



STATISTICAL REPORTING AND ANALYSIS PLAN

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

Protocol Number: 209510

Phase: 3

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Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	15 Feb 2019	Not applicable

Amendments incorporate all revisions to date.

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDRM	Blinded Data Review Meeting
CI	Confidence Interval
GOHAI	General Oral Health Assessment Index
MSA	Mucosal Score Assessment
MITT	Modified Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
OST	Oral Soft tissue
OHrQoL	Oral Health Related Quality of Life
OHIP-Edent	Oral Health Impact Profile-Edentulous
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SE	Standard Error
TEAE	Treatment emergent adverse event

The purpose of this Statistical Reporting and Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for 209510.

1 Summary of Key Protocol Information

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 improvement in the gum-health and to improve the OHRQoL of subjects who wear full dentures compared to the usage of no adhesive.

1.1 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. 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.

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 favor of the experimental adhesive after 12 weeks use.

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.

1.2 Study Objectives

The study objectives are as follows:

Objectives	Endpoints
Primary Objective	Primary Endpoint
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 Objectives	Secondary Endpoints
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, 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	Safety Endpoints
To assess the tolerability of an experimental denture adhesive.	Treatment emergent adverse events.

1.3 Treatments

The following study products will be supplied:

Table 1-2 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 of the protocol)	N/A
Return Requirements	All used/unused samples to be returned to GSK CH	N/A

1.4 Sample Size Calculation

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, similar questionnaires have been used and reported and 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 Modified Intent-to-Treat (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.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints the baseline value will be the corresponding pre-treatment assessment at Screening/Baseline (Visit 1).

Unless otherwise stated, if baseline data are missing no derivation will be performed and will be set to missing.

3.2 Subgroups/Stratifications

No subgroups or stratification factors are defined in this study.

3.3 Centres Pools

Since this is a single center study, pooling of centers is not applicable.

3.4 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the Section 1.1. Any deviation from the study schedule may be reviewed on case-by-case basis at the Blinded Data Review Meeting

(BDRM) to determine whether any data should be excluded from the Per-Protocol (PP) population.

4 Data Analysis

Data analysis will be performed by Syneos Health. The statistical analysis software used will be SAS (Studio) version 9.4 or higher.

Prior to database closure a BDRM will be conducted, during which various aspects of the trial will be discussed and agreed.

Unless otherwise described, all listings will be produced for all randomized subjects.

4.1 Populations for Analysis

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. An enrolled subject is a subject who has signed informed consent and is eligible to proceed beyond screening. The number of subjects screened, enrolled and randomized will be presented in [Table 14.1.1](#).

[Table 14.1.1](#) will also display the number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized. Percentages for screen failure subjects will be based on the total number of subjects screened.

Subject disposition will also be summarized as the number and percentage of subjects in each of the defined analysis populations, who complete the study and who discontinue the study broken down by reason for discontinuation. The summary will be presented by study product group and overall. The percentages are based on the study product specific total number of subjects randomized.

Subject disposition including demographic data (age, sex, race and ethnicity), screening date, study product start date, the subject status (completer, Yes/No), study completion/withdrawal date, duration (in days) in the study (defined as [(date of completion or withdrawal – screening date) + 1] and the primary reason for withdrawal will be listed ([Listing 16.2.1.1](#)).

Subject disposition information will be listed for non-randomized subjects ([Listing 16.2.1.2](#)), displaying subject number, demographic information (age, sex, race and ethnicity), screening date, reason for screen failure and any further details of reason for screen failure.

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and closure of the database to ensure all important deviations are captured and categorised. Subjects with important protocol deviations liable to influence the efficacy outcomes will be excluded from the PP population. Subjects may also be

identified as having important protocol deviations not leading to exclusion from the PP population.

Important deviations of the protocol procedures may include, but will not necessarily be limited to:

- Violation of inclusion or exclusion criteria at screening
- Non-compliance with study product use
- Use of prohibited treatment or medication before or during the study
- Violation of visit windows

The specific details of important protocol deviations and how these will be assessed will be specified in the Blind Data Review Plan and subjects with important protocol deviations will be identified at the BDRM.

The number and percentage of subjects with at least one important protocol deviation, important protocol deviations not leading to exclusion from PP population with reasons for deviations and subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations will be summarised by study product group ([Table 14.1.2](#)) and listed ([Listing 16.2.2.1](#)).

All protocol deviations captured on the case report form will be listed in [Listing 16.2.2.2](#). The listing will present date of deviation, deviation type and deviation description.

4.1.3 Analysis Populations

The analysis populations defined for this study are as follows:

Population	Definition / Criteria	Analyses Evaluated
Safety	All randomized subjects who receive at least one dose of study product. This population will be based on the product the subject actually received.	Safety
Modified Intent-To-Treat (MITT) (Treated or exposed)	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.	Efficacy
Per Protocol (PP)	All subjects in MITT population who comply with all study procedures and restrictions that may affect the interpretation of the primary response. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters.	Efficacy

NOTES :

Please refer to Attachment 1: List of Data Displays which details the population to be used for each displays being generated.

Subjects excluded from any of the analysis populations will be listed in [Listing 16.2.3.1](#).

The primary population for assessment of efficacy will be the MITT Population. PP population analysis will be performed only if 10% of MITT population is excluded from PP population.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics (n, mean, SD, median, minimum and maximum for continuous variables, frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for demographic variables by study product and overall. These variables include age, gender, race and ethnicity and will be presented for the Safety population ([Table 14.1.3.1](#)), the MITT population ([Table 14.1.3.2](#)) and the PP Population ([Table 14.1.3.3](#)) if applicable.

Demographic information will be listed ([Listing 16.2.4.1](#)) for all randomized subjects.

4.2.2 General Medical History

Medical history data will be listed ([Listing 16.2.4.2](#)) with start date and end date or ongoing at the start of the study.

4.2.3 Characteristics of Study Population

[Table 14.1.4.1](#) summarises the baseline characteristic data collected on the denture information (descriptive statistics of duration of denture use), denture history (descriptive statistics of current age of denture), criteria for well-made denture (frequency counts and percentages of all responses to each question), evaluation of well fit denture (frequency counts and percentages of each response under retention and stability and descriptive statistics for sum score retention and stability) and denture bearing tissue evaluation (frequency counts and percentages of responses to ridge shape, tissue resiliency and boarder tissue attachment) eCRF pages for the subjects in the Safety population.

The baseline characteristic table described above will be repeated for the MITT population ([Table 14.1.4.2](#)).

Denture information and history details ([Listing 16.2.4.3](#)), criteria for well-made denture ([Listing 16.2.4.4](#)), evaluation of well-fit denture ([Listing 16.2.4.5](#)) and denture bearing tissue evaluation information ([Listing 16.2.4.6](#)) will be listed as collected on the respective eCRF pages.

4.3 Treatments (Study Product, Rescue Medication, other Concomitant Therapies, Compliance)

Randomization details will be listed, including the planned study product, the actual study product the subject was randomized to and the randomization date ([Listing 16.1.7](#)).

4.3.1 Product Compliance

Product compliance of the experimental adhesive group will be recorded as number of missed product uses since last visit and number of additional product uses since last visit.

Compliance to experimental adhesive use will also be calculated as a percentage at each visit:

$$\text{Compliance} = (\text{actual number of uses} / \text{expected number of uses}) \times 100$$

Where:

Expected number of product uses = number of days between the two visits

Actual number of uses = expected number – missed product uses + additional product uses

The number of missed product uses, additional product uses and percentage compliance will be summarized using descriptive statistics (n, missing, mean, SD, median, minimum and maximum) at Weeks 1, 4, 8 and 12. In addition at Week 12, the number and percentage of subjects <80%, between 80% - 120% and >120% compliance will be presented. Compliance

data will be summarised and listed for the experimental adhesive group only in [Table 14.2.1.1](#) (Safety population) [Table 14.2.1.2](#) (MITT population) and [Listing 16.2.5.1](#).

4.3.2 Prior and Concomitant Medication

Prior or concomitant medication taken by or administered to a subject will be recorded in the case report form. The prior and concomitant medications will be coded using an internal validated medication dictionary, GSK Drug.

Prior medication will be listed by subject, with drug name, GSK drug synonym, dose, dose form, frequency, route, start date, study day relative to randomization date/first use of study product administration and end date ([Listing 16.2.5.2](#)). Prior medications are defined as those which stopped before the date of randomization/first use of the study product. If the stop date is unknown or incomplete and the medication cannot be considered as stopped prior to the randomization date/first use of study product then the medication will be considered as a concomitant medication.

Concomitant medications and significant non-drug therapy will be listed similarly ([Listing 16.2.5.3](#)) with either ongoing or end date displayed. Concomitant medications are defined as medications that are ongoing or started on or after the randomization date/first use of the study product.

For the assignment of prior and concomitant medications, the randomization date will be used for subjects randomized to the No Adhesive group and the date of first use of study product will be used for the subjects randomized to the Experimental Adhesive Group.

Unknown dates will not be imputed, however if the start or stop date is unknown, then it will be assumed to be concomitant medication unless the partial start date or stop date indicates differently.

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

4.4.2 Primary Efficacy Endpoint Definition

The primary endpoint is the change from baseline in the mean overall gum comfort questionnaire score after 12 weeks of study.

The gum-comfort questionnaire is comprised of 5 questions that record 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. The score from all 5 questions will be summed as the overall gum comfort score at each time point, which will have a range score of 0-20 where a low score is more favorable. See section 4.4.4.1 on how to deal with missing scores.

4.4.2.1 Statistical Hypothesis, Model, and Method of Analysis

Descriptive statistics (n, missing, mean, SD, SE, median, minimum and maximum) of the primary variable observed value will be provided ([Table 14.2.2.1](#)) at Baseline, Weeks 1, 4, 8 and 12, along with the change from baseline statistics at Weeks 1, 4, 8 and 12 by product group for the MITT population and ([Table 14.2.2.4](#)) for PP population.

Frequency distributions of the overall gum comfort score by product group will be provided displaying the complete range of responses from 0 – 20 at each week ([Table 14.2.2.2](#)) for MITT population.

The primary analysis is a comparison of the mean change from baseline in overall gum comfort score between Experimental Adhesive and No Adhesive at Week 12 for subjects eligible for the MITT population.

The null hypothesis for the primary endpoint is that the mean change from baseline in overall gum comfort score is equal between the 2 groups.

$$H_0: \mu_1 = \mu_2$$

The alternative hypothesis is that the mean change from baseline in overall gum comfort score is not equal between the 2 groups.

$$H_1: \mu_1 \neq \mu_2$$

The change from baseline in overall gum comfort score at Week 12 will be analysed using analysis of covariance (ANCOVA) with study product as a fixed effect and baseline overall gum comfort score as a covariate. Adjusted means and their SEs, 95% confidence intervals (CI), within treatment p-values for each product group will be displayed with product group difference, SE, 95% confidence interval of the difference and the between-treatment p-value in [Table 14.2.2.3](#) for MITT population and in [Table 14.2.2.5](#) for PP population. All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

This study will be considered successful if a statistically significant difference between the adjusted mean scores of the two product groups is observed to be in favor of the Experimental Adhesive.

The assumptions of the ANCOVA model i.e. normality of residual and equality of variances will be investigated. If the assumptions of the underlying model are violated, data transformations will be investigated and if suitable transformations cannot be found, an appropriate non-parametric test will be performed (e.g. Mann-Whitney U test).

All Gum Comfort Questionnaire responses with the overall and change from baseline scores will be listed ([Listing 16.2.6.1](#)).

4.4.2.2 Supportive Analyses

If there is more than 10% difference in the overall number of subjects between PP and MITT populations, a summary of the primary efficacy variable will be presented for all subjects in the

PP population (Table 14.2.2.4) and the same ANCOVA model applied to the primary analysis will be performed on the PP population (Table 14.2.2.5).

Secondary efficacy variables are defined in Section 4.5.

4.4.3 Handling of Missing Values/Censoring/Discontinuations

Subjects who withdraw from the study prematurely will be included in the statistical analyses up to the point of discontinuation.

4.4.3.1 Handling of Missing Values in Questionnaire Data

For any overall questionnaire score (with the exception of product sensory questionnaire) or functional domain score (where applicable), if there are $\leq 20\%$ of missing values/scores that are required for the derivation of the overall or functional domain score, the missing score will be imputed pro-rated. If there is $> 20\%$ of missing values, the score will be set to missing.

This $\leq 20\%$ imputation rule will therefore be dependent on the number of questions per functional domain or overall score. For example:

Number of Questions within Domain or Overall Score	Number of Scores Missing	Impute or Set to Missing
1 to 4	≥ 1	Set to missing
5 to 9	1	Impute
	≥ 1	Set to missing
10 to 15	1	Impute
	2	Impute
	≥ 2	Set to missing
16 to 19	1	Impute
	2	Impute
	3	Impute
	≥ 4	Set to missing

Scores will be imputed using the following calculation:

$$\text{Imputation score} = s \cdot n / (n - m)$$

Where:

s = total value of scores available

n = number of questions within the overall score or domain

m = number of missing values

Imputation examples are provided for a couple of the questionnaires below

Gum-Comfort Questionnaire

Gum-comfort questionnaire comprises of 5 questions; if 1 of the scores out of the 5 questions is missing, the overall gum comfort score will be derived as:

Question	Response
1) My gums feel comfortable when wearing my denture(s)	1
2) I feel my gums are cushioned from the impact of chewing and biting	2
3) My gums do not feel sore at the end of the day	3
4) My gums are not irritated by trapped food particles under my denture(s)	3
5) My gums do not feel tired at the end of the day	missing

Rating scale: [0] - Agree Strongly, [1] - Agree Somewhat, [2]- Neither Agree or Disagree, [3]- Disagree Somewhat, [4]- Disagree Strongly

Imputation of Overall score for above example: $(1+2+3+3)*5/4 = 11.25$

OHIP-Edent Questionnaire

OHIP-Edent Questionnaire comprises of 19 questions grouped into 6 functional domains (see section 4.5.1.4 for further details):

Domain	Question	Number of Questions within Domain	Response	Total Score
Functional limitations	1-3	3		missing
	1) Have you had difficulty chewing any foods because of problems with your teeth, mouth or dentures?		1	
	2) Have you had difficulty with food catching in your teeth or dentures?		2	
	3) Have you felt that your dentures have not been fitting properly?		missing	
Physical pain	4-7	4		missing
	4) Have you had painful aching in your mouth?		missing	
	5) Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?		1	
	6) Have you had sore spots in your mouth?		3	
	7) Have you had uncomfortable dentures?		2	
Psychological discomfort	8-9	2		3
	8) Have you been worried by dental problems?		1	
	9) Have you been self-conscious because of your teeth, mouth or dentures?		2	

Physical disability	10-12	3		4
10) Have you had to avoid eating some foods because of problems with your teeth mouth or dentures?			1	
11) Have you had to interrupt meals because of problems with your teeth, mouth or dentures?			3	
12) Have you been unable to eat because of problems with your teeth, mouth or dentures?			0	
Psychological disability	13-14	2		4
13) Have you been upset because of problems with your teeth, mouth or dentures?			1	
14) Have you been a bit embarrassed because of your teeth, mouth or dentures?			3	
Social disability	15-19	5		8.75
15) Have you had difficulty with being less tolerant of your spouse or family because of problems with your teeth, mouth or dentures?			1	
16) Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures?			missing	
17) Have you avoided going out because of problems with your teeth, mouth or dentures?			2	
18) Have you been unable to enjoy other people's company as much because of problems with your teeth, mouth or dentures?			2	
19) Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?			2	
Overall OHIP-Edent score	1-19	19	27	32.06

Rating Scale: [0] Never [1] Rarely [2] Occasionally [3] Often [4] Very Often

For the overall OHIP-Edent score is calculated as:

$$27 * 19 / 16 = 32.06$$

Where 16 (19-3) is the denominator due to the 3 missing scores in questions 3, 4 and 16.

Product Sensory Questionnaire

There will be no imputation of the product sensory score which comprises of 6 questions (see section 4.5.1.6 for further details). If one of more of the question scores is missing, then the product sensory score will be set to missing.

4.5 Analysis of Secondary Objectives

No correction to the testing level amongst the secondary variables will be made as these are considered non definitive and hypothesis generating. All analyses will be conducted on the MITT population only.

4.5.1 Efficacy (Secondary)

4.5.1.1 Overall Gum Comfort Score at Weeks 1, 4 and 8

Change from baseline in overall gum comfort questionnaire scores at Weeks 1, 4 and 8 (overall mean score) will be evaluated using the same model as used for primary efficacy analysis on the MITT population (Table 14.2.2.1).

4.5.1.2 Gum Comfort Questionnaire Individual Questions Scores

Summary of Individual Gum Comfort question scores will be presented (n, missing, mean, SD, SE, median, minimum and maximum) at Weeks 1, 4, 8 and 12 in Table 14.2.3.1. Individual Gum Comfort question scores will be statistical analyzed using the same model as used for primary efficacy analyses in Table 14.2.3.2.

4.5.1.3 Mucosal Score Assessment (MSA)

The MSA will be made on the denture bearing tissues using the scale described by Henriksen et al and summarized in Table 9-3 of the Protocol. The MSA score at each assessment is measure on a scale of 1 (normal appearance) up to 4 (severe inflammation).

A summary table of descriptive statistics (n, missing, mean, SD, SE, median, minimum and maximum) of the observed and change from baseline MSA values will be presented at each week (Table 14.2.4.1) for subjects in the MITT population.

Wilcoxon rank sum test will be used to compare the between-product group medians of change from baseline MSA values at each week and the Wilcoxon signed-rank test will be used to compare the within-product group medians of change from baseline MSA values at each week for subjects in MITT population. P-values for both tests will be reported along with median change from baseline values. (Table 14.2.4.2)

All MSA responses and change from baseline scores will be listed (Listing 16.2.6.2).

4.5.1.4 OHIP-Edent Questionnaire

This questionnaire comprises 19 questions grouped into 6 functional domains as provided in [Table 4-1](#). The questions have 5 possible responses ranging from 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 4-1 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

Summary tables of descriptive statistics (n, missing, mean, SD, SE, median, minimum and maximum) of the observed and change from baseline overall OHIP-Edent score will be presented ([Table 14.2.5.1](#)) at each week and for OHIP-Edent functional domain scores over time ([Table 14.2.5.3](#)) for subjects in the MITT population.

The change from baseline in overall OHIP-Edent score at Weeks 1, 4, 8 and 12 will be analyzed using ANCOVA with study product as a fixed effect and baseline overall OHIP-Edent score as a covariate. Adjusted means and their SEs, 95% CI, within treatment p-values for each product group will be displayed with product group difference, SE, 95% CI of the difference and the between-treatment p-value in ([Table 14.2.5.2](#)). All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$. Similar model will be used to analyze change from baseline OHIP-Edent functional domain scores at weeks 1, 4, 8 and 12 ([Table 14.2.5.4](#)).

As with the primary efficacy analysis, the model assumptions will be checked and suitable transformations or alternative non-parametric method will be performed if these are not met.

All OHIP-Edent responses for each question will be listed ([Listing 16.2.6.3](#)) by functional domain including the functional domain score, change from baseline domain score and overall OHIP-Edent observed and change from baseline values.

4.5.1.5 GOHAI Questionnaire

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) to 5 (never) scale for all questions except 3, 5 and 7 where the scoring is reversed, and thus the overall GOHAI scores can range from 0-60, where 60 is the best possible score.

The questions are grouped into 3 domains as detailed in [Table 4-2](#).

Table 4-2 The Functional Domains of the GOHAI Questionnaire

Table	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.

Summary tables of descriptive statistics (n, missing, mean, SD, SE, median, minimum and maximum) of the observed and change from baseline overall GOHAI score will be presented (Table 14.2.6.1) at each week for subjects in the MITT population.

The change from baseline in overall GOHAI score at Weeks 1, 4, 8 and 12 will be analyzed using ANCOVA with study product as a fixed effect and baseline overall GOHAI score as a covariate. Adjusted means and their SEs, 95% CI, within treatment p-values for each product group will be displayed with product group difference, SE, 95% CI of the difference and the between-treatment p-value in Table 14.2.6.2. All statistical tests of hypotheses will be two-sided and will employ a level of significance of $\alpha = 0.05$.

As with the primary efficacy analysis, the model assumptions will be checked and suitable transformations or alternative non-parametric method will be performed if these are not met.

A summary table for the GOHAI 3 functional domains will be presented individually and their respective questions (Table 14.2.6.3). Similar model used to analyze overall GOHAI score will be used to analyze the change from baseline GOHAI functional domain scores at weeks 1, 4, 8 and 12 (Table 14.2.6.4).

All GOHAI responses for each question will be listed (Listing 16.2.6.4) by functional domain including the functional domain score, change from baseline functional domain score and overall GOHAI observed and change from baseline scores.

4.5.1.6 Sensory Questionnaire

The sensory questionnaire will be completed by subjects at Week 4 (Day 28/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 experimental 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 overall sensory questionnaire score is 0-24 where a low score is more favorable.

A summary table of descriptive statistics (n, missing, mean, SD, SE, median, minimum and maximum) of the overall sensory questionnaire score and individual questions at Week 4 will be provided for the experimental adhesive group in Table 14.2.7

[Listing 16.2.6.5](#) will display all the sensory questionnaire responses to each question including the overall score.

4.5.2 Pharmacokinetic (Secondary)

Not Applicable

4.6 Analysis of Safety

The safety analysis will be performed on the safety population.

4.6.1 Adverse Events and Serious Adverse Events

All Adverse Events (AEs) will be reviewed by the Clinical Research Scientist or Designee prior to database lock and will be coded to a system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be classified by the dental examiner as either oral or non-oral on the AE page of the eCRF.

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the first study product use/date of randomization. AEs events with an onset date/time prior to the first study product use/date of randomization will be considered as non-treatment emergent.

For the assignment of TEAEs, the randomization date will be used for subjects randomized to the No Adhesive group and the date of first use of study product will be used for the subjects randomized to the Experimental Adhesive Group.

AEs will be summarized by the number and percentage of subjects with an AE, an AE in each SOC and each PT. The following summary tables (by product group for subjects in the Safety Population) and listings (for all Randomized Subjects) will be presented:

- Table of treatment-emergent AEs by SOC and TPT ([Table 14.3.1.1](#)). Summary of the number and percentage of subjects with at least one AE, total number of AEs, number and percentage of AEs within each SOC and PT will be displayed.
- Table of treatment-emergent AEs by Oral/Non-Oral and PT ([Table 14.3.1.2](#))
- Table of treatment related treatment-emergent AES by Oral/Non-Oral and PT ([Table 14.3.1.3](#))
- Listing of all AEs ([Listing 16.2.7.1.1](#) for all randomized subjects; [Listing 16.2.7.1.2](#) for non-randomized subjects)
- Listing of deaths ([Listing 14.3.2.1](#))
- Listing of non-fatal Serious Adverse Events ([Listing 14.3.2.2](#))
- Listing of treatment-emergent AEs leading to study or drug discontinuation ([Listing 14.3.2.3](#))
- Listing of treatment-emergent AEs classified as oral ([Listing 14.3.2.4](#))

In the event that there is nothing to report, a null table or listing will be produced.

4.6.2 Other Safety Variables

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.

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.

All Incidents will be listed in Listing [16.2.7.2](#).

Oral Soft Tissue Examination

Summary of oral soft tissue (OST) examination results (frequency counts and percentages) will be tabulated in [Table 14.3.1](#) at each visit and listed in [Listing 16.2.9.1](#).

4.7 Other Analysis

In addition to what was planned in the protocol, Cronbach's coefficient alpha will be calculated at Week 1, 4, 8 and 12 for OHIP-Edent domains ([Table 14.2.5.5](#)) and GOHAI domains ([Table 14.2.6.5](#)).

Cronbach's coefficient alpha is a measure of internal consistency, that is, how closely related a set of items are as a group. It is considered to be a measure of scale reliability which can be used to support the use of combined domain scales.

Cronbach's Coefficient will be calculated as:

$$\alpha = \left(\frac{k}{k-1} \right) \left(1 - \frac{\sum_{i=1}^k \sigma_{y_i}^2}{\sigma_x^2} \right)$$

... where: k refers to the number of scale items

$\sigma_{y_i}^2$ refers to the variance associated with item i

σ_x^2 refers to the variance associated with the observed total scores

A coefficient of 0.7 and above shows that the internal consistency/reliability between the domain is at least acceptable.

5 Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol are outlined in [Table 5-1](#).

Table 5-1 Changes to Protocol Defined Analysis Plan

Table	Reporting & Analysis Plan	
Statistical Analysis section	Statistical Analysis Plan	Rationale for Changes
<p>Section 12.2.1 Definition of Analysis Population</p> <p>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.</p>	<p>Section 4.1.3 Analysis Population</p> <p>PP population includes all subjects in MITT population who comply with all study procedures and restrictions that may affect the interpretation of the primary response. Deviations will be determined and applied prior to unblinding and consist of variations in criteria likely to affect the interpretation of the efficacy parameters.</p>	<p>To provide clarification of the definition.</p>
<p>Details were not included</p>	<p>Section 4.7 Other Analysis</p> <p>Cronbach coefficient alpha will be derived for OHIP-EDENT domains and GOHAI domains.</p>	<p>Cronbach's coefficient alpha is a measure of internal consistency, that is, how closely related a set of items are as a group. It is considered to be a measure of scale reliability which can be used to support the use of combined domain scales.</p>

Attachment 1: List of Data Displays



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