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CLINICAL PROTOCOL

A randomized, single-blind, efficacy study to evaluate oral health and quality of life associated with use of a denture adhesive

Protocol Number:	209510
Compound/Product Name:	Carboxymethylcellulose and Carbomer
United States (US) Investigational New Drug (IND) Number:	N/A
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Sponsor Information

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

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)
Amendment 1		
Amendment 2		

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

Principal Investigator Protocol Agreement Page

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

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

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1 PROTOCOL SUMMARY

Background and Rationale

Whilst the effectiveness of denture adhesives to increase the retention of dentures and to help prevent food ingress under dentures is well established, the overall impact of denture adhesive use on the gum health of users the oral health related quality of life (OHrQoL) has been less well investigated. This study will therefore evaluate whether usage of an experimental denture adhesive is able to impact the overall gum health and the OHrQoL of subjects through 12 weeks usage. The hypothesis being investigated is that usage of the experimental adhesive will lead to superior outcomes compared to the usage of no adhesive.

Objectives	**Endpoints**
Primary	
To compare the ability of an experimental denture adhesive to provide self-perceived mucosal benefits compared to the use of no adhesive after 12 weeks of product use.	Change from baseline in mean scores of subject responses to the Gum Comfort questionnaire after 12 weeks (overall mean score).
Secondary	
To compare the ability of an experimental denture adhesive to provide self-perceived mucosal benefits compared to the use of no adhesive after 1, 4 and 8 weeks of product use.	Change from baseline in mean scores of subject responses to the Gum Comfort questionnaire after 1, 4 and 8 weeks (overall mean score).
To compare the ability of an experimental denture adhesive to provide self-perceived mucosal benefits compared to the use of no adhesive after 1, 4 and 8 and 12 weeks of product use.	Change from baseline in mean scores of subject responses to the individual questions on the Gum Comfort questionnaire after 1, 4, 8 and 12 weeks.
To compare the ability of an experimental denture adhesive to reduce denture-bearing mucosal irritation compared to the use of no adhesive after 1, 4, 8 and 12 weeks of product use.	Change from baseline in examiner-derived scores from the mucosal assessment after 1, 4, 8 and 12 weeks.
To compare the ability of an experimental denture adhesive to provide self-perceived oral-health related quality-of-life benefits compared to the use of no adhesive after 1, 4, 8 and 12 weeks of product use.	Change from baseline in mean scores of subject responses to the OHIP-Edent and GOHAI questionnaires after 1, 4, 8 and 12 weeks (overall mean scores and average domain scores).
To assess the sensory attributes of an experimental denture adhesive.	Mean scores of subject responses to the sensory questionnaire after 28 days.
Safety	
To assess the tolerability of an experimental denture adhesive.	Treatment emergent adverse events.

Study Design

This will be a single center, controlled, single-blind (to the safety assessor and the examiner determining the Mucosal Score Assessment (MSA) score), randomized, two-treatment, parallel design in healthy subjects with a full conventional, acrylic denture in either or both dental arches, with a treatment period of 12 weeks, to assess the clinical effectiveness of an experimental denture adhesive in the improvement of denture-bearing tissue irritation related measures, and the subject's oral health related quality of life. The control arm, will have subjects use no denture adhesive which is representative of a significant number of denture wearers who currently do not use an adhesive (Coates, 2000). The test experimental adhesive will be applied once per day in accordance with typical usage instructions. Efficacy and safety will be assessed at Baseline, and after 1, 4, 8 and 12 weeks treatment to monitor clinical efficacy and safety.

At the Screening/Baseline visit, each subject's dentures (either or both of mandibular and maxillary dentures) will be cleaned then assessed as to whether they are well made. Subjects will then undergo an assessment of their denture stability and retention using the Kapur Index (Olshan Modification) (Kapur, 1967; Olshan et al, 1992) and undergo an oral soft tissue (OST) examination. Only those subjects with satisfactory dentures, with adequate retention and stability and who satisfy all of the inclusion and exclusion criteria will continue in the study. Eligible subjects will then undergo a MSA and complete the gum-health, OHIP-Edent (Allen and Locker, 2002) and GOHAI (Atchison and Dolan, 1990a) questionnaires after undergoing instruction in how to complete these questionnaires. Subjects will then be randomized to one of the 2 treatment groups. Subjects randomized to the experimental denture group will be dispensed their relevant study products and instructed in their proper use. All subjects will be dispensed diaries to record their product usage and denture cleaning occasions. All subjects will return in 7±1 days for Visit 2.

At Visit 2, and all subsequent Visits, subjects randomized to the experimental adhesive group will return their diaries and treatments to the site staff to evaluate compliance. These subjects will be reminded/reinstructed in the proper application of adhesive. Subjects randomized to the no-adhesive group will have their diaries assessed to ensure they have not used any adhesive and are compliant with the denture cleaning requirements. All subjects will then complete the Gum Comfort and OHIP-Edent questionnaires after undergoing instruction in how to complete these questionnaires. Subjects will then remove their dentures and undergo an OST examination including a MSA. Subjects will then complete the GOHAI questionnaire after undergoing instruction on how to complete this questionnaire. For Visit 3 only, subjects randomized to the experimental adhesive group will complete the sensory questionnaire after undergoing instruction on how to complete this questionnaire. At Visits 2-4, all subjects will have their diaries returned. At Visits 3 and 4, those subjects randomized to the experimental adhesive group will have new products dispensed to them. Subjects will then return to the site for their next Visit per the study schedule.

To avoid inter-examiner variation, a single examiner will be responsible for the MSA and OST assessments for the duration of the entire study for all study subjects. To maintain the blinding to the OST/MSA assessor, this assessor should be isolated from subjects undergoing any aspect of this study apart from their MSA/OST assessment. Subjects should also remove their dentures and any traces of adhesive from their mouths prior to the MSA/OST assessment. The absence of adhesive shall be confirmed by a second (unblinded) examiner prior to the MSA/OST assessment.

Safety will be assessed by examination of the oral soft tissues at the Screening/Baseline visit and at each of the subsequent Visits. Incidents will be recorded from the first use of a study medical device. Subject reported AEs and incidents will also be recorded.

Study Products

This study will evaluate an experimental denture adhesive containing carbomer and carboxymethylcellulose that will be applied to dentures once per day in accordance with the usage instructions. Subjects randomized to use of the negative control will use no adhesive.

Type and Planned Number of Subjects

This study will recruit healthy volunteers, of either gender aged 18-85 years who wear at least one full denture. The experimental denture adhesive, when marketed, will be indicated for the general population who wear dentures and therefore the inclusion criteria allows for investigation of typical denture users.

Sufficient subjects will be screened to randomize 126 (63 per treatment group) to ensure 114 evaluable subjects complete the entire study.

1.1 Schedule of Activities

The schedule of activities in Table 1-1 provides an overview of the subject visits and study procedures. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Visit 1 Screening / Baseline Day1	Visit 2 Day 7±1	Visit 3 Day 28±3	Visit 4 Day 56±3	Visit 5 Day 84±3
Informed consent	X				
Review inclusion/exclusion criteria	X	X	X	X	X
Demographics	X				
Medical history	X				
Dental history	X				
Current/concomitant medications	X	X	X	X	X
Urine pregnancy test[4]	X	X	X	X	X
Clean dentures	X				X
Well-made assessment of dentures	X				
Denture bearing tissue score	X				
Denture retention and stability assessment	X				
OST examination edentulous	X	X	X	X	X
Subject eligibility	X				
Mucosal score assessment	X	X	X	X	X
Subject-completed questionnaires (Gum-Comfort, GOHAI and OHIP-Edent)	X	X	X	X	X
Randomization	X				
Dispense treatment, application instructions, diary (with diary completion instructions) and brushes[3]	X		X	X	
Treatment usage demonstration[1]	X	X	X	X	
Subject returns treatment, diary and brush[5]		X	X	X	X
Review of subject compliance (diaries and returned product)		X	X	X	X
Return of treatment and brush to subjects[1]		X			
Return of diary to subjects		X	X	X	
Subject removes dentures. All traces of adhesive from mouth confirmed absent by second examiner[2]		X	X	X	X
Subject-completed sensory questionnaire[1]			X		
Adverse events and Incidents	X	X	X	X	X
Subject continuance		X	X	X	
Study conclusion					X

Abbreviations: OST = Oral Soft Tissue, OHIP-Edent = Oral Health Impact Profile-Edentulous, GOHAI = General Oral Health Assessment Index

Any serious adverse event, adverse event or incident assessed as related to study participation that occurs subsequent to the signing of informed consent will be recorded.

[1] for subjects randomized to the adhesive group only.

[2] the second (unblinded) examiner shall not be the examiner performing the MSA/OST assessment.

[3] brushes, treatment and application instructions dispensed to subjects randomized to the denture adhesive group only. Diary and application instructions will be dispensed only once at V1 unless subject requires a new copy of the instructions due to loss/spoilage.

[4] for females of childbearing potential only.

[5] subjects randomized to no-treatment use return only their diary.

2 INTRODUCTION

Whilst dentures may ameliorate some of the problems of tooth loss, they may have unfortunate consequences. In healthy dentate subjects, the stresses from mastication are transmitted through the teeth via the periodontal ligaments to mandibular and maxillary bones. For denture wearers, especially full denture wearers, the primary stress bearing area under the denture is the oral mucosa where cellular swelling, increased nuclear size, and intercellular oedema can occur when the mucosa is under compression. The mechanical denture injury is a common occurrence as result of constant denture movement and rubbing (Budtz-Jørgensen, 1981). Further, the quality of life of the denture wearer may be impacted through other effects. Allen and Locker (Allen and Locker, 2002) reported that ill-fitting dentures produced consequences on taste, oral health discomfort and self-consciousness among adults wearing new dentures.

Denture adhesives or fixatives have been used by edentulous patients to improve the retention and stability of dentures for many years (Grasso, 1996). The primary benefit of using a denture adhesive is to enhance treatment outcome by increasing retention of the prosthesis and by reducing food entrapment (Zarb et al, 2013). Further benefits of a denture adhesive have also been explored. Tarbet (Tarbet et al, 1980) demonstrated that the use of a denture fixative was associated with improvements in the oral-mucosal health of subjects. Denture adhesives have also been shown to reduce the number of denture dislodgements during eating and subsequently reduce the amount of food particles that migrate under dentures (Ahmad et al, 2010; Munoz et al, 2012; Tarbet et al, 1980). The oral health related quality of life (OHrQoL) associated with denture adhesive use has also been evaluated in two separate studies. OHrQoL has been defined as the impact of oral disease and disorders on aspects of everyday life that a subject or person values, that are of sufficient magnitude, in terms of frequency, severity or duration to affect their experience and perception of their life overall (Locker and Allen, 2007). Nicolas (Nicolas et al, 2010) evaluated subject's OHrQoL over a 6 month period of adhesive use using the General Oral Health Assessment Index (GOHAI) (Atchison and Dolan, 1990b) demonstrating that the pain/discomfort domain scores of the GOHAI statistically significantly increased (improved) during the course of the 6 months of the study for all subjects (all subjects in this monadic study used adhesive). A further OHrQoL study (Polyzois et al, 2015) evaluated OHrQoL of full denture wearers using the Oral Health Impact Profile – Edentulous (OHIP-Edent) questionnaire (Allen and Locker, 2002) through use of an adhesive for 30 days. This study found that most aspects (including the pain domain) were improved over the 30 days of the study. CCI [redacted]

The above studies withstanding, the impact of using a denture adhesive on both the oral mucosal health and the OHrQoL has been scarcely investigated as highlighted in the American College of Prosthodontists Guideline for the Care and Maintenance of Dentures (Felton et al, 2011).

The test denture adhesive under evaluation here has previously been evaluated to assess the effectiveness of the adhesive at increasing retention of dentures. A clinical study that compared the maximum bite force that could be achieved before the denture dislodged demonstrated that the denture adhesive was statistically significantly superior than using no adhesive (207545, 2017).

The experimental denture adhesive under test in this study is intended to be marketed and has been developed to provide gum comfort benefits to the user by providing greater cushioning of the denture. The purpose of this study is therefore to assess the gum health and overall OHrQoL benefits to the user. This study will be conducted at All Sum Research in Canada.

2.1 Study Rationale

The purpose of this study is to evaluate whether usage of an exploratory denture adhesive is able to demonstrate improvement in the gum-health and to improve the OHrQoL of subjects who wear full dentures. This study is required to evaluate whether potential claims associated with this product are valid as well as to inform the dental practitioner on the potential benefits of denture adhesives.

Complete information for this product may be found in the single reference safety document (SRSD), which for this study is the safety statement.

A very similar formulation to this adhesive (containing preservative and colourant which are not present in the test adhesive here) has previously been evaluated in a clinical study (207545, 2017) which found the adhesive to be well tolerated. The benefit of the adhesive was demonstrated in the same study which showed that the adhesive was successful at increasing the maximum bite force that a subject could exert. In conclusion the benefits outweigh the risks identified for the intended use of this denture adhesive.

2.2 Mechanism of Action/Indication

Denture adhesives function by forming an adhesive layer between the denture and gum surface that can help retain the denture to the oral tissues. Carbomer and Carboxymethyl cellulose are a mixture of polymers included in an experimental denture adhesive currently being evaluated in subjects with a complete set of dentures in either or both dental arches.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the ability of an experimental denture adhesive to provide self-perceived mucosal benefits compared to the use of no adhesive after 12 weeks of product use.	Change from baseline in mean scores of subject responses to the Gum Comfort questionnaire after 12 weeks (overall mean score).
Secondary	
To compare the ability of an experimental denture adhesive to provide self-perceived mucosal benefits compared to the use of no adhesive after 1, 4 and 8 weeks of product use.	Change from baseline in mean scores of subject responses to the Gum Comfort questionnaire after 1, 4 and 8 weeks (overall mean score).
To compare the ability of an experimental denture adhesive to provide self-perceived mucosal benefits compared to the use of no adhesive after 1, 4 and 8 and 12 weeks of product use.	Change from baseline in mean scores of subject responses to the individual questions on the Gum Comfort questionnaire after 1, 4, 8 and 12 weeks.

To compare the ability of an experimental denture adhesive to reduce denture-bearing mucosal irritation compared to the use of no adhesive after 1, 4, 8 and 12 weeks of product use.	Change from baseline in examiner-derived scores from the mucosal assessment after 1, 4, 8 and 12 weeks.
To compare the ability of an experimental denture adhesive to provide self-perceived oral-health related quality-of-life benefits compared to the use of no adhesive after 1, 4, 8 and 12 weeks of product use.	Change from baseline in mean scores of subject responses to the OHIP-Edent and GOHAI questionnaires after 1, 4, 8 and 12 weeks (overall mean scores and average domain scores).
To assess the sensory attributes of an experimental denture adhesive.	Mean scores of subject responses to the sensory questionnaire after 28 days.
Safety	
To assess the tolerability of an experimental denture adhesive.	Treatment emergent adverse events.

This study will be considered successful if a statistically significant difference between the mean scores from the Gum Comfort questionnaire is observed between subjects using the experimental denture adhesive compared to subjects using no adhesive in favour of the experimental adhesive after 12 weeks use.

4 STUDY DESIGN

4.1 Overall Design

This will be a single center, controlled, single-blind (to the safety assessor and the examiner determining the MSA score), randomized, two-treatment, parallel group design in healthy subjects with a full conventional, acrylic denture in either or both dental arches, with a treatment period of 12 weeks, to assess the clinical effectiveness of an experimental denture adhesive in the improvement of health of the denture-bearing tissues, and the subject's oral health related quality of life. The control arm, will have subjects use no denture adhesive which is representative of a significant number of denture wearers who currently do not use an adhesive (Coates, 2000). The test experimental adhesive will be applied once per day in accordance with typical use instructions. Efficacy and safety will be assessed at Baseline, and after 1, 4, 8 and 12 weeks treatment to monitor clinical efficacy and safety.

Approximately 126 healthy subjects with either or both maxillary and mandibular full dentures will be enrolled in this study.

At the Screening/Baseline visit, each subject's dentures (either or both of mandibular and maxillary dentures) will be cleaned then assessed whether they are well made. Subjects will then undergo an assessment of their denture stability and retention using the Kapur Index (Olshan Modification) (Kapur, 1967; Olshan et al, 1992) and undergo an oral soft tissue (OST) examination. Only those subjects with satisfactory dentures, with adequate retention and stability and who satisfy all the inclusion and exclusion criteria will continue in the study. Eligible subjects will then undergo a MSA of the denture bearing tissues and complete the gum-health, OHIP-Edent and GOHAI questionnaires after undergoing instruction in how to complete these questionnaires. Subjects will then be randomized to one of the 2 treatment groups. Subjects randomized to the experimental denture group will be dispensed their relevant study products and instructed in their proper use. Subjects should demonstrate appropriate use of the

denture adhesive on their dentures and then fit the dentures under supervision of site staff. All subjects will be dispensed diaries for them to record their product usage and denture cleaning occasions. All subjects will return in 7±1 days for Visit 2.

At Visit 2, and all subsequent Visits, subjects randomized to the experimental adhesive group will return their diaries and treatments to the site staff to evaluate compliance. These subjects will be reminded/reinstructed in the proper application of adhesive. Subjects randomized to the no-adhesive group will have their diaries assessed to ensure they have not used any adhesive and are compliant with the denture cleaning requirements. All subjects will then complete the Gum Comfort and OHIP-Edent questionnaires after undergoing instruction in how to complete these questionnaires. Subjects will then remove their dentures and undergo an OST examination including a MSA. Subjects will then complete the GOHAI questionnaire after undergoing instruction in how to complete this questionnaire. For Visit 3 only, subjects randomized to the experimental adhesive group will complete the sensory questionnaire after undergoing instruction on how to complete this questionnaire. At Visits 2-4, all subjects will have their diaries returned. At Visits 3 and 4, those subjects randomized to the experimental adhesive group will have new products dispensed to them. Subjects will then return to the site for their next Visit per the study schedule.

To avoid inter-examiner variation, a single examiner will be responsible for the MSA and OST assessments for the duration of the entire study for all study subjects. To maintain the blinding to the MSA/OST assessor, this assessor should be isolated from subjects undergoing any aspect of this study apart from their MSA/OST assessment. Subjects should also remove their dentures and any traces of adhesive from their mouths prior to the MSA/OST assessment. The absence of adhesive shall be confirmed by a second (unblinded) examiner prior to the MSA/OST assessment.

Safety will be assessed by examination of the oral soft tissues at the Screening/Baseline visit and at each of the subsequent Visits. Incidents will be recorded from the first use of treatment adhesive. Subject reported AEs and incidents will also be recorded.

4.2 Rationale for Study Design

The duration of this study will be 12 weeks. In a previous study (Nicolas et al, 2010) the OHrQoL was assessed after 12 and 24 weeks use of an adhesive and whilst in general large improvements were observed over the 24 weeks, the greatest improvement was observed between baseline and 12 weeks, with more modest improvement observed thereafter. To minimise subject exposure a 12-week period is therefore deemed sufficient.

Subjects who already adopt a cleaning routine will be recruited (outlined in Inclusion/ Exclusion Criteria) as the cleanliness of the denture may impact the efficacy of the adhesive. All subjects enrolled to this study will continue to use their existing denture cleaning methodologies through the duration of the study.

Subjects in this study must be habitual wearers of a full denture in either or both arches to ensure that they are familiar with their dentures in place and are likely to continue wearing them during waking hours. Subjects who are xerostomic are excluded since the proper function of denture adhesives requires adequate hydration from saliva.

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

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

a crossover design), however such a design is not practicable in a long-term study: a parallel design is therefore appropriate. The study design does not allow for double blinding since the subjects themselves will know whether they are using adhesive or not. The study examiner who performs the MSA and OST examination will be blinded to the treatments. The study is therefore described as single-blind (safety assessor and the examiner determining the MSA score).

An OST examination will be conducted at each treatment to evaluate potential AEs.

Assessment of oral mucosal health in the edentulous has been investigated by Tarbet (Tarbet et al, 1980) who demonstrated that the use of a denture fixative was associated with improvements in the oral-mucosal health of subjects. The scoring system used in this study for evaluation of the oral-mucosal health was perhaps not sufficiently discriminatory enough for accurate evaluation of these subjects who mostly scored zero on this scale. An alternative scoring index for oral mucosal health in the dentate/edentulous has been evaluated (the mucosal score (MS)) (Henriksen et al, 1999) although not yet used to investigate clinical interventions. MS would appear to be more sensitive than the Tarbet score system for evaluation of subjects who have mild/moderate mucosal conditions and will therefore be used in this study.

The Kapur-Olshan index is a composite score based upon stability and retention ratings for the maxillary and mandibular dentures (Kapur, 1967; Olshan et al, 1992). In this study, subjects presenting with a very low Kapur-Olshan score at Screening (< 3 for each denture [maxillary and/or mandibular]), defined as "Clinically Poor" (Olshan et al, 1992), will be excluded from this study since the study adhesive is not recommended for use with poor fitting dentures.

Subjects with temporomandibular joint disorders are excluded should the investigator believes that this could affect the subject's participation, principally regarding the ability for the subject to adequately chew. Subjects who use or have ever used bisphosphonate medications are specifically excluded from this study owing to the enhanced risk of bisphosphonate-related osteochemonecrosis of the jaw that is associated with reduced tissue tolerance to function with removable prostheses (Saldanha *et al*, 2012).

A no adhesive negative control treatment has been chosen to provide a continual reference point to allow interpretation of the results, and is representative of a significant number of denture wearers who currently do not use an adhesive (Coates, 2000).

4.3 Justification for Dose

The dose of adhesive and method and frequency of application is consistent with the intended label instructions for this adhesive and is also consistent with denture adhesives currently marketed.

4.4 End of Study Definition

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

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

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

This study will recruit healthy volunteers, of either gender aged 18-85 years who wear at least one full denture. The experimental denture adhesive, when marketed, will be indicated for the

general population who wear dentures and therefore the inclusion criteria allows for investigation of typical denture users.

Sufficient subjects will be screened to randomize 126 to ensure 114 evaluable subjects complete the entire study.

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions 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 of the following inclusion criteria to be eligible for enrollment into the study:

1. Subject provision of a signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Subject is male or female who, at the time of screening, is between the ages of 18 and 85 years, inclusive.
3. A subject who is willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. A subject in good general and mental health with, in the opinion of the investigator or medically qualified designee, no clinically significant/relevant abnormalities in medical history or upon oral examination, or condition, that would impact the subject's safety, wellbeing or the outcome of the study, if they were to participate in the study, or affect the individual's ability to understand and follow study procedures and requirements.
5. Female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for 5 days after the last dose of assigned treatment. Female subjects who are not of childbearing potential must meet requirements in Section 5.5.1.
6. Subject has denture prostheses that fulfil all of the following:
    a. A conventional acrylic full denture in either or both of the upper and lower arches. The full denture may be opposed by a partial denture, natural teeth or another full denture.
    b. Dentures are well fitting (Kapur (Olshan Modification) Retention and Stability Index Sum Score ≥ 3 for each denture [maxillary and/or mandibular]) (Olshan et al, 1992) with no individual stability or retention scores <1.
    c. Denture(s) are well made (according to the well-made assessment).
7. Subject is a habitual wearer of their denture(s) defined as subjects who wear their dentures for the majority of their time whilst awake.
8. Subject has worn their full denture(s) for at least a year.
9. Subject has not used any denture adhesive in the last year.
10. Subject currently adopts acceptable denture cleansing habits and routine (a minimum would include daily brushing with a chemical cleaner such as toothpaste or soap, in addition to at least once a week soaking in commercial denture cleansing product). *Note unacceptable cleaning would include cleaning with water alone or using other non-specialised cleaning methods.*

5.3 Exclusion Criteria

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

1. A subject who is an employee of the investigational site, either directly involved in the conduct of the study or a member of their immediate family; or an employee of the investigational site otherwise supervised by the investigator; or, a GlaxoSmithKline Consumer Healthcare (GSK CH) employee directly involved in the conduct of the study or a member of their immediate family.
2. A subject who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.
3. A subject with, in the opinion of the investigator or medically qualified designee, an acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator or medically qualified designee, would make the subject inappropriate for entry into this study.
4. A subject who is a pregnant female.
5. A subject who is a breastfeeding female.
6. A subject with known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients.
7. A subject who, in the opinion of the investigator or medically qualified designee, should not participate in the study.
8. A subject unwilling or unable to comply with the Lifestyle Considerations described in this protocol.
9. A subject who has previously been enrolled in this study.
10. A subject who has had recent (within 30 days) gingival surgery.
11. Taking or have taken a bisphosphonate drug (i.e. Fosamax, Actonel, Boniva).
12. A subject with any clinically significant or relevant oral abnormality (e.g. temporomandibular joint problems) that, in the opinion of the investigator, could affect the subject's participation in the study.
13. A subject with any condition or medication which, in the opinion of the investigator, is currently causing xerostomia.
14. A subject with recent history (within the last year) of alcohol or other substance abuse.
15. A subject with OST examination findings such as stomatitis, open sores, lesions, or swelling which in the opinion of the investigator, would interfere with the conduct of the study. Mild, chronic conditions commonly expected from the use of dentures in the investigators opinion, are acceptable in this study.
16. A subject who is using any medication that, in the opinion of the investigator, would interfere with the conduct of 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

During the entire study (screening – completion of study):

- Subjects will not be permitted to have any dental/denture work performed during the time they are in the study, unless discussed and permitted by the examiner. This is to ensure that the denture fit will not be altered during the study.
- Subjects will not be able to use any denture adhesive product other than that supplied by the investigator.
- Subjects should continue using their usual denture cleansing methodology throughout the study.

5.5.1 Contraception

Female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for 5 days after the last dose of investigational product.

The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy that meets the GSK definition (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of reproductive potential with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive (Hatcher and Nelson, 2007))
4. Injectable progestogen (Hatcher and Nelson, 2007)
5. Contraceptive vaginal ring (Hatcher and Nelson, 2007)
6. Percutaneous contraceptive patches (Hatcher and Nelson, 2007)
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject (Hatcher and Nelson, 2007). The documentation on male sterility can come from site personnel review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological

cause; status may be confirmed by having a serum follicle-stimulating hormone level confirming the post-menopausal state;

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

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, and any adverse events or incidents as applicable.

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

5.7 Sponsor's Qualified Medical Personnel

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

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

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

5.8 Rater/Clinical Assessor Qualifications

The assessor performing the well-made, denture retention and stability, denture bearing tissue score, MSA and OST assessments shall be a suitably qualified dentist with expert knowledge of prosthodontics.

6 INVESTIGATIONAL/STUDY PRODUCTS

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

6.1 Investigational/Study Product Supplies

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

Table 6-1 Investigational/Study Product Supplies

	Test Product	Negative Control
Product Name	Experimental Denture Adhesive	No Adhesive
Pack Design	Denture adhesive tube fitted with a precision nozzle	N/A
Dispensing Details	New tubes of denture adhesive will be dispensed at each study visit	N/A
Product Master Formulation Code (MFC)	CCI [redacted]	N/A
Dose/Application	A sufficient quantity of denture adhesive to be applied to the maxillary and/or mandibular dentures once per day in the pattern described in the application instructions.	N/A
Route of Administration	Applied to denture which is placed in mouth	N/A
Usage Instructions	As per the Product Application Instructions (Section 15.2)	N/A
Return Requirements	All used/unused samples to be returned to GSK CH	N/A

Table 6-2 Sundry Items to be supplied

Item	Supplied By	Pack Design	Dispensing Details	Return/Disposal Details	
				Used Samples	Unused Samples
Oral B Denture brushes (Canadian marketplace)	GSK CH	Commercial pack	1 at screening for use by site to clean the dentures 1 for subjects to use at home to remove denture adhesive at end of day. The at home brush to be replaced at each visit	Destroy at site using site disposal procedures	Return
Polident Dentu Crème Denture cleansing paste (Canadian marketplace)	GSK CH	Commercial pack	Screening visit	Destroy at site using site disposal procedures	Return
Urine Pregnancy Tests (Canadian marketplace)	GSK CH	Commercial pack	Use as per study schedule	Destroy at site using site disposal procedures	Return

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

The test product is a Class I device in Canada and as such there is no requirement to obtain an Investigational Testing Authorization from Health Canada prior to study start.

6.1.1 Dosage Form and Packaging

The experimental denture adhesive will be supplied in individual tubes.

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

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. Subjects should be instructed to not remove or deface any part of the study label.

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

6.1.2 Preparation and Dispensing

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

Study product will be dispensed by qualified unblinded site personnel per the dosage/administration instructions. These staff members will not be involved in any safety, efficacy assessments or other aspects other study that could be influenced by the knowledge of product a subject has been assigned to use. An additional site member of site staff, should ensure the dispensing procedures are completed accurately. Additional re-dispensing of denture adhesive and denture brushes should occur at each visit to the site. The dispensing should be performed in a room away from other subjects and blinded study staff (especially the examiner performing the MSA and OST assessments, who will be prevented from viewing subjects once they have their study products).

Subjects should be advised as to correct product application in accordance with the Application Instructions at each visit.

6.2 Administration

Subjects will be instructed to self-administer their assigned product per the usage instructions Application Instructions provided to the subject.

6.2.1 Medication/Dosing Errors

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 dosing errors occurring to a study subject are to be captured in the case report form (CRF).

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

6.3 Investigational/Study Product Storage

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

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

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

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

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

6.4 Investigational/Study Product Accountability

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

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

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

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

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

6.4.1 Destruction of Investigational/Study Product Supplies

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

using the return instructions provided. Used denture brushes, denture cleansing paste and pregnancy test kits should be disposed of in accordance with the site disposal procedures.

6.5 Blinding and Allocation/Randomization

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

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

This study is described as single-blind (the safety assessor and the examiner determining the denture-bearing tissue score clinical examiner will be blinded to the product received). The study statistician, data management staff, other employees of the Sponsor and vendors acting on behalf of the Sponsor, who may influence study outcomes will also be blinded to the product allocation.

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

Subjects will be instructed not to remove study products from the opaque bags provided outside of the dispensing room, while at the study site. Subjects randomized to test adhesive use will have the study test product, the denture cleaning brush and their diary and usage instructions contained within the bag, whilst the subjects randomized to no adhesive usage will have their diary in the bag.

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

6.6 Breaking the Blind

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

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

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

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

6.7 Subject Compliance

Subjects randomized to the test denture adhesive arm will be instructed in/reminded of the correct usage of the product at every visit by the dispensing staff.

A diary will be supplied to promote compliance and to capture details of product use throughout the study period. Subjects may also record additional information such as AEs or medications used. Any additional details relevant to efficacy or safety should be reviewed by the investigator (or suitably qualified designee) with the subjects, and transcribed to the CRF as appropriate.

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

6.8 Concomitant Medication/Treatment(s)

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

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

Medication/treatments taken within 7 days prior to signing the informed consent form will be documented as a prior medication/treatment. Medications/treatments taken after signing the informed consent form will be documented as concomitant medication/treatments.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

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

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

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

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

7.2 Lost to Follow up

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

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

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

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

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

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

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

8 STUDY PROCEDURES

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

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

8.1 Visit 1/Screening

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

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

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

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Medical History and Prior Medication/Treatment
- Dental History
- Clean Dentures
- Well-Made Assessment of Dentures
- Denture Bearing Tissue Score

- Denture Retention and Stability Assessment
- OST (Edentulous) Examination
- Urine Pregnancy Testing (for females of child-bearing potential only)
- Subject Eligibility

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. Two copies of the informed consent form (ICF) will be signed and dated by the subject, the subject will retain one copy and the other will be kept at site.

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

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

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

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

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

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

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

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

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

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

8.1.2 Demographics

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

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be documented in the CRF. The well-made assessment of dentures, denture retention and stability assessment, denture bearing tissue score, MSA and OST examination should be performed by suitably qualified personnel with expertise in prosthodontics.

8.1.4 Medical History and Prior Medication/Treatment

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

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

8.1.5 Dental History

The Investigator, or medically qualified designee, will take a dental history from each subject. Dental history will include information of all prostheses in the mouth, maxillary and mandibulary, as well as information regarding the age of the dentures, how long the subject has worn dentures, the prosthetic teeth material and whether the subject has used denture adhesives in the past (including the reason for abstaining from adhesive use and how long since abstaining from adhesive use).

8.1.6 Subject Eligibility

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

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

8.2 Study Period

Remind subject to inform the site if they experience any untoward medical occurrence or use any medications while enrolled in the study.

8.2.1 Visit 1/Day 1 (Baseline)

Following screening, enrolled subjects will undergo, in the following order (wherever possible), and findings documented in the CRF:

- Mucosal Score Assessment.
- Subjects complete the Gum Comfort questionnaire.
- Subjects complete the OHIP-Edent questionnaire.
- Subjects complete the GOHAI questionnaire.
- Randomization of subject to treatment group.
- Dispense subject diaries to all subjects.

- For subjects randomized to the denture adhesive treatment:-
  - Dispense denture cleaning brushes, study test product and application instructions.
  - Demonstrate adhesive application.
  - Subject applies adhesive to dentures and fits dentures under supervision of site staff.
- Instruct all subjects in diary completion.
- AEs and incidents recorded.

8.2.2 Visit 2 / Days 7±1

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

- Changes in concomitant medication or non-drug treatments/procedures.
- 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.
- Urine Pregnancy Test (for females of child-bearing potential only).
- Subject returns diary, treatment and brush.
- Subjects compliance to treatment and denture cleaning assessed through examination of subject diary and product usage.
- Review of inclusion/exclusion criteria.
- Decision on whether subject continues in the study.
- Subjects complete the Gum Comfort questionnaire.
- Subjects complete the OHIP-Edent questionnaire.
- For subjects randomized to the denture adhesive treatment the absence of denture adhesive in the mouth/ on the dentures should be confirmed by a second (non-blinded) examiner to ensure the blinded MSA/OST assessor is not inadvertently unblinded. Any residual adhesive present should be removed by the subject/ second (non-blinded) examiner prior to MSA/OST examination.
- Subject undergo an OST examination and MSA.
- Subjects complete the GOHAI questionnaire.
- For subjects randomized to the denture adhesive treatment:-
  - Return of their denture cleaning brushes and study test product.
  - Demonstration of adhesive application.
  - Subject applies adhesive to dentures and fits dentures under supervision of site staff.
- Return of diaries to all subjects and instruction to all subjects in diary completion.
- AEs and incidents recorded.

8.2.3 Visit 3 / Day 28±3

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

- Changes in concomitant medication or non-drug treatments/procedures.
- 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.

- Urine Pregnancy Test (for females of child-bearing potential only).
- Subject returns diary, treatment and brush.
- Subjects compliance to treatment and denture cleaning assessed through examination of subject diary and product usage.
- Review of inclusion/exclusion criteria.
- Decision on whether subject continues in the study.
- Subjects complete the Gum Comfort questionnaire.
- Subjects complete the OHIP-Edent questionnaire.
- For subjects randomized to the denture adhesive treatment the absence of denture adhesive in the mouth/ on the dentures should be confirmed by a second (non-blinded) examiner to ensure the blinded MSA/OST assessor is not inadvertently unblinded. Any residual adhesive present should be removed by the subject/ second (non-blinded) examiner prior to MSA/OST examination.
- Subject undergo an OST examination and MSA.
- Subjects complete the GOHAI questionnaire.
- For subjects randomized to the denture adhesive treatment:-
  - Subject completes the sensory questionnaire.
  - Dispensation of denture cleaning brushes and study test product.
  - Demonstration of adhesive application.
  - Subject applies adhesive to dentures and fits dentures under supervision of site staff.
- Return of diaries to all subjects and instruction to all subjects in diary completion.
- AEs and incidents recorded.

8.2.4 Visit 4 / Day 56±3

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

- Changes in concomitant medication or non-drug treatments/procedures.
- 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.
- Urine Pregnancy Test (for females of child-bearing potential only).
- Subject returns diary, treatment and brush.
- Subjects compliance to treatment and denture cleaning assessed through examination of subject diary and product usage.
- Review of inclusion/exclusion criteria.
- Decision on whether subject continues in the study.
- Subjects complete the Gum Comfort questionnaire.
- Subjects complete the OHIP-Edent questionnaire.
- For subjects randomized to the denture adhesive treatment the absence of denture adhesive in the mouth/ on the dentures should be confirmed by a second (non-blinded) examiner to ensure the blinded MSA/OST assessor is not inadvertently unblinded. Any residual adhesive present should be removed by the subject/ second (non-blinded) examiner prior to MSA/OST examination.
- Subject undergo an OST examination and MSA.

- Subjects complete the GOHAI questionnaire.
- For subjects randomized to the denture adhesive treatment:-
  - Dispensation of denture cleaning brushes and study test product.
  - Demonstration of adhesive application.
  - Subject applies adhesive to dentures and fits dentures under supervision of site staff.
- Return of diaries to all subjects and instruction to all subjects in diary completion.
- AEs and incidents recorded.

8.2.5 Visit 5 / Day 84±3

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

- Changes in concomitant medication or non-drug treatments/procedures.
- 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.
- Urine Pregnancy Test (for females of child-bearing potential only).
- Subject returns diary, treatment and brush.
- Subjects compliance to treatment and denture cleaning assessed through examination of subject diary and product usage.
- Review of inclusion/exclusion criteria.
- Decision on whether subject continues in the study.
- Subjects complete the Gum Comfort questionnaire.
- Subjects complete the OHIP-Edent questionnaire.
- For subjects randomized to the denture adhesive treatment the absence of denture adhesive in the mouth/ on the dentures should be confirmed by a second (non-blinded) examiner to ensure the blinded MSA/OST assessor is not inadvertently unblinded. Any residual adhesive present should be removed by the subject/ second (non-blinded) examiner prior to MSA/OST examination.
- Subject undergo an OST examination and MSA.
- Clean dentures.
- Subjects complete the GOHAI questionnaire.
- AEs and incidents recorded.
- Subjects reminded to inform the site if they experience any untoward medical occurrence in the next 5 days. All ongoing AEs to be followed up by site.
- Study conclusion.

8.3 Diary Review

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

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

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

8.4 Study Conclusion

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

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

8.5 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, in particular further OST examinations.

9 STUDY ASSESSMENTS

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

9.1 Screening Assessments

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

9.1.1 Clean Dentures

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

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

Dentures should be cleaned at screening and at the end of the study (V5) prior to the subject leaving the site.

9.1.2 Well Made Assessment

Clinical Acceptability

Each denture (maxillary and mandibular) will be examined. 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 each denture (maxillary and mandibular), the examiner will indicate acceptable or unacceptable on the CRF.

Denture Finish and Contour

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

9.1.3 Denture Bearing Tissue Score

The denture bearing tissue score (Kapur, 1967) will be assessed by the investigator and recorded for both or either of the maxillary/mandibular dentures as appropriate on the appropriate CRF. There are no eligibility requirements associated with this measure in this clinical trial.

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

Ridge Shape (for both Maxillary and Mandibular)

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

Tissue Resiliency (for both Maxillary and Mandibular)

1= Flabby
2= Resilient
3= Firm

Location of Border Tissue Attachment

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

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

Each denture (maxillary and mandibular) will be examined for retention and stability using the Kapur Index (Olshan Modification) (Kapur, 1967; Olshan et al, 1992) by an examiner with expert knowledge of prosthodontics. A sum score (retention + stability) of ≥ 3 for each denture is required for inclusion. This assessment is to be performed with no denture adhesive present.

Retention:

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

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

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

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

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

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

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

Stability:

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

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

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

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

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

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

9.2 Efficacy Assessments

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

9.2.1 Subject Questionnaires

On assessment days, the subject will complete 3 questionnaires that assess the subject's gum health and OHrQoL and at Visit 3 subjects randomized to the denture adhesive groups will also complete a questionnaire to evaluate the sensory attributes of the adhesive. The subject responses should be transcribed by the study staff to the CRF. The study staff should be mindful that whilst the questionnaires do not solicit safety information, any information on safety outcomes recorded by subjects on a questionnaire should be evaluated by the investigator to ensure all AEs are recorded. To ensure that the examiner who performs the MSA and OST assessments is blinded to the assignment of denture adhesive treatment, the examiner will not have access to these questionnaires and should not have knowledge of who is completing the questionnaires and will remain blinded to the distribution and completion of all questionnaires.

Questionnaires should be completed one at a time, and the next questionnaire should not be administered to the subject until they have returned the previous completed questionnaire. For consistency purposes, it is intended that the order that subjects receive their questionnaires remains regular for the duration of the study. The gum-comfort questionnaire is the first to be administered since this is the primary endpoint for this study. The OHIP-Edent will then be administered and then the subject will have the MSA/OST assessments performed. Finally the

GOHAI questionnaire should be administered. This ordering has been chosen to allow the subject some respite from questionnaires with the OST/MSA between the OHIP-Edent and GOHAI questionnaires.

Subjects should be advised in the correct completion of the questionnaires at every visit and should ambiguous response be given (i.e. more than one result circled for a question) be clarified with the subject before they leave the study site.

9.2.1.1 Gum-Comfort Questionnaire

The gum-comfort questionnaire will be administered to the subjects prior to their OST examination and administration of the OHIP-Edent questionnaire at the baseline and all assessment visits (Visits 1-5). This questionnaire is comprised of 5 questions that inform on the subject-perceived comfort of their denture-bearing tissues. The questions have 5 possible responses (Agree Strongly, Agree Somewhat, Neither Agree or Disagree, Disagree Somewhat, Disagree Strongly) and are scored on a 0 (Agree Strongly) to 4 (Disagree Strongly) scale for all questions. Thus, the range of the total questionnaire score is 0-20 where a low score is more favorable.

9.2.1.2 OHIP-Edent Questionnaire

The OHIP-Edent questionnaire is a well-established questionnaire for evaluation of OHrQoL (Allen and Locker, 2002). This questionnaire will be administered to subjects after completion of the gum comfort questionnaire and prior to their OST examination at the baseline and all assessment visits (Visits 1-5). This questionnaire is comprised of 19 questions grouped into 6 functional domains per Table 9-1. The questions have 5 possible responses (Never, Rarely, Occasionally, Often and Very Often) that the subjects should indicate by marking the appropriate box. The responses are scored on a 0 (Never) to 4 (Very Often) scale for all questions and thus a low score is more favorable and the overall score range is 0-76 where 0 is the best possible score.

Table 9-1 The functional domains of the OHIP-Edent questionnaire.

Domain	Questions	Score range
Functional limitations	1-3	0-12
Physical pain	4-7	0-16
Psychological discomfort	8-9	0-8
Physical disability	10-12	0-12
Psychological disability	13-14	0-8
Social disability	15-19	0-20

9.2.1.3 GOHAI Questionnaire

The GOHAI questionnaire (Atchison and Dolan, 1990a) will be administered to the subjects at all assessment visits after the gum-comfort questionnaire has been completed. This questionnaire is comprised of 12 questions with 6 possible responses to each question (always, very often, often, sometimes, seldom and never). The responses are scored on a 0 (always) -5 (never) scale for all questions except 3, 5 and 7 where the scoring is reversed, and thus the range of scores for the questionnaire is 0-60, where 60 is the best possible score. The questions are grouped into 3 domains as in Table 9-2.

Table 9-2 The functional domains of the GOHAI questionnaire

Domain	Questions	Score range	Meaning
Functional	1-4	0-20	Subject's ability to eat, speak and swallow
Psychosocial	6,7,9-11	0-25	Subject's concerns, relationships and appearance
Pain/Discomfort	5,8,12	0-15	Subject's discomfort during chewing, sensitivity to hot/cold/sweets and use of medications to manage oral pain.

9.2.1.4 Sensory Questionnaire

The sensory questionnaire will be completed by subjects after the GOHAI questionnaire has been completed and retrieved at Visit 3 only. This questionnaire comprises 6 questions that inform on the sensory attributes of the adhesive, and thus will only be administered to subjects randomized to the adhesive group. The questionnaire allows for 5 possible responses (Agree Strongly, Agree Somewhat, Neither Agree or Disagree, Disagree Somewhat, Disagree Strongly) and are scored on a 0 (Agree Strongly) to 4 (Disagree Strongly) scale for all questions. Thus the range of the questionnaire score is 0-24 where a low score is more favorable.

9.2.2 Mucosal Score Assessment (MSA)

The health of the denture-bearing tissues should be assessed using the scale described by Henriksen et al (Henriksen et al, 1999) and summarized in Table 9-3.

The MSA should be performed by a suitably qualified dental professional and ideally the same examiner should be used throughout the study. The MSA will be made on the denture bearing tissues for either/both of the subject's dentures across the whole mouth and therefore the examiner should record the highest applicable score (ie should a subject have normal appearance of their mandibula denture-bearing tissue, yet display ulcers caused by denture in the maxillary tissue, a score of 3 should apply). The result of the examination will be recorded in the CRF.

The MSA may be performed at the same time as the OST examination. The absence of any residual denture adhesive in the mouth must be confirmed by a second (non-blinded) examiner prior to the subject attending to the MSA or OST examination to ensure the OST/MSA assessor remains blinded to treatment.

Table 9-3 The MSA Scale per Henriksen (Henriksen et al, 1999)

Score	Appearance
1	Normal appearance of the gingiva and oral mucosa
2	Mild inflammation • slight redness and/or hypertrophy/hyperplasia of the gingiva • slight redness in some areas of the palatal mucosa, including red spots indicating inflamed salivary duct orifices
3	Moderate inflammation • marked redness and hypertrophy/hyperplasia of the gingiva, which bleeds easily when pressure is applied • marked redness in large areas (2/3 or more) of the palate • marked inflammatory redness of the oral mucosa in sites other than in the palate • ulceration(s) caused by denture(s) • red and inflamed fibro-epithelial hyperplasias caused by denture(s)
4	Severe inflammation • severe redness and hypertro hypertrophy/hyperplasia of the gingiva • spontaneous gingival bleeding

Score	Appearance
	• marked palatal granulations • inflamed oral mucosal areas which easily “break” and bleed under pressure, e.g., when dentures are inserted

9.3 Safety and Other Assessments

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

9.3.1 Oral Soft Tissue (OST) Examination - Edentulous

The OST examination should be performed by a suitably qualified dental professional and ideally the same examiner should be used throughout the study. The OST Exam-Edentulous will include the labial mucosa (including lips), buccal mucosa, tongue, edentulous gingival mucosa, sublingual area, hard and soft palates, mucogingival folds, submandibular area, salivary glands, tonsilar and pharyngeal areas. Observations will be made of any erythema, desquamation and ulcerations, and other relevant clinical observations. The results of the examination will be recorded in the CRF as either normal or abnormal. The location and brief description of any abnormalities will also be recorded.

An OST examination should be performed at screening and at each visit to the study site and the findings recorded in the CRF. A single examiner should complete this assessment for all the subjects. If this is not possible, then the same examiner should perform this procedure for the same subject for all the visits wherever possible.

The OST examination may be performed at the same time as the MSA. The absence of any residual denture adhesive in the mouth must be confirmed by a second (non-blinded) examiner prior to the subject attending to the MSA or OST examination to ensure the OST/MSA assessor remains blinded to treatment.

9.3.2 Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, will be performed at every visit to the study site. Results will be obtained prior to dosing during each period.

The investigator and site personnel will remind subjects at each visit to inform site personnel if their menstrual cycle has changed or if they have any other reason to suspect they may be pregnant (e.g. had unprotected intercourse since the last visit).

A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active study period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of IRBs/ECs or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or medical device),

whether or not considered related to the study product, including any washout or lead-in product (or medical device).

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

Events Meeting the AE Definition:

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

Events NOT meeting the AE definition:

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

10.2 Definition of a Serious Adverse Event (SAE)

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

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

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

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

10.3 Reporting of Adverse Events

10.3.1 Reporting Period

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

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

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

10.4 Reporting Procedures

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

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

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

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

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

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

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

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

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

10.4.1 Reporting of an Adverse Event

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

10.4.2 Reporting of a Serious Adverse Event

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

investigator study master file. Original SAE forms will be retained in the investigator study master file.

It is essential to enter the following information:

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

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

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

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

Email Serious Adverse Events to:

PPD

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

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

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

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

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

- Severe: An event that prevents normal everyday activities.

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

10.5.2 Assessment of Causality

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

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

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

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

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

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

10.6 Follow-up of Adverse Events

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

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

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

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

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

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

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

10.7 Withdrawal Due to an Adverse Event

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

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

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

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

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

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

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

10.8 Pregnancy

10.8.1 Time Period for Collecting Pregnancy Information

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

10.8.2 Action to be Taken if Pregnancy Occurs

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

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

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

Any female subject who becomes pregnant while participating will discontinue study treatment and be withdrawn from the study

10.9 Definition of and Procedure for Reporting Medical Device Incidents

Medical devices are being provided by GSK CH for use in this study; the medical devices in this study are the test denture adhesive, the denture brush and the denture cleansing paste.

10.9.1 Definition of an Incident

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

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

It is sufficient that:

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

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

- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents:

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

10.9.2 Reporting of Incidents and Malfunctions

All incidents must be reported to GSK CH within 24 hours (or sooner if possible) of the investigator or designee becoming aware of the situation.

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

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

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

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

Email the Incident Report Forms to:
PPD

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

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

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

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

All communications regarding a medical device incident should be directed towards the GSK CH study manager. In order to maintain blinding, these communications will not involve the study statistician or the study clinical research scientist. The study manager will assess if follow up action is required, and if necessary utilize study-independent scientists who will not be involved in the analysis and reporting of this study.

10.9.3 Follow-up of Medical Device Incidents

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

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

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

10.9.4 Regulatory and Ethics Reporting Requirements for Incidents

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

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

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

11 DATA MANAGEMENT

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

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

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

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

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

11.1 Case Report Form

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

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

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

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

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

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

11.2 Data Handling

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

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

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

11.2.1 Data Queries

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

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

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also

run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Patient Reported Outcomes

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

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

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

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

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

The primary response variable is the change from baseline in the average of the 5 questions in the Gum Comfort Questionnaire at 12 weeks. There are no comparable data available for the consideration of the analysis of the responses to the Gum Comfort Questionnaire. However, (i) similar questionnaires have been used and reported and (ii) the nature of the response variables using changes from baseline on a 5-point questionnaire allow us to predict the likely distributional aspects of such responses. From this exercise we can assume the standard deviation (SD) of the overall mean of gum comfort response can be represented by a Normal (0.8, 0.0862) random variable.

For a large number of simulated studies 100,000 the SD was sampled from this normal (prior) distribution. A clinically meaningful treatment effect was defined as -0.5 with adhesive vs no adhesive and was introduced into the simulated studies. With 57 evaluable subjects the power to detect such a difference with statistical significance (2-sided) at the 5% level was found to be 90%. This represents the average power to detect a mean difference of -0.5 between treatments over a plausible range (prior distribution) for the unknown SD and is often termed assurance.

In order to account for subject drop outs (assumed as 10%), 63 subjects per treatment arm should be randomized to ensure 57 subjects per arm are evaluable. The MITT population will be used for the primary analysis, and no correction to the alpha testing level will be made in respect of secondary endpoints.

12.2 Statistical Methods and Analytical Plan

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

12.2.1 Definition of Analysis Populations

- The Safety population will comprise all randomized subjects who receive at least one dose of the study product. This population will be based on the product the subject actually received.
- The Modified Intent-To-Treat (Treated or Exposed) population (MITT) will comprise all randomized subjects who receive at least one dose of study product and have at least one post randomization measure of gum comfort recorded via the questionnaire. This population will be based on the study product to which the subject was randomized. Any subject who receives a randomization number will be considered to have been randomized.
- The per protocol (PP) population includes all MITT subjects who fully comply with all study procedures and restrictions. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters.

12.2.2 Exclusion of Data from Analysis

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

12.2.3 Demographic and Baseline Characteristics

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

12.2.4 Study Drug/Product Compliance

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

12.2.4.1 Prior and Concomitant Medications

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

12.2.5 Primary Analysis

The primary endpoint is the change from baseline in the mean overall gum comfort questionnaire after 12 weeks of study. The subjects mean change from baseline for the Gum Comfort Questionnaire will be compared between groups using analysis of covariance (ANCOVA) and test between treatment groups at the 5% level of significance. The model will include the baseline value as covariate. Frequency distributions of the responses by treatment group will be provided to detail the whole range of responses. Within and between group estimates of treatment effects will be provided with 95% confidence intervals (CI's). The direction of the effect is anticipated in the direction of an improved gum comfort OHrQoL in favour of the experimental denture adhesive over the no adhesive group.

In the case of the assumptions underlying the model not being supported, a suitable transformation or non-parametric procedure will be used.

No imputation for missing values will be used.

The MITT population will be considered primary for this analysis. Analysis of the PP population (if applicable) will be secondary.

12.2.6 Secondary Analyses

Analysis of the same primary variable at 1, 4 and 8 weeks will be identical to that of the primary variable at 12 weeks.

Other Questionnaire data at each time of assessment, the OHIP-Edent and GOHAI (including any subscales of each) will be analyzed in a similar fashion to the primary variable.

A summary of the Product Sensory Questionnaire at 28 days will be provided for the adhesive wearing group.

A summary of the incidence of denture bearing tissue assessments at each time of assessment on a scale of 1-4 will be presented.

No correction to the testing level amongst the secondary variables will be made as these are considered non definitive and hypothesis generating.

Further details will be given in the Reporting and Analysis Plan which will be finalized prior to database lock.

12.2.7 Safety Analysis

All AEs will be coded using MedDRA. AEs will be categorised as oral and non-oral by the Clinical Research Director/ Scientist or designee prior to database lock. Treatment-emergent adverse event (Oral AEs as well as all AEs) will be associated with the most recent treatment received. The number of AEs and number of subjects with AEs will be listed and tabulated by treatment. The results of OST exams will be tabulated. Incidents will be listed. The safety analysis will be performed on the safety population.

12.2.8 Handling of Dropouts and Missing Data

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

12.2.9 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

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

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

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

- Data are authentic, accurate, and complete.

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

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

13.2 Quality Assurance

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

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

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

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

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

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

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

13.3.2 Ethical Conduct of the Study

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

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

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP (ICH, Nov 2016) , and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

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

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

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

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

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

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

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

13.3.4 Subject Recruitment

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

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

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

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

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

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

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

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

13.5 Provision of Study Results to Investigators

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

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

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

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

13.6 Records Retention

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

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

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

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

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

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

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

13.7 Conditions for Terminating the Study

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

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

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

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

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15 APPENDIX

15.1 ABBREVIATIONS

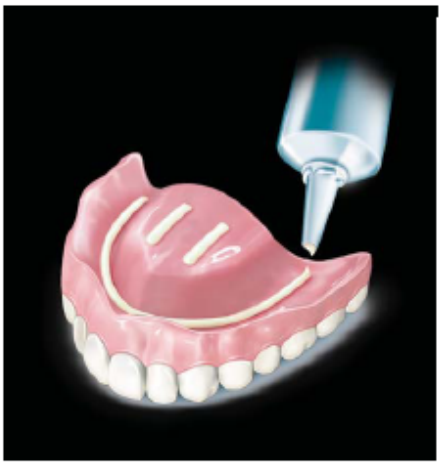
The following is a list of abbreviations that may be used in the protocol.

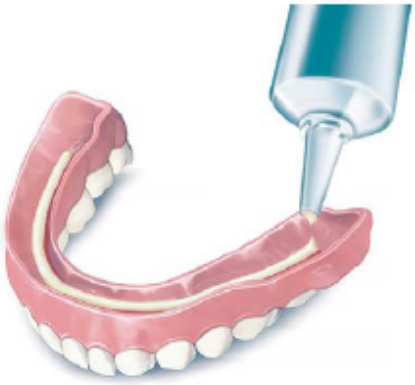
Table 15-1 Abbreviation

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
BDM	biostatistics and data management
CI	confidence interval
CRF	case report form

Abbreviation	Term
CTA	clinical trial application
DMS	Data management system
EC	ethics committee
ECG	electro cardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ePRO	Electronic patient reported outcome
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FRP	Females of Reproduction Potential
GCP	Good Clinical Practice
GOHAI	General Oral Health Assessment Index
GSK CH	GlaxoSmithKline Consumer Healthcare
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	institutional review board
IRT	Interactive Response Technology
LSLV	last subject last visit
MedDRA	medical Dictionary for Regulatory Activities
MITT	modified intent to treat
MSA	mucosal score assessment
N/A	not applicable
OHIP-Edent	Oral Health Impact Profile for Edentulous Patients
OHrQoL	Oral health related quality of life
OST	oral soft tissue
PI	principal investigator
PII	Personally identifiable information
PP	per protocol
PRO	patient reported outcome
SAE	serious adverse event
SRSD	single reference study document
SS	safety statement
SUSAR	suspected unexpected serious adverse reactions
US	United States

15.2 Application Instructions:





- Apply product (thin strips) to clean and **dry** dentures as:
  - Upper denture – Apply product in a long continuous strip, not too close to the denture edge, as shown in the image above. In the center, apply 2 shorter strips in the middle of the denture, as shown in the image above.
  - Lower Denture - Apply product in a long continuous strip, not too close to the denture edge, as shown in the image above.
- Rinse your mouth with tap water before inserting dentures.
- Press dentures into place, hold firmly, and bite down for a few seconds to secure hold.
- Adhesive should be applied once daily.
- For the first time, use a small amount then use more if needed. Too much adhesive can cause oozing; apply less next time if this occurs. It may take a few tries to find the right amount for your denture.

Removal Instructions:

- Swish mouth with water.
- Slowly remove denture using a rocking motion.
- Remove adhesive residue from denture and mouth with warm water and supplied denture brush.
- Thoroughly clean your denture in your usual manner and then rinse with water.

15.3 Example of the Gum-Comfort Questionnaire

Example Only

Please answer the following questions using the rating scale below:

Over the last few weeks (baseline)/Since your last visit to the study site (V2 onwards)…

1) My gums feel comfortable when wearing my denture(s).

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

2) I feel my gums are cushioned from the impact of chewing and biting.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

3) My gums do not feel sore at the end of the day.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

4) My gums are not irritated by trapped food particles under my denture(s).

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

5) My gums do not feel tired at the end of the day

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

15.4 Example of the Oral Health Impact Profile for Edentulous Patients (OHIP-Edent) Questionnaire

Example Only

Please answer the following questions using the rating scale below:

Over the last few weeks (baseline)/Since your last visit to the study site…

1) Have you had difficulty chewing any foods because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

2) Have you had difficulty with food catching in your teeth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

3) Have you felt that your dentures have not been fitting properly?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

4) Have you had painful aching in your mouth?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

5) Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

6) Have you had sore spots in your mouth?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

7) Have you had uncomfortable dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

8) Have you been worried by dental problems?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

9) Have you been self conscious because of your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

10) Have you had to avoid eating some foods because of problems with your teeth mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

11) Have you had to interrupt meals because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

12) Have you been unable to eat because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

13) Have you been upset because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

14) Have you been a bit embarrassed because of your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

15) Have you had difficulty with being less tolerant of your spouse or family because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

16) Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

17) Have you avoided going out because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

18) Have you been unable to enjoy other people's company as much because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

19) Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?

Never	Rarely	Occasionally	Often	Very Often
☐	☐	☐	☐	☐

15.5 Example of the General Oral Health Assessment Index (GOHAI) Questionnaire

Example Only

Please answer the following questions using the rating scale below:

Over the last few weeks (baseline)/Since your last visit to the study site…

1) How often did you limit the kinds or amounts of food you eat because of problems with your teeth or dentures?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

2) How often did you have trouble biting or chewing any kinds of food, such as firm meat or apples?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

3) How often were you able to swallow comfortably?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

4) How often have your teeth or dentures prevented you from speaking the way you wanted?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

5) How often were you able to eat anything without feeling discomfort?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

6) How often did you limit contacts with people because of the condition of your teeth or dentures?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

7) How often were you pleased or happy with the looks of your teeth and gums, or dentures?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

8) How often did you use medication to relieve pain or discomfort from around your mouth?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

9) How often were you worried or concerned about the problems with your teeth, gums or dentures?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

10) How often did you feel nervous or self-conscious because of problems with your teeth, gums or dentures?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

11) How often did you feel uncomfortable eating in front of people because of problems with your teeth or dentures?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

12) How often were your teeth or gums sensitive to hot, cold or sweets?

Always	Very Often	Often	Sometimes	Seldom	Never
☐	☐	☐	☐	☐	☐

15.6 Example of the Product Sensory Questionnaire

Example Only

Using the rating scale below, please answer the following questions about the denture fixative product you have been using:

1) I feel the product has a smooth texture on my gums.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

2) I feel the product is gentle on my gums.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

3) I feel the product flavor soothes my gums.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

4) I feel the product flavor cools my gums.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

5) I feel the product is easy to apply.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐

6) I feel less rubbing from my denture throughout the day when using this product.

Agree Strongly	Agree Somewhat	Neither Agree or Disagree	Disagree Somewhat	Disagree Strongly
☐	☐	☐	☐	☐