing sieve, USA #60 (coded in the same manner as the beakers above).

18. The residue remaining on the screen will be washed repeatedly with hot water to remove any adhesive or saliva.
19. The collected peanut particles will be air-dried overnight on the screen.
20. The dried particles will be transferred from the screen to the pre-weighed coded (in the same manner as the beakers and sieves above) aluminum weighing pans using a spatula and then will be dried in an oven at 40°C (105°F) for 5 hours.
21. The pan will be removed from the oven, cooled to room temperature and then weighed (in grams, to 4 decimal places) to determine the mass of the particles from each denture. The weighing of the peanut particles will be carried out by a different operator than the operator that has carried out steps 1-19 and this operator will be blinded to treatment allocation.

Prior to commencing this testing, the subjects will have their entire food occlusion and denture dislodgement assessment procedure explained to them at each visit. A standard script will be used to ensure consistency in procedures.

9.2.2 Subject Questionnaire

After the food occlusion testing and following removal of the dentures on Test Days (Visits 2 and 3), the subject will complete a questionnaire (Appendix 15.3) on their experience during the chewing procedure. The subject responses should be transcribed by the study staff to the CRF. The study staff should be mindful that whilst the questionnaire does not solicit safety information, any information on safety outcomes recorded by subjects on the questionnaire should be evaluated to ensure all AEs are recorded prior to the subject leaving the site. Subjects who answer no to question 1 will not be required to answer question 2-4, and they will automatically be assigned a score of 0 for these questions.

9.2.3 Denture Photographs at Treatment Visits

For the first five randomized subjects in the study at Visits 2 and 3, extra oral digital photographs will be taken of the underside of each denture immediately after their removal to document the appearance of migrated particles for sponsor review. This procedure should be performed by appropriately trained/experienced staff. It is expected that approximately 5 sets of dentures be photographed per treatment, and where possible that consistency of subjects between treatments is maintained (i.e. a subject will be identified at visit 2 as being suitable for denture imaging and will have their dentures photographed at visit 2 and 3). Digital photographs and their filenames will not contain any personally identifiable information. The digital file should be appropriately named to identify the subject screening number and the treatment period. The only photographs that will be taken will be of dentures outside of the mouth. No images of subjects will be obtained.

9.3 Safety and Other Assessments

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

9.3.1 Oral Soft Tissue (OST) Examination- Edentulous

The OST examination should be performed at every visit by a qualified dentist and ideally the same examiner should be used. The OST Exam- Edentulous will include the labial mucosa

(including lips), buccal mucosa, tongue, gingival mucosa, sublingual area, hard and soft palates, mucogingival folds, 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. Any obvious deposits present in the mouth e.g. food, calculus or denture adhesive observed during any of the OST examinations should be removed by the subject/examiner.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

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

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

Events <u>Meeting</u> the AE Definition:

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

Events <u>NOT</u> meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g. endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g. appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

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

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

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

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

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

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

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

10.4 Reporting Procedures

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

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

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

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

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

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

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

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

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

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

It is essential to enter the following information:

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

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

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

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

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

10.5.2 Assessment of Causality

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

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

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

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

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

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

10.6 Follow-up of Adverse Events

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

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

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

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

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

Investigators are not obliged to actively seek AEs in former subjects. However, if the investigator learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the investigator will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD). The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD).

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

10.7 Withdrawal Due to an Adverse Event

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

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

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

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

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

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

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

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

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

10.8.2 Action to be Taken if Pregnancy Occurs

The investigator will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box (PPD) within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD). Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the investigator to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD). Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

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

10.9 Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSK CH for use in this study; the medical devices in this study are the COREGA Máximo Sellado/Selamento Denture Adhesive, the denture brushes and denture cleansing paste.

10.9.1 Definition of an Incident

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

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

It is sufficient that:

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

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

Examples of incidents:

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

10.9.2 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH 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, if in accordance with the investigator's normal clinical practice, and on the appropriate Incident Report Form. In addition, for incidents fulfilling the definition of an AE

(serious and non-serious), the appropriate AE CRF page and SAE form will be completed and reported as per the AE and SAE reporting sections.

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

The completed Incident Report Form should be scanned and emailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email as soon as possible, **but not more than 24 hours** after study site personnel learn of the event. If there is an SAE, the completed SAE form should be sent together with this report form. However, if a copy of the SAE report is sent with this form, this does not replace the procedure to report an SAE. The original Incident Report Form will be retained in the investigator study master file.

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

Email the Incident Report Forms to:
PPD

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

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

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

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

10.9.3 Follow-up of Medical Device Incidents

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

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

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

10.9.4 Regulatory and Ethics Reporting Requirements for Incidents

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

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

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

11 DATA MANAGEMENT

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

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

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

The source documents (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries, questionnaires, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Section 8 and 9. The CRF can be used as a source document at the discretion of data management.

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

11.1 Case Report Form

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

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

Management of clinical data will be performed in accordance with Third Party Biostats and Data Management (BDM) Vendor applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

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

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

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

11.2 Data Handling

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

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

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

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

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

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

11.3 Processing Patient Reported Outcomes

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

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

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

To protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO that will be forwarded to GSK CH or Third-Party Vendor.

11.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

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

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

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

The primary endpoint is the combined mass (mg) of peanuts from both dentures. Based upon a Modified Intent to Treat (MITT) analysis of a previous study data 208397 using a logarithmic transformation and an estimate of the within subject variability as the square-root of the (208397 study) Mean Square Error (MSE) (0.5075), 48 subjects in a 2-period crossover design analyzed with a logarithmic transformation (base 10), will have 81% power to detect a multiplicative difference of 2 (0.3010 on log scale), i.e. 2-fold more peanuts (indicating twice as many peanuts by mass) with no adhesive compared to the active adhesive subjects using a two-sided significance test at the 5% level. For a multiplicative difference of 2.25 (0.3522 on log scale) the power will be approximately 91% with 48 evaluable subjects. 52 subjects should be randomized to ensure 48 are evaluable.

These were calculated using the Power Analysis and Sample Size (PASS) software for a two-period crossover trial and using the Sw option for the variability estimate as 0.5075. An extensive simulation study, supported the above calculations conducted in PASS.

A non-parametric alternative (Wilcoxon Signed Rank Test) if the logarithmic transformation is not indicated will have similar power.

12.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical reporting and analysis plan (RAP), which will be written following finalization of the protocol and prior to study Database lock.

12.2.1 Definition of Analysis Populations

- The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject received.
- The MITT (Treated or Exposed) population will comprise all randomized subjects who receive at least one dose of study product and have at least one on therapy assessment of efficacy. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.

- The Per-Protocol (PP) population includes all subjects who fully comply with all study procedures and restrictions. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters.

12.2.2 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.2.3 Demographic and Baseline Characteristics

Age and other continuous variables will be summarized using descriptive statistics such as means, medians and standard deviation. Gender, race and other categorical variables will be summarized using frequency counts and percentages for the safety and MITT populations.

12.2.4 Study Drug/Product Compliance

Compliance to the study product use will be tabulated and summarized for the safety and MITT populations.

12.2.5 Prior and Concomitant Medications

Prior medications, concomitant medications and significant non-drug therapies taken during treatment will be listed for the safety population.

12.2.6 Primary Analysis(es)

Food occlusion will be measured by mass of peanut particles (mass of retrieved peanuts in milligrams). Analysis will be performed on the Log_{10} transformed masses of peanuts recovered from the combined mandibular and maxillary dentures. Raw means, standard deviations, standard errors, minimum and maximum values will be reported by treatment.

A Mixed model ANOVA will be used with Log_{10} peanut mass as response and treatment and period as fixed explanatory effects and subject as a random effect. In case of any zero counts a small value will be used in the analysis. In case of issues with model assumptions (residual distributions etc), alternative transformations may be sought or non-parametric equivalents (Wilcoxon Signed Rank Test) used.

The study will be considered successful if there is a statistically significant difference between the mass of peanuts under dentures of subjects using denture adhesive versus when using no adhesive. The MITT population will be considered primary for this analysis.

12.2.7 Secondary Analysis(es)

An identical analysis will be conducted on the peanut mass (g) obtained on each of the two dentures separately. In case of any zero counts a small value will be used in the analysis.

The number of denture dislodgments will also be analysed. Raw means, standard deviations, standard errors, minimum and maximum values will be reported by treatment.

For the subjects' responses to questionnaires (0-10), descriptive statistics (number of subjects and percentages) will be provided for each question response category by treatment.

Secondary variables include the number of denture dislodgments and subject responses to questionnaires (0-10), similar statistical presentations will follow the primary analysis approach without transformation.

For all secondary analyses the MITT population is primary. No alpha adjustments will be made for multiple secondary endpoints due to the exploratory nature of the inferences.

No interim analyses are planned.

12.2.8 Safety Analysis(es)

All AEs will be coded using MedDRA. AEs will be categorised as oral and non-oral by the Clinical Research Scientist (CRS) prior to database lock. Treatment-emergent adverse events (Oral AEs as well as all AEs) will be associated with the most recent treatment received. The number of AEs and number of subjects with AEs will be listed and tabulated by treatment. The results of OST exams will be tabulated and any abnormality from an OST examination will be regarded as an adverse event. Incidents will be listed.

12.2.9 Other Analysis(es)

The photographs will be presented in the study report and may be included with any publications / presentations arising from this study in order to help explain the study findings.

12.2.10 Handling of Dropouts and Missing Data

Missing data will not be replaced or imputed. Dropouts will be included in the analysis up to the last assessments at the point of discontinuation.

12.2.11 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

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

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

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation. As per the Regulatory Determination for this study, the experimental adhesive is categorized as a medical device and therefore a Nonsignificant Risk (NSR) application will be required as part of the IRB submission to conduct this study in the US.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for

International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

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

13.3.3 Subject Information and Consent

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

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

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

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

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials,

but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of denture adhesives at any time. For multicenter studies (if applicable), this can occur at one or more or at all sites.

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

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

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

13.8 Definition of Study End/End of Study

The end of the study will be the date of the Last Subject Last Visit (LSLV). For this study the LSLV date will be the primary completion date (PCD).

14 REFERENCES

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15 APPENDIX

15.1 ABREVIATIONS

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

Table 15-1 Abbreviation

Abbreviation	Term
°C	Degree Centigrade
°F	Degree Fahrenheit
AE	Adverse Event
ANOVA	Analysis of Variance
BDM	Biostats and Data Managment
CI	Confidence Interval
CRF	Case Report Form
CRS	Clinical Research Scientist
CSA	Clinical Study Agreement
CTA	Clinical Trial Application
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
g	Gram
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSK CH	GlaxoSmithKline Consumer Healthcare
ICF	Inform Consent Form
ICH	International Conference on Harmonisation

Abbreviation	Term
IRB	Institutional Review Board
MITT	Modified Intent to Treat
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
N/A	Not Applicable
OST	Oral Soft Tissue
PASS	Power Analysis and Sample Size
PI	Principal Investigator
PP	Per Protocol
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
SS	Safety Statement
US	United States

15.2 Example Form to Record Number of Dislodgments and Subject Completed Questionnaire

Date:

Subject Number:

Visit Number:

Tick a new box every time you feel your denture dislodge whilst you are chewing the peanuts.

15.3 Example Subject Completed Questionnaire

Date:

Subject Number:

Visit Number:

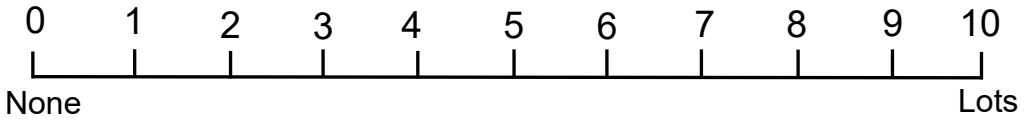
The following questions are about the peanut chewing you have just undertaken. Thinking about **only the peanuts you have just chewed** please circle one answer for each question.

1) Were you aware of peanut pieces under your denture? (Please circle your answer)

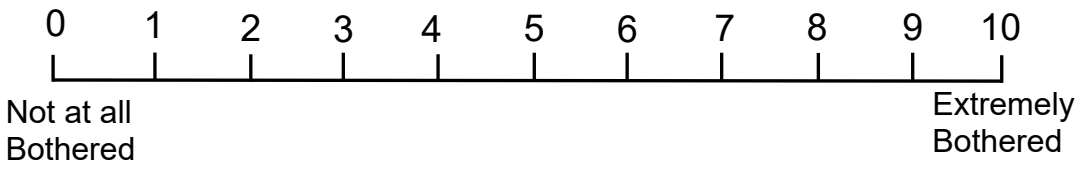
Ye No

If you have answered "No" to question 1, you do not need to answer questions 2 and 3.

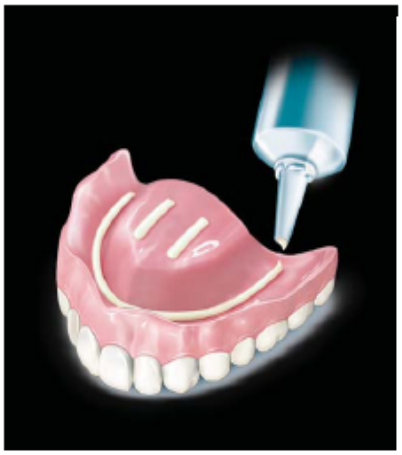
2) On a scale of 0 to 10 how would you rate the amount of peanut pieces that went under your denture? (Please circle your answer)

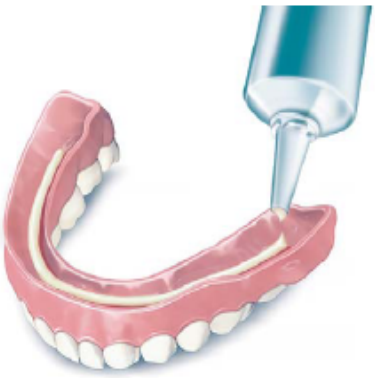


3) On a scale of 0 to 10 how bothered were you by the peanut pieces that went under your denture? (please circle your answer)



15.4 Product Application Instructions





For the Test group:

1. Clean and dry dentures
2. Apply product directly from primary packaging in long, continuous strips as shown in the diagram, not too close to the denture edge:
    a. 1g of product should be applied to the upper denture (3 strips should be applied to the upper denture)
    b. 0.6g of product should be applied to the lower denture (1 strip should be applied to the lower denture)
3. Have the subject rinse their mouth with water and expectorate before inserting the dentures.
4. Have the subject press dentures into place firmly, and bite down for a few seconds to secure hold.

For the Control group:

1. Clean and dry dentures.
2. Have the subjects rinse their mouth with water and expectorate before inserting the dentures.
3. Have the subject press dentures into place firmly, and bite for a few seconds to secure hold.