CLINICAL PROTOCOL

A Randomized, Single-Blind Clinical Study Assessing the Maximum Maxillary Bite Force When Using Two Novel Denture Adhesives Compared to Using No-Adhesive

Protocol Number:	218042
Compound/Product Name:	Experimental denture adhesives
United States (US) Investigational New Drug (IND) Number:	N/A
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This document contains confidentiality statements that are not relevant for this publicly available version

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1	2.0	Nine administrative changes:- • Change from data queries being performed from monthly to every 8 weeks in Section 11.2.1. • Deletion of erroneous entry in Section 8.2.1 which described taking a baseline KO measure. This procedure does not need to be performed and is inconsistent with the rest of the protocol. • Correction of reference to sections 15.4 or 15.5 to correct reference of section 15.2. These corrections are made in Sections 6.1.2, 6.1.3 and 9.1.4 • In sections 9.3.1 and 9.3.2 addition that a water rinse could be performed prior to OST/OHT examinations at examiner's discretion. • In section 4.1 tolerance for time window for bite force reads changed from ±5 mins to ±5 mins at the 0.5hr measurement and ±10 mins for all other times. This aligns with rest of the protocol. • Clarification to section 12.1 from "(b) superiority of either or both of EXP1 and EXP2 products compared to…" to "(b) superiority of either or both of the experimental denture adhesives products compared to…". • Sections 6.1.1 and 8.1.5 clarified to allow the denture cleansing paste to be used to clean dentures at the end of the test day. • Addition of instructions to Section 6.1.3 to discard first 1-2 inches of extruded denture adhesive if syneresis is observed. • Section 9.1.4 modified to allow repeated bites to be performed in the event of a methodological error.

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 applicable portions of EU MDR 2017/745 and European Nation International Organisation for Standardisation (ISO) 14155:2011 and ISO 14155:2020.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

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

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1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

A Randomized, Single-Blind (to the examiner performing the bite force assessment) Clinical Study Assessing the Maximum Maxillary Bite Force When Using Two Novel Denture Adhesives Compared to Using No-Adhesive.

Background and Rationale:

The two experimental denture adhesives being tested in this study require clinical evidence of efficacy in delivering denture hold to support intended claims. Measurement of the maximum incisal Bite force (BF) achievable prior to denture dislodgment is a commonly used measure of denture hold and will, therefore, be used in this study.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the maximum incisal bite force until maxillary denture dislodgement of two experimental denture adhesives to no adhesive over 12 hours	Area over baseline in bite force over 12 hours
Secondary	
To compare the maximum incisal bite force until maxillary denture dislodgement of two experimental denture adhesives to no adhesive for time periods up to 9 hours.	Area over baseline up to 0.5, 1, 3, 6 and 9 hours
Safety	
To assess the local tolerability of two experimental denture adhesives	Treatment emergent adverse events and incidents

Study Design:

This will be a single-centre, controlled, randomized, single-blind (with respect to the examiner performing the incisal bite force (BF) measurements), 4-treatment, 4- period, cross-over study to evaluate the maximum maxillary BF in a population of full maxillary denture wearers. The aims of this study are to investigate the hold properties of two experimental denture adhesives using established maximum incisal BF methodology. A currently marketed denture adhesive will be used as a positive control, whilst use of no adhesive will be employed as a negative control. This study design is similar to that employed in previous studies (Axe et al., 2018, Jose et al., 2018, Varghese et al., 2019).

Study Products:

The two experimental adhesives being investigated in this study have been formulated to provide denture hold throughout the day.

In this study the experimental denture adhesives will be compared to no adhesive for all BF assessments.

A marketed denture adhesive with extensive clinical evidence of efficacy, Super Poligrip Free (SPF), will be used as a positive control to assess study validity. All adhesive applications will be applied by clinical site dispensing staff and will be controlled by weight for the maxillary denture only (1.00g ± 0.05grams (g)). If subjects also wear a mandibular denture (either full or partial), then SPF will be used to stabilize the mandibular denture.

Type and Planned Number of Subjects:

A sufficient number of healthy subjects with full maxillary dentures will be screened to randomize at least 45, to ensure at least 42 evaluable subjects complete the entire study. Subjects will be male or female, aged 18-85 years.

The primary efficacy endpoint is the area-over-baseline (AOB) over 12 hours for the incisal bite force (in pounds [lbs]) (denoted by $AOB_{0\text{-}12}$). The primary objective is to compare incisal bite force of the two test adhesives, independently, versus no adhesive over 12 hours, $AOB_{0\text{-}12}$. The study validity will first be evaluated by comparing Super Poligrip Free vs no adhesive for $AOB_{0\text{-}12}$. Demonstrating study validity ($p<0.05$ for Super Poligrip Free vs no adhesive) is a prerequisite to performing all other treatment comparisons. No further significance testing will be performed if the initial validation step is not achieved.

An analysis of covariance (ANCOVA) model will be used to analyze $AOB_{0\text{-}12}$, with treatment and period as fixed effects; the covariates in this model are the subject level baseline and period level baseline minus subject level baseline. Subject will be included as a random effect. Pairwise treatment comparisons will be obtained as a difference in adjusted means and presented with 95% confidence intervals (CI) and associated p-values.

The secondary endpoints $AOB_{0\text{-}0.5}$, $AOB_{0\text{-}1}$, $AOB_{0\text{-}3}$, $AOB_{0\text{-}6}$, $AOB_{0\text{-}9}$ will be defined and analyzed in a similar manner as $AOB_{0\text{-}12}$.

No adjustments for multiplicity will be carried out for hypothesis testing of primary and secondary endpoints. The analyses will be repeated for each experimental adhesive with no splitting of alpha or hierarchical order between the two joint primary endpoints of $AOB_{0\text{-}12}$, for each test adhesive.

1.2 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, 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		Visit 2 Treatment Period 1		Visit 3 Treatment Period 2		Visit 4 Treatment Period 3		Visit 5 Treatment Period 4
Informed consent	X	Between 1 and 28 days		Between 1 and 28 days		Between 1 and 28 days		Between 1 and 28 days	
Medical history	X								
Dental history	X								
Demographics	X								

Procedure/Assessment	Screening	Study Period							
	Visit 1		Visit 2 Treatment Period 1		Visit 3 Treatment Period 2		Visit 4 Treatment Period 3		Visit 5 Treatment Period 4
Current/prior/concomitant medication review	X		X		X		X		X
Denture cleaning[6]	X		X		X		X		X
Denture Bearing Tissue Assessment	X								
Criteria for well-made and fitting dentures	X								
Kapur-Olshan Index assessment to determine eligibility	X								
Inclusion/exclusion Criteria	X		X		X		X		X
OST Examination[1]	X		X		X		X		X
OHT Examination[2]	X								X
Mandibular denture stabilization[3]	X		X		X		X		X
Training bites (3 incisal BF measurements with no adhesive)	X								
Qualifying bites (4 Incisal BF measurements with no adhesive)	X								
Subject eligibility	X								
Practice bites (3 Incisal BF measurements with no adhesive)			X		X		X		X
Baseline (pre-treatment) incisal BF measurements			X		X		X		X
Subject continuance			X		X		X		X
Randomization			X						
Product application to maxillary denture by site staff			X		X		X		X
Incisal BF measurements (0.5, 1, 3, 6, 9, 12hr)			X		X		X		X
Denture cleaning at end of study visit day with removal of excess adhesive from mouth[4]	X		X		X		X		X
Adverse events and incidents review[5]	X		X		X		X		X
Study conclusion/subject exit from study									X

Abbreviations: OST: Oral Soft Tissue, OHT: Oral Hard Tissue, BF: Bite force

Footnotes:

1. OST exam performed before denture stabilization (if required) and/or commencement of BF assessments; and again after denture and residual adhesive removal at end of each study visit.
2. OHT exam performed at Screening (Visit 1) following the first OST exam; and at the end of Treatment Period 4 (Visit 5), following the last OST exam.
3. Mandibular denture can be stabilized, if present, and re-stabilized using adhesive up to 2 times (max 3 adhesive applications per day) at examiner's discretion.
4. Study site staff who confirm absence of denture adhesive in the mouth at Visits 2-5 will not be the same person as performing any blinded assessments.
5. Adverse Events (AEs), Serious Adverse Events (SAEs), medical device incidents collected immediately after subject provides consent to participate in the study and throughout the study.
6. Denture cleaning to be performed prior to well-made assessment at Screening or product application (or denture insertion for subjects randomized to no adhesive treatment) at V2-5.

2 INTRODUCTION

Denture adhesives (or fixatives) have been used by edentulous subjects to improve the retention and stability of their dentures for many years. The primary benefits of using a denture adhesive cream are to enhance retention and stability of the prosthesis, and to reduce food entrapment (Zarb et al., 2013). Adhesives contain materials that become hydrated when they come into contact with saliva, allowing the adhesive to stick readily to both the mucosal surface and the fit surface of the denture (Shay, 1997).

There are a number of recognized methods which have been used to demonstrate the efficacy of a denture adhesive. These include the Kapur Index (Kapur, 1967) and bite force (BF) until denture dislodgement (Howell and Manly, 1948) to measure denture retention and stability; denture dislodgement (Tarbet et al., 1980) to measure denture movement in function; and masticatory performance (Kapur, 1967) as an indicator of chewing efficiency. The BF clinical model has been used successfully to demonstrate the efficacy of cream denture adhesives to improve denture hold for up to 12 hours and as early as 30 minutes after the adhesive application, while also demonstrating differences in strength among various adhesive formulations (Grasso, 2004, Chew et al., 1985, Chew et al., 1984). This study investigates BF as a measurement of retention of the maxillary denture.

In this study, a BF transducer system will be used to measure incisal bite force until denture dislodgement of maxillary complete dentures. Subjects in this study will have dentures judged to be clinically acceptable and moderately well-fitting using the Kapur index that was modified by Olshan et al. (Olshan et al., 1992). Dentures will also be judged to be well-made and using the design and construction criteria to ensure they are clinically acceptable for the study.

This clinical study is designed to support the efficacy of two experimental denture adhesive creams. The adhesive hold properties of the experimental products compared to the use of no adhesive will be assessed through evaluation of the maximal incisal biteforce that can be achieved before denture dislodgement.

2.1 Study Rationale

The two experimental denture adhesives require a clinical trial to establish clinical efficacy through the measurement of denture retention in order to support intended claims for either of these adhesives.

The maximum achievable incisal bite force prior to denture dislodgement is a commonly used measure of denture hold for denture adhesives and will therefore be used in this study.

This is a Phase III study that is planned to be performed by a clinical site in the United States of America (USA) with experience in the bite force methodology and equipment.

2.2 Background

A BF transducer will be used to measure the maxillary incisal bite force over a 12-hour time period. BF indicates denture retention by measuring the maximum force that can be applied by the incisors prior to dislodgement of the maxillary denture (Munoz et al., 2012). This is line with previous GSK studies CCI [redacted]) where the BF clinical model has been successfully used to demonstrate the efficacy of denture adhesives to improve denture hold for up to 12 hours and as early as 30 mins after adhesive application, whilst also demonstrating differences in strength among various adhesive formulations.

Based upon their compositions and pre-clinical *in vitro* testing methodology, the two experimental adhesives are expected to provide sufficient hold to meet the objectives of this study. Both share similarities with the positive control adhesive which has previously been shown to be effective in this clinical design (CCI [redacted]).

2.3 Benefit/Risk Assessment

The primary benefit of usage of a denture adhesive is to provide greater hold and stability of the denture within the oral cavity. In this study the two experimental denture adhesives are anticipated to provide adequate denture hold.

As detailed in the Safety Statement for this study, on the basis of the toxicological and safety data available for the ingredients contained in the experimental denture adhesives (CCI [redacted] and CCI [redacted] and the marketed product Super Poligrip Free (CCI [redacted] Adhesive Cream (CCI [redacted] and the history of use of CCI [redacted] and similar marketed products, these formulations are considered suitable for use in the proposed clinical study. In addition, there are no known safety concerns regarding the use of Oral B Denture Brush and Polident Dentu Crème Denture Cleansing Paste during this bite force evaluation study. All these products are considered suitable for use under the conditions of this clinical study. The clinical study methodology is commonly used as an effective means of evaluating the hold performance of a denture adhesive. No interaction with the denture adhesives under evaluation and any concomitant medications/treatments is expected. The benefit risk profile of this study is therefore favorable.

2.4 Mechanism of Action/Indication

Denture adhesives function by forming an adhesive layer between the denture and gum surface thereby reducing denture movement and improving hold. These adhesive properties are driven by a combination of different adhesive polymers in the adhesive creams, including carboxymethyl cellulose (CMC), carbomer and polyvinyl methyl ether/maleic anhydride co-polymer. The polymers are dispersed in a hydrocarbon medium as a cream. In the oral cavity, the cream absorbs water and the polymers hydrate providing adhesiveness between the denture and the denture bearing tissues.

3 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the maximum incisal bite force until maxillary denture dislodgement of two experimental denture adhesives to no adhesive over 12 hours	Area over baseline in bite force over 12 hours
Secondary	
To compare the maximum incisal bite force until maxillary denture dislodgement of two experimental denture adhesives to no adhesive for time periods up to 9 hours.	Area over baseline up to 0.5, 1, 3, 6 and 9 hours
Safety	

To assess the local tolerability of two experimental denture adhesives	Treatment emergent adverse events and incidents

This study will be considered successful if either or both of the experimental denture adhesives are shown to have a statistically significantly greater area over baseline in bite force over 12 hours (AOB_{0-12}) compared to no adhesive use. In addition, to ensure assay sensitivity and for the study to be deemed valid, the positive control denture adhesive will be required to demonstrate statistically significantly superiority to no adhesive using the same endpoint.

4 STUDY DESIGN

4.1 Overall Design

This will be a single-center, controlled, randomized, single blind (with respect to the examiner performing incisal bite force readings), 4-treatment, 4 treatment-period, cross-over study to evaluate maximum maxillary bite force in a population of full maxillary denture wearers.
A sufficient number of subjects will be screened, aged between 18-85 years, with well-made and moderately well-fitting complete maxillary dentures. A sufficient number of healthy subjects with full maxillary dentures will be screened to randomize at least 45, to ensure at least 42 evaluable subjects complete the entire study.

This study consists of 5 visits (1 screening visit and 4 treatment periods). At Visit 1, Screening, subjects will be assessed for eligibility based on the inclusion/exclusion criteria and will undergo an Oral Soft Tissue (OST) examination. The subject's maxillary denture will be assessed for retention and stability using the Kapur Index (Olshan Modification) and whether they are well made and will also undergo a denture bearing tissue assessment. Following these screening assessments, if a subject has a mandibular denture, this will be secured using a marketed denture adhesive. Subjects will then be instructed on the use of the BF equipment and they will undergo 3 training bites (without adhesive) to familiarize them with the BF transducer and how to perform a valid bite. After the training bites, subjects will perform 4 qualifying bites (without adhesive). All 4 of the qualifying bites must be $\leq$ 9lbs (pounds) and at least 2 of the 4 bites must be reproducible (±2lbs). Subjects that meet all inclusion criteria with no exclusions will return for Visit 2 (treatment period 1).

On each test day (Visit 2 to Visit 5) subjects will return to site without denture adhesive being used, where subject continuance will be assessed and confirmed, an OST-edentulous examination performed. Subject's dentures will then be cleaned, the mandibular denture will be stabilized (as required) and the subject will rinse their mouth with potable water prior to placement of the dentures in the mouth. Subjects will then perform 3 practice bites to re-familiarize them with the BF transducer and then they will undergo the baseline incisal BF measurement (the different bites are summarized in Table 4-1). Following randomization, for subjects randomized to use of an adhesive, 1.0g (± 0.05g) adhesive product will be applied only to the maxillary denture as per the application instructions (Appendix 1), and the subject will refit their denture. For subjects randomized to no adhesive use, the clean and dried denture will be refitted without adhesive.

Table 4-1 Incisal Bite Force Descriptions

Bite	When Performed	Purpose
Training	Screening, Visit 1	3 bites to familiarize subjects with BF equipment and performing a bite.

Bite	When Performed	Purpose
Qualifying	Screening, Visit 1	4 bites that must equal ≤9lbs with 2 of these bites within (±2lb) as part of inclusion criteria.
Practice	Test days (Visit 2-5) pre baseline measurements and adhesive application	3 bites to re-familiarize subjects with performing valid bite.
Baseline	Test days (Visit 2-5) pre adhesive application	A single bite to determine Baseline measurement without adhesive application. Must be ≤9lbs and within ±2lbs of one of the practice bites performed on the same day.
Test	Test days (Visit 2-5) following adhesive application	Single test bites taken at 0.5, 1, 3, 6, 9 and 12hrs.

Test incisal BF measurements will be taken at 0.5, 1, 3, 6, 9 and 12 hrs (± 5 mins for the 0.5 hr measurement, ±10 mins for all other time points) after denture refitting. Following the 12hr incisal BF measurements, the dentures, and any excess adhesive will be removed, and the dentures will be cleaned before returning to the subject after a further OST- examination.

Safety will be monitored throughout the study through the reporting of AEs, incidents and OST/OHT examination. The examiner performing the BF assessment should remain blinded to the treatment.

4.2 Scientific Rationale for Study Design

Dentures are unique to each individual, and so the most appropriate method to evaluate their performance with and without adhesive is a within subject comparison, and therefore a cross over design will be used for this study.

A minimum washout period between treatment visits is considered sufficient to minimize any carryover effects. 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 minimum 1-day between each treatment period is considered adequate recovery from test day procedures. There will be a maximum of 28 days between study visits to facilitate subject visit scheduling.

Incisal BF until denture dislodgment is a measure of maxillary denture retention and is a commonly used objective test method that has been used to demonstrate the efficacy of denture adhesive CCI [redacted]). The methodology will use a calibrated electronic BF transducer system to ensure accuracy.

Subjects with complete maxillary dentures will be recruited for this study. Subjects with poorly fitting dentures are generally advised to seek prosthodontic advice to improve the fit (i.e. by relining etc.), and therefore only subjects with a well-made and moderately-to-well-fitting maxillary denture (as determined using the Kapur Index (Olshan modification) for denture retention and stability (Kapur, 1967, Olshan et al., 1992) will be considered for enrollment.

A stable lower dentition/denture is required to enable an accurate BF measurement and therefore, if a partial or full mandibular denture is worn, this will be secured (if deemed

necessary by the examiner) using the supplied marketed denture adhesive (Super Poligrip Free), which may be reapplied, at the examiner's discretion, a maximum of 2 times (total of 3 applications per day) at each visit period.

At Screening, Visit 1, training BF measurements will be taken to allow subjects to familiarize themselves with the biteforce measurement and to understand how to bite in a consistent manner for BF technique and to allow the examiner to establish whether subjects understand and are able to conduct the necessary bites. If subjects are unable to conduct a valid bite, they may be withdrawn from the study at the examiner's discretion. Training bites will be followed by 4 qualifying bites that will form part of the inclusion criteria. Subjects will be required to perform practice bites on each test day to re-familiarize themselves with the equipment.

Whilst blinding is an important consideration for any clinical study, the nature of this study prevents blinding to the subject since they will be aware of having adhesive or no adhesive present. Additionally, for the same reason, the site staff who administer the products cannot be blinded. The level of blinding is therefore restricted to the examiner who performs the biteforce assessment, and hence the study will be single-blind (to the examiner performing the biteforce assessment).

A positive control has been included in this study as a measure of assay sensitivity using a currently marketed denture adhesive (Super Poligrip Free) which will be used to ensure study validity. SPF has been chosen as a positive control for this study as it is currently marketed and numerous data exists demonstrating its bite force efficacy versus no adhesive ([redacted]). A 'no adhesive' control arm is included to provide a continual reference point of no adhesive use over the 12-hour period. No adhesive use is representative of a significant number of denture wearers (~81% of 750 million denture wearers, GSK data on file). In addition, a no adhesive arm will aid interpretation of the results of this study and allow comparison with previous studies.

The pattern of application of the experimental denture adhesives will be as per the intended application instructions for the planned marketed product. The pattern of application of the SPF denture adhesive (as the positive control) on the maxillary denture will be as per the marketed label instruction. The application of experimental and control denture adhesives on the maxillary denture will be controlled by weight of 1.00g (±0.05g) (Appendix 15.2). Controlling and standardizing the application of the adhesive by weight will limit any variations related to the amount of adhesive applied.

The application of the SPF to stabilize the mandibular denture will be per label instruction and will not be weighed (see Appendix 15.2).

Due to longevity of study test days (12-14hrs), subjects will be provided with 3 meals (breakfast, lunch and dinner) and snacks. These meals and snacks will be standardized and will be specially chosen to avoid particularly tough or chewy foods and will mainly consist of foods that are not likely to migrate under dentures and cause irritation (avoiding e.g. fruits and vegetables with seeds, shelled/unshelled nuts, breads with grain/seeds etc). Additionally, subjects will be allowed to snack *ad lib*.

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 or bite. Subjects who use or have ever used bisphosphonate medications

are specifically excluded from this study owing to the enhanced risk of bisphosphonate-related osteonecrosis of the jaw (BRONJ) that is associated with reduced tissue tolerance to function with removable prostheses (Saldanha et al., 2012). Subjects who are xerostomic are excluded since the proper function of denture adhesives requires adequate hydration from saliva.

As the investigational adhesives are medical devices no pregnancy warning on labelling is planned, and so pregnancy testing will not be required. Subjects will, however, need to provide verbal confirmation of negative pregnancy status and this must be documented as part of the exclusion criteria.

Demography 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.

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 to assess for possible AEs. Similarly an oral hard tissue (OHT) examination will be performed at the start (visit 1) and end (visit 5) of the study to assess for potential AEs.

4.3 Justification for Dose

Adhesive application will be weight controlled with 1.00g (±0.05g) being applied to the maxillary denture. This dosing is in line with previous GSK CH studies ([redacted]), is consistent with standard usage of a denture adhesive and eliminates the variability associated with not controlling the mass of 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

Sufficient subjects will be screened to randomize at least 45 to ensure at least 42 evaluable subjects complete the entire study.

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

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

Subject eligibility to participate in the clinical study should 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 the following inclusion criteria to be eligible for enrollment into, and continuance in 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. A male or female subject who, at the time of screening, is between the ages of 18-85 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, 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 or 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. A subject with a **completely edentulous maxillary arch** restored with a conventional maxillary full denture with an acrylic base. The maxillary denture prosthesis must fulfil all of the following:
    a. At least moderately well-fitting (Kapur Index, Olshan Modification: retention score ≥2, stability score ≥2) at the Screening (V1) visit,
    b. Is well made (according to the well-made assessment).
6. A subject with BF measurements which satisfy all the following criteria:
    a. The qualifying BF measurements (without adhesive) at V1 (Screening) must be ≤9lbs.
    b. At least 2 of the 4 qualifying BF measurements (without adhesive) at V1 (Screening) must be reproducible (within ±2lbs).
    c. The Baseline BF measurement (without adhesive) at V2-5 must be ≤9lbs.
    d. The Baseline BF measurement (without adhesive) at V2-5 and at least 1 of the 3 practice BF measurements must be within ±2lbs of each other.
7. A subject who is dentate in the mandibular arch or has a partial or full denture in the mandibular arch that is:
    a. sufficiently stable, in the opinion of the investigator, to enable the bite force determination to be performed.
    b. well made (according to the well-made assessment).

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from 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 Visit 1 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 experimental 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 pregnant (self-reported) or intending to become pregnant over the duration of the study.
5. A subject who is breastfeeding.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
8. A subject who is currently taking or has taken a bisphosphonate drug (i.e., Fosamax, Actonel, Boniva).
9. A subject who uses any medication or has a condition (e.g. insulin dependent diabetes) that, in the opinion of the investigator, would interfere with the conduct of the study.
10. A subject who has any clinically significant or relevant oral abnormality (e.g. temporomandibular joint [TMJ] problems or tooth abnormalities) that, in the opinion of the investigator, could affect the BF measurements or subject safety.
11. A subject who has any condition or medication which, in the opinion of the investigator, is currently causing xerostomia or which could interfere with the conduct of the study.
12. A subject with a recent history (within the last year) of alcohol or other substance abuse.
13. A subject with OST examination findings (at V1) such as stomatitis, open sores, lesions, cavitied caries lesions, redness or swelling which in the opinion of the investigator, could interfere with the conduct of the study.
14. A subject who has previously been enrolled in this study.
15. A subject who is unable to comply with study requirements and/or who is not able to reliably perform a valid bite at the examiner's discretion.
16. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.

5.4 Randomization Criteria

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

5.5 Lifestyle Considerations

5.5.1 Meals/Dietary and Lifestyle Requirements and Restrictions

- Subjects will be required to remain on site for the duration of the treatment visit day.
- On treatment visit days, subjects will only be permitted to consume the standardized meals and snacks and cold drinks provided.
- Subjects are not permitted to chew gum whilst at the study site.

Throughout the study day, subjects will be provided with 3 standardized meals (breakfast, lunch and dinner) and snacks. These meals and snacks will consist of foods that are not likely to

migrate under dentures and cause irritation (avoiding fruits and vegetables with seeds, shelled/unshelled nuts, breads with grain/seed etc.). Subjects will be allowed to snack *ad lib* but will not be permitted to eat any other foods other than those provided.

Breakfast will be served within 1hr after the 1hr BF measurement. Lunch will be provided within 1hr after the 6hr BF measurement. Dinner (or snacks) will be provided within 1hr after the 9hr BF measurement.

5.5.2 Alcohol and Tobacco Restrictions

- Subjects will not be permitted to smoke, including e-cigarettes and use chewing tobacco or other tobacco products or consume alcohol for the duration of the screening visit and each treatment day (12-14hrs) until completion of all assessments.

5.5.3 Medication and Treatment Restrictions

- The details of current and concomitant medications will be collected, and subjects will be allowed to participate if these medications are judged to be non-interfering by the investigator as per inclusion and exclusion criteria.
- Subjects will not be permitted to have any routine dental/denture work performed during the time that they are in the study, unless it is for emergency treatment that should not be delayed. This is to ensure that the denture fit will not be altered during the study.
- If a subject uses denture adhesive as part of their normal routine, then they can continue using the adhesive between treatment visits, but they should not change the routine of adhesive use during the course of the study.
- Subjects will be instructed to report to the study site on treatment visit days (Visits 2-5) without denture adhesive on their maxillary denture and mandibular denture (if present).

5.6 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, any protocol deviations and any adverse events or incidents as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

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

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

The contact number is not intended for direct use by study subjects. To facilitate access to appropriately qualified medical/dental personnel on study-related medical/dental questions or problems, subjects will be provided with a contact card. The contact card will provide, as a

minimum, protocol identifiers, the subject's study identification number, contact information for the investigational site, and contact details in the event that the investigational site cannot be reached to provide advice on a medical question or problem identified by a healthcare professional other than the investigator.

5.8 Rater/Clinical Assessor Qualifications

Suitably qualified dental professionals with expertise in prosthodontics will be required to perform the OST examination, KO index and the screening assessments relating to denture fit and condition for this study. An examiner that is suitably trained in carrying out the incisal BF measurements will also be required to perform the BF assessments in this study. Wherever possible the same examiners should perform the same assessments throughout the study.

6 INVESTIGATIONAL/STUDY PRODUCTS

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

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 Products		Reference Product
Product Name	Experimental Denture Adhesive 1	Experimental Denture Adhesive 2	Super Poligrip Free (US market)
Pack Design	Single Tubes (fitted with precision nozzle)		Single Tubes (fitted with flat ribbon nozzle)
Dispensing Details	One Tube per subject at treatment visit		
Product Master Formulation Code (MFC)	CCI	CCI	CCI
Manufacturer	PPD		PPD
Dose/Application	See Section 15.2 for Adhesive application pattern. A single application per subject will be administered by the study site staff.		
Route of Administration	*Oral topical- denture adhesive*		

The two experimental adhesives are intended for commercialization and the application instructions here are consistent with the intended label instructions. The test denture adhesives shall be tracked by reference to their unique batch numbers. The test denture adhesives do not contain any medicinal or biologically active substances or materials derived from humans or animals.

The reference adhesive and the adhesive intended for use to stabilize the lower denture, the denture brushes and the denture cleansing paste are all marketed medical devices and will be used in accordance with the label instructions for these products.

Within the USA, the experimental adhesives are categorized as Class 1, 510(k) exempt medical devices and therefore a Nonsignificant Risk (NSR) application will be required as part of the IRB submission to conduct this study in the USA. These products are considered to be NSR devices based upon their similarity with marketed denture adhesives in terms of their intended use, composition, directions for use and target treated population.

Table 6-2 Sundry Items

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

Name of Item	Purpose
Super Poligrip Free Adhesive Cream (USA marketplace)	To stabilize the lower denture (apply 2 dabs to the lower denture [if required]; to retain lower denture) as per the product label instructions (Section 15.2.3)
Oral B Denture brushes	Brush to clean dentures
Polident Dentu Crème Denture Cleansing Paste (USA)	Cleaning of dentures
Nitrile Finger Cots	Covering transducer prongs
Large Anti-Static Weighing Boats	Weighing and transporting dentures

All products will be supplied in their commercial packaging. 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 study in time for study close out visit.

6.1.1 Medical Devices

The definitions and procedures detailed are in accordance with ISO 14155:2020. The GSK manufactured medical devices provided for use in this study are:

- The experimental denture adhesive creams for evaluation. Instructions for use are provided in (Section 15.2.1 Maxillary Denture Adhesive Application Instructions for Experimental Adhesives)
- Super Poligrip Free (used as positive control and mandibular denture stabilization). Instructions for use are provided in (Sections 15.2.2 and 15.2.3)
- Polident Dentu Crème Denture Cleaning Paste for cleaning of dentures. Instructions for use provided in (Section 8.1.5)

Other medical devices (not manufactured by or for GSK) provided for use in this study are:

- Oral B Denture Brush for cleaning of dentures prior to testing. Instructions for use provided in (Section 8.1.5)

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (Section 10.10 Medical Device Incidents) and appropriately managed by the sponsor.

6.1.2 Dosage Form and Packaging

The test products are 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 15.2). The content of the product labels will be in accordance with all applicable regulatory requirements and will be the responsibility of the GSK CH Global Clinical Supplies group. Each study label will contain, but not be limited to, protocol number, directions for use and storage requirements.

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

The investigational denture adhesives will be applied from the intended final product packaging and the control denture adhesive will be applied from the primary product packaging.

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

6.1.3 Preparation and Dispensing

Test (investigational and positive control) denture adhesives will be applied to the maxillary dentures by qualified unblinded site personnel according to the Product Application Instructions in Appendix 15.2.

Subjects will be assigned to products in accordance with the randomization schedule.

Study product will be dispensed by qualified unblinded site personnel per the dosage/administration instructions. These staff members will not be involved in any safety, efficacy assessments or other aspects of the study that could be influenced by the knowledge of product a subject has been assigned to use. An additional member of site staff should ensure the dispensing procedures are completed accurately.

SPF used for mandibular denture stabilization will also be applied by site personnel as per Appendix 15.2

Syneresis is a common occurrence with anhydrous denture adhesives and presents no safety risk to the subjects. Should syneresis be observed with any denture adhesive in this study, the first 1-2 inches of the extruded product should be discarded to avoid using excessively oily product.

6.2 Administration

Subject's dentures will first be cleaned to remove all traces of denture fixative, plaque and particulates/debris then and dried prior to application of randomized adhesive (Section 8.1.5). 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 BF testing. Both maxillary and mandibular (if present) dentures should be cleaned.

Experimental and positive control adhesives will be applied to maxillary denture directly from the product packaging onto the dentures as per the Product Application Instructions (Appendix 15.2). 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 randomized to no adhesive, the dentures should refitted by the subject following cleaning and drying.

Only subjects enrolled in the study may receive study products and only authorized site staff may supply or administer study products. All study products must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the authorized site staff only.

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 case report form (CRF). In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours.**

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

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

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

6.2.2 Overdose

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

Overdose is not likely to occur in this study since the dose will be accurately dispensed by the study site staff.

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

6.3 Investigational/Study Product Storage

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study products received and any discrepancies are reported and resolved before use according to the supplied shipping documentation.

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

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

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

6.4.1 Destruction of Investigational/Study Product Supplies

At the end of the study, an inventory of all used and unused study products and sundry items will be compiled. The investigational/study product accountability record for returned study products will then be completed. Destruction of all the study products (used and unused) for this clinical study will be managed by the study site staff in accordance with national, state and local regulations and provide GSK with a certificate of destruction.

6.5 Blinding and Allocation/Randomization

Blinding

This study is described as single blind or examiner-blind (the examiner performing the bite force evaluation will be blinded to the product received). Other staff from the study site will not be blinded to treatment received.

To ensure the examiner performing the bite force evaluation remains blinded throughout the study, staff involved in the preparation and dispensing of study products will work in a separate area.

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

Randomization

All subjects will be randomized according to the randomization schedule provided by the study biostatistician at PPD. Before the study is initiated, training, login information and directions for Study products will be dispensed according to the randomization schedule at the appropriate study visits. Returned study products should not be re-dispensed to any subject.

A unique screening number will identify each subject screened for study participation. Screening numbers will be assigned in ascending numerical order as each subject signs their consent form. Subjects who meet all inclusion and exclusion criteria will be randomized according to the randomization schedule. Randomization numbers will be assigned in ascending numerical order as each subject is determined to be fully eligible. The randomization schedule will indicate the treatment order sequence; one of the three treatments or no adhesive (negative control) to be used for each of the four study periods. The randomization will use a Williams Square layout appropriate for a 4-period crossover study. The study site will receive one randomization schedule with de-coded treatments. This schedule will be used to dispense study treatments to the subjects.

6.6 Breaking the Blind

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.

To break the blind, the study coordinator will use the randomization schedule to inform the investigator of the treatment assignment for the subject for the appropriate study visit.

6.7 Compliance

Study products will be administered by investigator site personnel.

The number of any missed or additional applications will be captured as protocol deviations 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 medications/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 criterion 9) and any medications that in the opinion of the investigator would interfere with the conduct of this study (exclusion criterion 10).

Medication/treatments taken within 7 days of signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after application of first treatment (test adhesives or no adhesive as per randomization schedule) will be documented as concomitant medication/treatments.

Subjects will be instructed not to have any non-emergency 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.

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

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

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

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 withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected except for any pertinent safety information. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening

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

Subjects will be screened within 1-28 days prior to administration of the treatment (test adhesive or no adhesive as per randomization schedule) to confirm that they meet the subject selection criteria for the study.

The following procedures will be completed in the order specified where possible and the outcomes recorded in the CRF:

- Informed consent
- Medical history and prior and current medications/treatments
- Dental history
- Inclusion/exclusion criteria assessment
- Demographics
- Current/prior/concomitant medication review
- Maxillary denture cleaning
- Kapur-Olshan Index (well-fitting assessment) only for maxillary dentures.
- Well-made assessment for maxillary dentures, and mandibular dentures if present.
- OST examination prior to denture adhesive application (if required for mandibular stabilization) and/or commencement of BF measurements.

- OHT examination
- Mandibular denture cleaning followed by stabilization (if present)
- Perform BF training bites and qualifying bites
- Subject eligibility assessed
- Removal of denture and excess adhesive from mouth (used for mandibular stabilization)
- OST examination post mandibular denture and denture adhesive removal
- Post BF assessment denture cleaning
- Adverse events and medical device incidents review

8.1.1 Informed Consent

The investigator, or designee, must obtain informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The informed consent form (ICF) will be signed and dated by the subject, the subject will receive a copy and the original 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 be documented in the CRF as this is the point from which all Adverse Events will be captured.

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

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

8.1.2 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.

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.

8.1.2.1 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 dentures, how long the subject has worn dentures, the prosthetic material and whether the subject is a regular user of denture adhesives. This will be documented in the CRF.

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF.

The well-fitting and well-made and the OST assessments should be performed by suitably qualified personnel/examiner with expertise in prosthodontics. The bite force assessments should be performed by an assessor appropriately trained in the technique.

8.1.4 Demographics

The following demographic information will be recorded in the CRF: year of birth, gender, race and ethnicity.

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 experimental denture adhesives being tested are intended to be marketed in the US.

Descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic and baseline data.

8.1.5 Denture Cleaning

Wearing gloves, denture cleaning will be performed by suitably qualified site staff. Sufficient denture cleaning paste will be applied to the supplied denture brush. All surfaces of the denture(s) will be thoroughly cleaned to remove all visible traces of denture fixative, plaque and particulate/debris. The denture(s) will then be rinsed thoroughly with running water.

Denture(s) should then be dried using clinical paper towels. Denture cleaning paste should only be used extra-orally and not directly in the mouth. Hands should be washed thoroughly following application and use of the denture cleaning paste. If a subject has two full dentures, both maxillary and mandibular dentures should be cleaned prior to treatment application or prior to denture insertion if subject is randomized to no adhesive group. The denture cleaning paste and/or warm water can be used to clean the dentures at the end of the day at the examiner's discretion.

8.1.6 Mandibular Denture Stabilization

Prior to all bite force measurements, any mandibular denture (partial or complete) will be fully stabilized using the supplied denture adhesive, to ensure accuracy of BF measurements. The mandibular denture will be thoroughly cleaned as per Section 8.1.5 before adhesive application. The denture adhesive will be applied in accordance with label instructions and will not be controlled by weight to ensure the mandibular denture is securely held in place to avoid interfering with maxillary BF measurements. The mandibular denture may be re-stabilized a further 2 times throughout the test day (maximum of 3 three applications per day) at the examiner's discretion.

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. 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.

Once subject eligibility is confirmed against screening inclusion/exclusion criteria, study specific screening tests will be carried out. These include the Kapur Olshan Index assessment, criteria for well-made and fitting dentures, OST exam and BF assessments for training and qualifying bites on the BF transducer. Details of each of these assessments are given in Section 9.1.4. All assessments will be documented in the CRF.

8.2 Study Period

8.2.1 Visits 2-5/ Treatment Periods 1-4

There will be a washout period of a minimum of 1 day (max 28 days) between treatment visits. The following procedures/ assessments will take place in the order listed below as much as possible and recorded in the CRF:

- Review of concomitant medications and non-drug treatments/procedures and lifestyle restrictions
- Review of inclusion/exclusion criteria
- OST examination prior to denture adhesive application
- Mandibular denture cleaning followed by stabilization (if present)
- BF measurement - practice bites
- BF measurement- pre-treatment baseline incisal BF measurement
- Subject continuance assessed and confirmed
- Randomization (only at Visit 2, Treatment period 1)
- Product application (for subjects randomized to an adhesive treatment arm). For subjects randomized to no adhesive, the maxillary denture will be cleaned, dried and re-fitted into subject's mouth.
- BF assessment at 0.5hrs
- BF measurement at 1hr
- BF measurement at 3hrs
- BF measurement at 6hr
- BF measurement at 9hr
- BF measurement at 12hr
- Removal of denture(s) (by either site staff or subject) and excess adhesive from mouth (by site staff) once all bite force assessments completed
- OST examination post denture and denture adhesive removal
- OHT examination (only at Visit 5, Treatment period 4)
- Post-testing denture cleaning
- Adverse events and medical device incidents review
- Study conclusion (only at Visit 5/Treatment period 4)

All procedures and assessments are detailed in Section 9.

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.

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

8.4 Follow-up Visit/Phone Call

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 wellbeing 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 Denture Bearing Tissue Score

The denture bearing tissue score (Kapur, 1967) will be assessed by the investigator and recorded for the maxillary denture only on the appropriate CRF. A score will be allocated for each of the criteria (ridge shape, tissue resiliency and location of border attachment) according to Table 9-1. There are no eligibility requirements associated with this measure in this bite force trial.

Table 9-1 The denture bearing tissue score (Kapur, 1967)

Score	Ridge Shape	Tissue Resiliency	Location of Border Attachment
1	Flat	Flabby	Low
2	V-shaped	Resilient	Medium
3	Shaped between U and V	Firm	High
4	U shaped	-	-

9.1.2 Kapur-Olshan Index (Well Fitting Assessment)

Only the maxillary denture will be examined for retention and stability during screening using the Olshan modification of the Kapur Index (Olshan et al., 1992, Kapur, 1967) by an examiner with expert knowledge of prosthodontics. This assessment is to be performed with no denture adhesive present.

Retention:

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

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

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

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

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

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

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

Stability:

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

4= Excellent- when denture offers excellent stability; demonstrates no rocking on its supporting structures under pressure.

3= Good- when denture offers good stability; demonstrates very slight rocking on its supporting structures under pressure.

2= Fair- when denture offers sufficient stability; demonstrates slight rocking on its supporting structures under pressure.

1= Poor- some stability; when a denture base demonstrates moderate rocking on its supporting structures under pressure.

0= No stability- when a denture base demonstrates extreme rocking on its supporting structures under pressure.

9.1.3 Well Made assessment

The maxillary denture, and mandibular denture if present, will be assessed for this study.

Clinical Acceptability

Only dentures 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 the maxillary denture, the examiner will indicate acceptable or unacceptable on the CRF.

Denture Finish and Contour

The contour and finish of the denture 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 the maxillary denture, the examiner will indicate acceptable or unacceptable on the CRF.

9.1.4 Maxillary Bite Force Assessment (Training and Qualifying Bites)

The mandibular denture, if present, will be stabilized using denture adhesive (Appendix 15.2). Subjects will then be instructed in the execution of the BF assessment. The subject will be instructed sit and hold their head in a natural position so that the occlusal plane is parallel to the floor. The examiner will stand in front of the subject holding the bite force transducer parallel to the floor at a comfortable level for the subject. In order to facilitate insertion of the BF transducer, the examiner may angle the BF plates as necessary. To prevent cross contamination between subjects, the examiner will place a clean finger cot over the bite force plates in addition to a clean infection control syringe sleeve over the transducer hand piece. The examiner will insert the bite force plates into the subject's mouth and then ensure that the muscles of mastication are relaxed. The examiner will signal the subject to bite until movement on the maxillary denture is observed at which time they will be instructed to release their bite. If, in the opinion of the examiner, the subject will be unable to successfully complete the required BF system training, the subject will be withdrawn from the study.

Should a bite described below be compromised through a methodological or instrumental error, e.g. by misalignment of the transducer in the mouth, the bite can be repeated at the examiner's discretion.

9.1.4.1 Training Bites

During the Screening visit, the examiner will record a triplicate bite force measurement without any denture adhesive. The performance of training bites will be confirmed in the CRF (individual training bite values will not be recorded).

9.1.4.2 Qualifying Bites

Four further BF measurements, known as qualifying bites, will be performed after the training bites. All 4 qualifying bites must be ≤9lbs. In addition, two out of the 4 qualifying bites must be reproducible within ±2lb for a subject to be eligible to participate in the study. This will form the subject eligibility/adherence for study continuance (as per Inclusion criterion 6).

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 (as much as possible) in the Study Procedures section of this protocol.

If in the opinion of the examiner a subject is between defined grades/scores, a conservative approach should be used to provide the final score. The same approach should be applied throughout the study to ensure consistency in the grading of the scores at all timepoints.

9.2.1 Treatment Day (Visits 2-5) Maxillary Bite Force Assessments (Practice, Baseline and Test Bites)

All BF measurements will be conducted by an examiner (preferably by the same examiner throughout the study) that is fully trained in the use of the BF transducer equipment and is experienced in performing BF measurements. Prior to any BF measurements on treatment days (Visit2-5) the mandibular dentures, if present, will be stabilized (Section 9.1.4).

9.2.1.1 Practice Bites

On each treatment day, the examiner will take 3 BF measurements without denture adhesive, known as practice bites. The purpose of this is to re-familiarize the subject with the BF transducer equipment and how to perform a valid bite.

9.2.1.2 Baseline Bite

Following the practice bites, a 4th bite will be performed, without any denture adhesive, and this will be the baseline pre-treatment BF measurement.

For a subject to be eligible, 1 of the 3 practice bites must be within ±2lbs of the baseline pre-treatment bite. In addition, only subjects whose pre-treatment baseline BF is ≤9lbs will be eligible to proceed in the study. If a subject does not meet these criteria at any of the treatment day visits, they will be discontinued from the study.

9.2.1.3 Test Bites

Additional BF measurements will be taken at 0.5, 1, 3, 6, 9 and 12 hours after application of test adhesive (or no adhesive as per randomization schedule). The reading should be taken no earlier than the stated time, and a tolerance of 5 minutes for the 30 min bite and 10 minutes for all other time points is acceptable.

9.3 Safety and Other Assessments

9.3.1 Oral Soft Tissue Examination

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects for all visits. The OST examination will be accomplished by direct observation and palpation, using retraction aids as appropriate, and will include examination of the oral labial mucosa (including lips), buccal mucosa, and mucogingival folds, edentulous gingival mucosa, including any gingival mucosa surrounding any mandibular dentition as applicable, hard palate, soft palate, tonsillar area, pharyngeal area, tongue, sublingual area, submandibular area and salivary glands. The results of the examination will be recorded in the CRF as either normal or abnormal with details of any abnormalities. Any abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OST examination carried out at Screening, Visit 1, will be recorded as an AE.

The OST examination will be performed at the start of Screening, Visit 1, before any adhesive application (if required for mandibular stabilization) and/or commencement of screening BF assessments, and again at the end of the day following denture and adhesive removal (if applied for mandibular stabilization).

During the study treatment periods (Visit 2 to 5), an OST examination will be performed prior to adhesive application (or no adhesive as per randomization schedule) and also after the completion of all efficacy assessments at the end of each test day following denture and adhesive removal, and all findings will be recorded in the CRF. The OST examination should be performed by a suitably qualified dental professional with expertise in prosthodontics. The subject may be asked to perform an oral rinse with water to remove debris from the mouth before or during this examination, at the examiner's discretion.

9.3.2 Oral Hard Tissue Examination

Where possible, this procedure should be conducted by a single dental examiner or clinically qualified designee for all subjects. Examination of the oral hard tissues (all facial, lingual/ palatal, mesial/distal and occlusal surfaces) will only be carried out on a subject's mandibular dentition (as applicable) and will be accomplished by direct/indirect observation, using retraction aids as appropriate. Enamel irregularities, tooth fracture, defective/faulty restorations (all direct & indirect restorations including fixed/removable prostheses), carious lesions, non-carious hard tissue loss (abrasion, attrition, abfraction and erosion), and any other hard tissue irregularity (e.g. hypo/hypermineralisation, decalcification) will be recorded.

Observations will be listed as either absent or present, and conditions noted as present will be described in the CRF. Any abnormality or worsening of a pre-existing condition observed by the clinical examiner or reported by the subject from the OHT examination carried out at Screening, Visit 1, will be recorded as an AE. Findings from the screening examination will be used to determine subject eligibility.

The OHT examination will be performed at the start of Screening, Visit 1, before any adhesive application (if required for mandibular stabilization) and/or commencement of screening BF assessments, and at the end of the last study visit after denture and adhesive removal, and all findings will be recorded in the CRF. The OHT examination should be performed by a suitably qualified dental professional with expertise in prosthodontics. The subject may be asked to perform an oral rinse with water to remove debris from the mouth before or during this examination, at the examiner's discretion.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

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

10.1 Definition of an Adverse Event (AE)

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

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

Events Meeting the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE if they fulfill the definition of an AE.

Events NOT meeting the AE definition:

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

10.2 Definition of a Serious Adverse Event (SAE)

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

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

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether

"hospitalization" occurred, or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

10.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs will be collected immediately after a subject provides consent 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.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

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.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading questions such as "How do you feel" will be assessed and any AE's recorded in the CRF and reported appropriately.

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

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

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

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

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

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

The investigator (or medically qualified designee) will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be 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. Copies of the 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 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 AEs and SAEs

After the initial AE/SAE 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.

10.8 Regulatory Reporting Requirements for SAEs

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.

Both the investigator and the sponsor will comply with all local medical device reporting requirements

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

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

10.9 Pregnancy

10.9.1 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.

10.9.2 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 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 discontinue study treatment and be withdrawn from the study.

10.10 Medical Device Incidents

The definitions and procedures detailed are in accordance with ISO 14155:2020.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

Medical devices are being provided by GSK CH for use in this study; the medical devices in this study are the supplied denture adhesive creams, the denture cleansing paste and the denture cleaning brushes.

10.10.1 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.

10.11 Reporting of Incidents

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

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

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

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

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

Email the Incident Report Forms to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the Incident Report Form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group

mailbox (PPD), responsible for the study and other GSK CH personnel as appropriate.

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

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

- Notify GSK CH immediately (by following the process described above).
- Schedule the subject to return to the site promptly to return the failed device.
- Record any incidents on the CRF and Incident Report Form following instructions given in the section above.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by GSK CH, return the failed device to the sponsor as soon as possible, including documentation of the details of the failure.
- For any incident/malfunction occurring with a medical device (including those that are part of combination products) supplied by the Investigator site, report the incident to the device manufacturer and follow the manufacturer instructions for the return of the failed device (whilst keeping GSK CH informed).

10.12 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.

10.13 Regulatory Reporting Requirements for Medical Device 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 collected on paper CRF's.

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

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

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

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

11.2 Data Handling

Management of clinical data will be performed in accordance with OHRI 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.

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

All study data will be transcribed from paper source documentation into the electronic REDCap system. Any changes or corrections to data will be performed in the REDCap 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.

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system; the design will favor entry from limited options over free entry to further reduce errors. In addition, quality checks will be programmed in SAS version 9.4 and run after the first subject, every 8 weeks. Logs and reports of each query run will be retained.

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

Any queries found using SAS checks will be entered in the EDC System and routed to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The course and outcome of each query will be tracked and stored within the EDC system and transferred to the REDCap system to be maintained as part of the audit trail. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Sufficient subjects will be screened to randomize at least 45 subjects to ensure that at least 42 evaluable subjects complete the study. A sample size of 42 subjects completing all treatment periods will provide 90% power to demonstrate study success. Study success is defined as achieving both (a) study validity (Super Poligrip Free superior to no adhesive) and (b) superiority of either or both of the experimental denture adhesives products compared to no adhesive (two primary objectives). Prior clinical data supports a delta of 2.30 lbs for $AOB_{0\text{-}12}$, using two-sided t-tests with family wise significance level of 5% based on the Dunnett's adjustment with a 5% significance level assuming a residual standard deviation (square root of within mean square error) of 2.83 lbs. The estimate of residual standard deviation was obtained as the higher of the observed variability from two previous bite force studies conducted at OHRI (GSK studies CCI [redacted]).

12.2 Populations for Analyses

Safety

All analyses of safety will be made on the safety population which will be defined as all subjects who are randomized and received treatment at least once during the study. The safety population will be analyzed as per treatment received.

Efficacy

Efficacy analyses will be based on the Modified Intention-To-Treat (MITT) population which is defined as all randomized subjects with at least one post baseline assessment of efficacy. This will be the primary population for the efficacy analysis which will be performed as per the planned randomized treatment.

The Per-Protocol (PP) population will be a subset of the MITT population. Subjects with a protocol violation that is deemed to affect efficacy assessments in all study periods will be excluded from the PP population. Subjects with a protocol violation that is deemed to affect efficacy assessments in some (but not all) study periods will be part of the PP population, but their data will be excluded from the period(s) affected by the protocol violation for a PP analysis. An analysis on the PP population will be performed for the primary efficacy variable if the number of subjects evaluable in any of the treatment groups for the MITT and PP

populations differs by 10% or more. The decision on whether a PP analysis will be performed will be made prior to study unblinding.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to database lock, agreement of study populations and study analysis. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

12.3.1 Primary Analysis

The primary efficacy endpoint is AOB over 12 hours for the incisal bite force (lbs) (denoted by $AOB_{0\text{-}12}$) for each experimental adhesive. The primary objectives are to compare incisal bite force of the two test adhesives versus no adhesive over 12 hours, $AOB_{0\text{-}12}$. The study validity will first be evaluated by comparing Super Poligrip Free vs no adhesive for $AOB_{0\text{-}12}$. Demonstrating study validity ($p<0.05$ for Super Poligrip Free vs no adhesive) is a prerequisite to performing all other treatment comparisons. No further significance testing will be performed if the initial validation step is not achieved. Therefore, study success is defined as achieving both (a) study validity (Super Poligrip Free superior to no adhesive) and (b) superiority of the experimental denture adhesive 1 compared to no adhesive, or experimental denture adhesive 2 compared to no adhesive.

To calculate $AOB_{0\text{-}12}$, first the AUC is calculated from 0 to 12 hours using the trapezoid method; we denote this by $AUC_{0\text{-}12}$. $AOB_{0\text{-}12}$ is defined as $(AUC_{0\text{-}12})/12$ minus baseline BF (lbs). This transformation will return the measurement to the same scale as the original observations whilst also looking at the average amount of improved force over time by subtracting the baseline value. Higher values of AOB demonstrate a stronger BF over time than lower values. Missing readings will be ignored and interpolation will be made between pre and post the missing values, if necessary. In the case of more than one missing value or if the 12-hour value is missing, the AOB will be set to missing.

An ANCOVA model will be used to analyze $AOB_{0\text{-}12}$, with treatment and period as fixed effects for each experimental adhesive; the covariates in this model are the subject level baseline and period level baseline minus subject level baseline. Subject will be included as a random effect. Pairwise treatment comparisons will be obtained as a difference in adjusted means and presented with 95% confidence intervals (CI) and associated p-values. Violations of normality and homogeneity of variance assumptions may be evaluated and if found will be overcome using transformations or performing a non-parametric analysis. The primary objectives are to compare incisal bite force of the test adhesive 1 and also test adhesive 2 versus no adhesive over 12 hours, $AOB_{0\text{-}12}$. The study validity will first be evaluated by comparing Super Poligrip Free vs no adhesive for $AOB_{0\text{-}12}$.

12.3.2 Secondary Analyses

$AOB_{0\text{-}0.5}$, $AOB_{0\text{-}1}$, $AOB_{0\text{-}3}$, $AOB_{0\text{-}6}$, $AOB_{0\text{-}9}$ AOB for 0.5, 1, 3, 6 and 9 hours will be defined and analyzed in a similar manner as $AOB_{0\text{-}12}$ for each experimental adhesive. From each ANCOVA model, treatment differences will be provided along with 95% CIs and p-values. In the event that the model assumptions are violated, a transformation or non-parametric analysis will be performed. No adjustments for multiplicity will be carried out.

12.3.3 Safety Analysis

Safety will be assessed based on any oral AEs (this includes those that are identified as Treatment Emergent OST abnormalities and spontaneously reported oral AEs). AEs will be categorized as oral and non-oral by the examiner prior to database lock. AEs will be deemed to be treatment emergent if they occur after the first supervised use of the randomized treatment. No formal statistical analyses of AEs will be performed. A list of incidents will also be included as part of the safety analyses. No specific risks or anticipated adverse device effects are expected to be observed within this study, however all AEs and medical device incidents will be assessed to evaluate the tolerability and safety of the treatments.

12.3.4 Exclusion of Data from Analysis

The following will be considered violations that may lead to the exclusion of data from the PP population and hence PP analyses:

- Violation of inclusion or exclusion criteria at screening that may affect efficacy
- Violation of pre-treatment baseline bite force continuance criteria
- Treatment administration errors
- Use of prohibited treatment or medication before or during the study, which it is felt will affect the assessment of efficacy.

Other reasons for protocol violations will be provided in the Statistical Analysis Plan (SAP) as necessary. Violations will be agreed between the Biostatistician and Clinical Research Director/Scientist or designee, ahead of breaking the study blind. Further details of methodology for identifying data to be included in PP analysis will be provided in the SAP.

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

12.3.5 Demographic and Baseline Characteristics

Descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum and maximum for continuous variables, and frequency and percentage for categorical variables) will be provided for demographic and baseline data.

12.3.6 Study Product Compliance

Compliance with the planned treatment regime will be tabulated and summarized for the safety and MITT populations.

12.3.6.1 Prior and Concomitant Medications

Prior medications and concomitant medications (medications taken between screening and Visit 5) will be listed as appropriate, summary tables may be produced if deemed necessary.

12.3.7 Handling of Dropouts and Missing Data

No imputations will be made for missing data. Additional detail on data handling rules for each timepoint and endpoint will be specified in the SAP.

12.3.8 Interim Analysis

No interim analyses are 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

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. All correspondence with the IRB should be retained in the investigator file. Copies of IRB 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 approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences, 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2017), guidelines for GCP (ICH, Nov 2016), 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, applicable portions of EU MDR 2017/745, ISO 14155:2011 and ISO 14155:2020 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, applicable portions of ISO 14155, 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.

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 as per the signed contractual agreement, from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

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

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH. In addition, GSK CH retains the right to discontinue development of the experimental denture adhesives at any time.

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 CRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

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

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

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15 APPENDICIES

15.1 ABBREVIATIONS

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

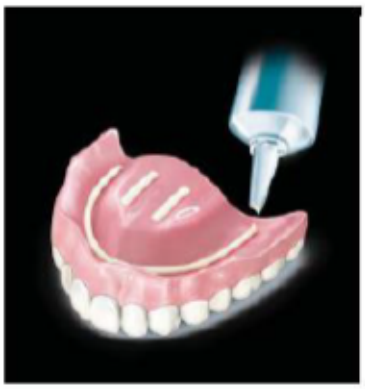
Table 15-1 Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
AOB	area over baseline
BDR	blinded data review
BF	Bite force
CI	confidence interval
CMC	Carboxymethyl cellulose
CRF	case report form

Abbreviation	Term
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GSK CH	GlaxoSmithKline Consumer Healthcare
ICF	Informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug
IRB	institutional review board
ISO	International organization for standardisation
PPD	PPD
N/A	not applicable
NSR	Non-significant risk
OHT	Oral hard tissue
OST	Oral soft tissue
PI	principal investigator
SAE	serious adverse event
SOP	standard operating procedure
SPF	Super Poligrip Free
TMJ	Temporomandibular joint
USA	United States of America

15.2 Application Instructions

15.2.1 Maxillary Denture Adhesive Application Instructions for Experimental Adhesives



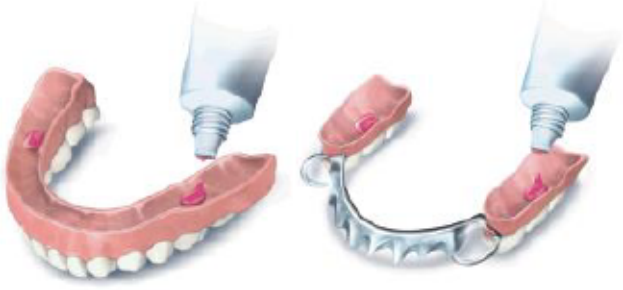
1. Clean and dry dentures.
2. Apply product directly from primary packaging in long, continuous strips as shown in the diagram, not too close to the denture edge. A total of 1.00±0.05g (weighed) of denture adhesive will be applied to the upper denture.
3. Have the subject rinse their mouth with potable water and expectorate before inserting the denture.

4. Have subject press dentures into place, hold firmly, and bite down for a few seconds to secure hold.

15.2.2 Maxillary Denture Adhesive Application Instructions for Control Adhesive

1. Clean and dry dentures.
2. Apply product directly from primary packaging in short strips as shown in the diagrams, not too close to the denture edges (3 strips should be applied to the upper denture). A total of 1.00±0.05g (weighed) of denture adhesive will be applied to the upper denture.
3. Have the subject rinse their mouth with potable water before inserting denture.
4. Have subjects press dentures into place, hold firmly, and bite down for a few seconds to secure hold.

15.2.3 Mandibular Denture Adhesive Application Instructions – to stabilize the mandibular denture only (if required)



1. Clean and dry denture.
2. Apply product in short strips as shown in the diagrams, not too close to the denture edges (2 strips on the lower denture in the posterior regions, a third strip may be applied in the anterior region as needed).
3. Have subjects rinse their mouth with water before inserting dentures.
4. Have subjects press dentures into place, hold firmly, and bite down for a few seconds to secure hold.

Signature Page for 218042 TMF-216101 v2.0

Reason for signing: Approved	Name: PPD Role: A nature: PPD PPD

Signature Page for TMF-216101 v2.0