POOLED ANALYSIS PROTOCOL

A Post-hoc Pooled Analysis of GSK CH Clinical Data Investigating the Efficacy of Denture Adhesive creams containing PMV/MA &CMC on Denture Retention and Bite Force
213380

Protocol Number:	213380
Compound/Product Name:	30% Poly (methylvinylether/Maleic Acid) Sodium-Calcium Mixed Partial Salt + 24% Sodium Carboxymethylcellulose
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Phase:	N/A

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSK CH)** St. George's Avenue, Weybridge, Surrey, KT13 0DE, UK Tel: PPD

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.

Table of Contents

List of in text tables

1 Introduction

Denture adhesives or fixatives have been used by edentulous patients to improve the retention and stability of dentures for many years. 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 and Fenton, 2013).

There are a number of recognized methods which have been used to demonstrate the clinical efficacy of a denture adhesive. These include the Kapur Index (Kapur, 1967) and measurement of the maximum incisal bite force (BF) until denture dislodgement (Howell and Manly, 1948) to measure denture retention and stability, denture dislodgement (Tarbet et al, 1980) to measure denture movement in function, and masticatory performance (Kapur, 1967) an indicator of chewing efficiency.

Incisal BF can be used as a measure of maxillary denture retention and is a recognized objective test method that has been used to demonstrate the efficacy of denture adhesive (Varghese et al, 2019). Studies using BF as a clinical model have routinely utilized a sample size of 35-50 subjects with clinically poor-good fitting maxillary dentures (Kapur, 1967). In this population, the BF clinical model has been used successfully to demonstrate that cream denture adhesives improve denture hold for 12 hours or longer and to also demonstrate differences in strength among various adhesive formulations (Grasso, 2004). The dental literature also contains a number of studies that indicate benefits for different brands or formulations of denture adhesive in well-fitting dentures (Chew et al, 1985; Grasso, 2004)

Data on the efficacy of denture adhesive creams containing the same adhesive ingredient, a combination of poly methyl vinyl /maleic anhydride and carboxymethylcellulose (PMV/MA&CMC), on denture hold and BF improvement exists for individual GlaxoSmithKline Consumer Healthcare (GSK CH) studies (Table 3-1). Varghese and colleagues showed statistically significantly superiority of the denture adhesive compared to no adhesive using incisal BF measurements (Area-Over-Baseline AOB over 12 hours) in participants with a well-made and moderately well-fitting complete maxillary denture (Varghese et al, 2019). Similar results were observed in another 2 studies demonstrating statistically significantly higher BF measurements after the first hour of adhesive application (Munoz et al, 2012) as well as at all time points (0.5, 1, 3, 6, 9 and 12 hours - Axe et al, 2018). Furthermore, Jose *et al.* showed the superiority of PMV/MA&CMC also compared to experimental adhesives reporting significantly higher BF AOB for all time points (Jose et al, 2018).

The aim of this pooled analysis is to aggregate individual subject level data from GSK CH BF studies conducted on denture adhesive creams containing 30% PMV/MA & 24% CMC to assess efficacy overall and within sub-groups, with the intention of providing evidence to enable the dental health care professional to recommend the most appropriate treatment for their patients' needs.

1.1 Mechanism of Action/Indication

Denture adhesives work through their ability to both adhere the denture to the oral mucosa in order to improve retention and stability and to occlude gaps between the denture and the oral mucosa which might otherwise be susceptible to food particle ingress (Ozcan et al, 2005).

PMV/MA&CMC is a well-investigated and marketed denture adhesive technology (Grasso, 2004). In this adhesive, CMC has high solubility and is believed to be involved in initial adhesive hydration and therefore responsible for initial adhesive strength when fitted to a denture. As this hydration proceeds, the less soluble PMV/MA then hydrates, and a stronger and longer hold develops. Additionally, the hydration of denture adhesives through contact with saliva leads to expansion of the adhesive, occluding gaps between the denture and the underlying oral mucosa (Han et al, 2014).

1.2 Background and Rationale

Dentures are custom prosthetic devices, unique to an individual, that helps restore form and function. However, the BF achieved with dentures is often 4-5 times less than that achieved with natural dentition (Haraldson et al, 1979; Fontiin-Tekampl et al, 2000), often limiting the range of foods that denture wearers are able to consume which may potentially impact nutritional status (Nair and Latheef, 2019).

Denture adhesive are a well-known adjuvant to improve denture retention, comfort and to reduce the ingress of food particles under the denture. They function through formation of a seal between the denture and oral soft tissues and thus provide a firm hold for dentures. Improved retention facilitates increased BF and improves the chewing ability of denture wearers which can improve denture function.

A series of GSK CH sponsored clinical studies have been conducted to provide strong support for the efficacy of the GSK denture adhesive creams, containing 30% PMV/MA & 24% CMC, primarily around claims of 12-hour hold (Table 3-1). In addition, study (GSKCH Clinical Study Report L3510566, 2008; Munoz et al, 2012) showed a 38% increase in BF as evaluated at a one-hour period.

This study will summarize all GSK CH available clinical data investigating denture adhesive creams with the same adhesive material that are considered similar to the currently marketed product. Nine BF studies have been identified in which formulations varied on flavorings/preservatives, vitamin E and colorants, but these characteristics would not be expected to materially impact the mode of action and the efficacy of the products.

The aim of this pooled analysis study is to aggregate individual subject level data from GSK CH BF studies on denture adhesive creams containing 30% PMV/MA & 24% CMC to reinforce the current claim sets (denture hold and BF improvements over 12- hour period), which will be evaluated as primary and secondary objectives in this study (Section 2), and to unlock new claims.

In the literature, the beneficial role of denture adhesives on masticatory functions and maximum incisal BF improvements considering retention, stability (FELLER et al, 1986) and conditions of denture bearing tissues (DBTs) (Fujimori et al, 2002) has been investigated. Furthermore, Tarbet and colleagues have shown that not only unsatisfactory tissue conditions have an impact on baseline BF but also that they might be an important determinant of denture stability and retention, even when the denture is well adapted (Tarbet et al, 1981). Data on denture fitting and DBTs have been collected in majority of GSK CH studies but their role on the adhesive performance has not been fully evaluated. Therefore, additional analyses will be conducted to further explore new claims opportunity.

2 Objectives

The aim of this study is to pool data from GSK CH clinical studies to investigate the efficacy of denture adhesives creams containing a combination of 30% PMV/MA & 24% CMC, on maximum BF over 12-hour period.

Objectives	**Endpoints**
Primary	
To compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PVM/MA & 24%CMC denture adhesive to no adhesive over 12 hours	AOB over 12 hours
Secondary	
To compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PVM/MA & 24%CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 9 hours	AOB up to 0.5, 1, 3, 6 and 9 hours
To compare and evaluate maximum incisal BF made with 30% PVM/MA & 24%CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 12 h	Raw mean BF measurement between adhesive and no adhesive at 0.5, 1, 3, 6, 9 and 12 hours
To compare and evaluate maximum incisal BF made with 30% PVM/MA & 24%CMC denture adhesive and no adhesive to baseline over 12 h	Within-treatment change from baseline in raw BF measurement up to 0.5, 1, 3, 6, 9 and 12 hours
Exploratory	
To compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PVM/MA & 24%CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 12 hours, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF	AOB up to 0.5, 1, 3, 6, 9 and 12 hours in 3 categories: **Kapur score** (Clinically Fair 4, clinically Good 5-7, clinically very good >7) **DBT score** (Poor <7, satisfactory 7-9, good >9) **Baseline BF measurements** (Baseline BF ≤2.5 pounds (lbs), Baseline BF >2.5 lbs)

Objectives	Endpoints
To compare and evaluate maximum BF made with 30% PVM/MA & 24%CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 12 h, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF	Raw mean BF measurement between adhesive and no adhesive at 0.5, 1, 3, 6, 9 and 12 hours in 3 categories: **Kapur score** (Clinically Fair 4, clinically Good 5-7, clinically very good >7) **DBT score** (Poor <7, satisfactory 7-9, good >9) **Baseline BF measurements** (Baseline BF ≤2.5 lbs, Baseline BF >2.5 lbs)
To compare and evaluate maximum BF made with 30% PVM/MA & 24%CMC denture adhesive and no adhesive to baseline over multiple measure time points from 0.5 to 12 h, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF	Within-treatment change from baseline in raw BF measurement up to 0.5, 1, 3, 6, 9 and 12 hours in 3 categories: **Kapur score** (Clinically Fair 4, clinically Good 5-7, clinically very good >7) **DBT score** (Poor <7, satisfactory 7-9, good >9) **Baseline BF measurements** (Baseline BF ≤2.5 lbs, Baseline BF >2.5 lbs)
To evaluate the baseline BF with respect to the maximum observed BF	Percentage changes of baseline BF value from the maximum BF force measurement at any given post baseline timepoint
To evaluate the effect of retention, stability and conditions of DBTs on baseline BF	Baseline BF including Kapur Index and DBT in the model to be assessed
To evaluate the relative BF at all measure time points with respect to the maximum observed BF	Percentage changes of BF value at 0.5, 1, 3, 6, 9 and 12 h from the maximum BF force measurement

The objectives listed above will be analyzed for the pooled data only. The study will be considered successful should there be a statistically significant difference and a difference of greater than 2 lbs between the 30% PVM/MA & 24% CMC adhesive creams compared with the negative control in maximum incisal BF over 12 hours period, as detailed in section 5.2.

Having reviewed the planned treatment differences in previous studies (respective sample size Table 5-1) included in this pooled analysis, it seems that an approximate average of 2 lbs treatment difference is considered to be an appropriate treatment difference value.

3 Selection, design and methodology of studies

3.1 Study selection criteria

The study criteria for inclusion in the pooled analysis include:

i. Clinical studies conducted by GSK CH, including:

   a. Access to study protocols, study reports, and

   b. Access to anonymized individual information sources/ study data

ii. Study design and subject inclusion criteria in agreement with pre-defined study selection criteria (Table 3-1):

   a. Subject eligibility based on study inclusion criteria:

      i. Completely edentulous maxillary arch

      ii. Well-made complete dentures according to the design and construction criteria used in GSK studies (GSKCH Clinical Study Report L3510566, 2008; CCI [redacted])

      iii. Qualifying maxillary incisal BF readings (without adhesive) less than or equal to 9 lbs at the Screening and subsequent pre-treatment baseline bites

   b. Raw BF data available

   c. Comparable treatment (30% PVM/MA & 24% CMC denture adhesive creams) CCI [redacted] and variants (CCI [redacted])

Table 3-1 Summary of GSKCH denture adhesive BF studies

Study No.	Timepoints evaluated	Adhesive used	Study Design	Kapur score	DBT Score	'No Adhesive' arm	Included in this pooled analysis	Year conducted
CCI	0.5, 1, 3, 6, 12h	CCI	Crossover	Yes	Yes	No	No*	2011
CCI	0.5, 1h	Fittydent®	Crossover	Yes	Yes	No	No*	2012
CCI	0.5, 1, 3, 6, 12h	Fixodent®	Crossover	Yes	Yes	No	No*	2012
CCI	0.5, 1, 3, 6, 12h	CCI	Crossover	Yes	Yes	No	No*	2013
CCI	0.5, 1, 3, 6, 16h	CCI	Crossover	Unknown	Unknown	Unknown	No*	2002
CCI	0.5, 1, 3, 6, 12h	SPG Free	Unknown	Unknown	Unknown	Unknown	No*	2010
(GSKCH Clinical Study Report RH02625, 2015) (Axe et al, 2018)	0.5, 1, 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	No	No*	2014-2015
CCI	0.5, 1, 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	No	Yes	2013
CCI)	0.5, 1, 3, 6, 12h	CCI	Monadic	Unknown	No	No	Yes	2013
CCI	0.5, 1, 3, 6, 9, 12h	CCI	Parallel	Yes	Yes	Yes	Yes	2013
(GSKCH Clinical Study Report L3510566, 2008) (Munoz et al, 2012)	1h	CCI	Crossover	Yes	Yes	Yes	Yes	2008
CCI	0.5, 1, 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	Yes	Yes	2014
CCI	0.5, 1. 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	Yes	Yes	2014-2015

Study No.	Timepoints evaluated	Adhesive used	Study Design	Kapur score	DBT Score	'No Adhesive' arm	Included in this pooled analysis	Year conducted
(GSKCH Clinical Study Report 203114, 2016) (Jose et al, 2018)	0.5, 1, 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	Yes	Yes	2015-2016
(GSKCH Clinical Study Report 206233, 2017) (Atassi et al, 2020)	0.5, 1, 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	Yes	Yes	2017
(GSKCH Clinical Study Report 207545, 2017) (Varghese et al, 2019)	0.5, 1, 3, 6, 9, 12h	CCI	Crossover	Yes	Yes	Yes	Yes	2017

* = reason for exclusion - RH01449 and RH01531: competitor products were used to validate the methodology and the retention time of marketed products and the treatment of interest of this pooled analysis was not used; RH01696: the treatment of interest of this pooled analysis was not used; RH02625 and L7791299: products used have different mineral oil content and polymers ratio, respectively, compared to the treatment of interest of this pooled analysis; BF2002-3 and BF2010-03: no raw data available

AUC = Area under the curve; DBT = Denture Bearing Tissue; ® = registered trademark

3.2 Design and Methodology of the Clinical Studies

Listed in Table 3-2 are the 9 clinical studies, selected based on the criteria identified in section 3.1, which assessed the efficacy of 30% PVM/MA & 24%CMC denture adhesives in improving denture retention and BF. These studies included subjects aged >18yrs, in good general and mental health, with completely edentulous maxillary arch and using a well-made, moderately well-fitting dentures (except for CCI [redacted] where Kapur Index was not considered).

All studies were single-center, examiner-blind, up to 4 treatments, randomized, crossover group (with exception of studies CCI [redacted] and CCI [redacted] which were parallel and monadic group, respectively). Overall, these studies have been selected for similar subject eligibility criteria, endpoints and the use of the same interventional product. Only studies with Kapur score (retention ≥2 and stability ≥2) and DBT Score (GSKCH Clinical Study Report 203114, 2016; GSKCH Clinical Study Report 206233, 2017; GSKCH Clinical Study Report 207545, 2017; GSKCH Clinical Study Report L3510566, 2008; CCI [redacted]) will be included in the respective sub-group analyses (as described in the exploratory objectives, section 2).

In all studies, subjects entered the screening visit during which eligibility for the study was determined. The subject populations included male and non-pregnant, non-lactating female subjects at least 18 years of age with certain inclusion criteria (section 3.1) as determined by an appropriately qualified clinical examiner.

Before any study procedures, denture cleansing was performed (upper and lower dentures, where necessary) by suitably qualified site staff in order to thoroughly clean all traces of denture fixative, plaque and particulates/debris. Prior to all BF measures, any lower denture (partial or complete) was fully stabilized by the investigator using a marketed denture adhesive. At Screening, subjects were instructed on BF system training tasks in order to obtain triplicate BF measurements (training bites) without denture adhesive as pre-treatment baseline. Only subjects able to complete the 4 'qualifying' bites as required per eligibility/adherence for continuation in the study (2 bites being reproducible (±2lb) and all 4 to be less than or equal to 9 lbs) were enrolled.

Eligible subjects were then randomly assigned to one of intervention products (30% PVM/MA & 24%CMC denture adhesive creams), or a no adhesive negative control arm (except for CCI [redacted] and CCI [redacted] where 'no adhesive' arm was not included) and allocated study treatment for a 12-hour period.

In all these included studies, the maximum incisal BF until denture dislodgement was measured before and after application of the denture adhesive. The endpoints evaluated varied between these studies, in some direct comparison of BF between treatments or compared to baseline were made, in others, where BF measurements were performed at multiple time points after adhesive application, the Area-Under-the-Curve (AUC) was calculated as the integrated BF over the time span of interest. In other studies, the AOB was calculated as the AUC minus the baseline BF integrated over the same time span.

Studies GSKCH Clinical Study Report 206233, 2017 and GSKCH Clinical Study Report 207545, 2017 also included assessments of adhesive ooze, flavor/ after-taste, texture and assess ease of removal, ease of extrusion of the product from the tube; study GSKCH Clinical Study Report 203114, 2016 also included questionnaires for flavor, texture, ease of removal and oral tolerance; GSKCH Clinical Study Report L3510566, 2008 also included food occlusion evaluation (as primary) and masticatory efficacy (as secondary), none of which will be included in this pooled analysis given that they are not measures of denture hold and improvement in BF.

The pooled analysis will not include studies CCI [redacted] because only competitor products were used to validate the methodology and the retention time of marketed products; as well as studies CCI [redacted] because no raw data are available. In addition, study CCI [redacted] will not be included because the treatment of interest (30% PVM/MA & 24%CMC denture adhesive cream) of this pooled analysis was not used; as well as GSKCH Clinical Study Report RH02625, 2015 and CCI [redacted] because the products used have different mineral oil content and polymers ratio, respectively, compared to the treatment of interest of this pooled analysis (as specified in Table 3.1).

A single population was defined for each study for all safety, baseline and demographic summaries, as well as for the analysis of efficacy measures. These variables were originally analyzed individually and have not previously been pooled and analyzed together. In this study, pooled data from safety population will not be analyzed because this study will focus on efficacy and information on AE/safety profile can be obtained from single studies.

Table 3-2 Overview of studies selected for inclusion in pooled analysis

GSK Study	(GSKCH Clinical Study Report L3510566, 2008)	CCI [redacted]	CCI [redacted]	(GSKCH Clinical Study Report 206233, 2017)	(GSKCH Clinical Study Report 207545, 2017)	(GSKCH Clinical Study Report 203114, 2016)	CCI [redacted]	CCI [redacted]	CCI [redacted]
Study period	Mar2008-Apr2008	Oct2014-Jan2015	Jun2014-Aug2014	Mar2017-Apr2017	Feb2017-May2017	Oct2015-Feb2016	Nov2013-Dec2013	Jan2013-Jan2013	Oct2009-Oct2009
Study Location	University of Buffalo (NY)	OHRI (Indianapolis)	TKL Research Inc. (NJ)	TKL Research Inc. (NJ)	OHRI (Indianapolis)	OHRI (Indianapolis)	University of Buffalo (NY)	University of Buffalo (NY)	GSK Sensory Research Area (NJ)
Product appl.	denture adhesives were applied to the dentures as per product label instructions								
Treatment groups Test No Adhesive	30% PVM/MA & 24%CMC No Adhesive						30% PVM/MA & 24%CMC N/A		
Timepoints	1h	0.5, 1, 3, 6, 9, 12h						0.5, 1, 3, 6, 12h	
Endpoints Primary Secondary Exploratory	BF	BF, AOB_{0-12}	BF, AOB_{0-12}	AOB_{0-12} AOB_{0-9}	AOB_{0-12} AOB_{0-9}	AOB_{0-12} AOB_{0-9}	BF AOB_{0-12}	BF, AUC	BF
No. randomized subjects (N=xx)	37	48	45	23	44	48	22	42	13
ITT population (N=xx)	37	48	45	23	44	48	22	42	13
Gender (%Male/ Female)	51.4/48.6	41.7/58.3	31.1/68.9	21.7/78.3	40.9/59.1	39.6/60.4	40.9/59.1	45.2/54.8	30.8/69.2

3.3 Description of variables

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

The Kapur Index (Olshan Modification) (Kapur, 1967; Olshan et al, 1992) is an assessment used to examine the denture (maxillary and mandibular) for retention and stability. The score obtained was used as inclusion criteria in GSK CH studies and it will be used in this pooled analysis for one of sub groups analysis.

Retention:

The examiner attempted to unseat the maxillary and mandibular denture by applying an opposing vertical force at the canine/lateral incisor region of the denture. The examiner scored retention as 0-5 using the following criteria:

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

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

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

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

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

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

Stability:

The examiner attempted to rock the seated dentures by placing alternate horizontal force at the cuspid and contralateral molar regions of the maxillary and mandibular dentures. The examiner scored denture stability as 0-4 using the following criteria.

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

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

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

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

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

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

The sum score is the total score for both upper and lower dentures. Maxillary and mandibular dentures are scored separately for retention and stability criteria and only maxillary (upper) scores are used in BF studies.

For the purposes of this analysis and considering the data available (inclusion criteria for each study: Kapur score retention ≥2 and stability ≥2) the combined retention and stability score for the maxillary denture alone will be rated as:

Fair 4; Good 5-7; Very Good >7

3.3.2 Denture Bearing Tissue Score

The DBT score (Kapur, 1967) was assessed by the investigator at screening and recorded for the maxillary edentulous arch only. There were no eligibility requirements associated with this measure in GSK studies. It will be used as stratification factor in this pooled analysis for one of the sub groups analysis

Ridge Shape - (for both Maxillary and Mandibular)

1= Flat

2= V-shaped

3= Shaped between U & 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*

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

Sum score for an individual of <14 = Poor DBTs

Sum score for an individual of 14-17 = Satisfactory DBTs

Sum score for an individual of >17 = Good DBTs

The sum score is the total score for both upper and lower dentures. Maxillary and mandibular dentures are scored separately, and only maxillary scores will be evaluated in this pooled analysis:

Poor <7; Satisfactory 7-9; Good >9

3.3.3 Bite Force Measures

A BF transducer system was used to measure incisal BF at the maxillary denture. The transducer system is composed of two plates embedded with a strain gauge that measures the force applied (in lbs) by the incisors during biting.

BF measures were recorded in triplicate without denture adhesive. These three measurements were referred to as "practice bites", where the goal was to have the subject re-familiarize themselves with the system. The 4th bite of the series was captured as pre-treatment baseline BF. Baseline BF readings must have been within ±2 lbs for 1 of the 3 "practice bites" and the pre-treatment baseline bite. In addition, only subjects whose test day pre-treatment baseline BF was less than or equal to 9 pounds were eligible.

Additional post-treatment BF measures took place at different time points, usually 0.5, 1, 3, 6, 9 and 12 hours, after application of test adhesive (or no adhesive as negative control). These post-treatment bites were performed only once at each time point.

4 Investigational plan

4.1 Pooling strategy

Data from each study will be anonymized as per STD GSKF 407 (Preparation of anonymized data for GSK HSR) and SOP-52209 (Use of Individual Human Data for R&D Purposes).

Efficacy data for each study will be pooled and analyzed together. Analyses will focus on the 12h period because it is the longest time point in these studies and considered to be a scientifically valid endpoint to inform on potential efficacy. Further details of the statistical analyses will be documented in the reporting and analysis plan (RAP).

4.2 Efficacy variables

To evaluate the efficacy of denture adhesives on denture hold, AOB over 12h will be the primary efficacy focus of this study, whereas secondary efficacy variables will be AOB over multiple measure time points (0.5, 1, 3, 6) up to 9h and incisal BF measurements at each time point (0.5, 1, 3, 6, 9 and12 h).

The efficacy variables for this pooled analysis will be recalculated using anonymized raw data from each study. For AOB, where raw BF data are available, this endpoint will be derived.

This pooled analysis will also explore the efficacy of the denture adhesives on sub-group populations, specified in the objective section 2. Individual studies will not be re-analyzed however data will be used for pooling.

5 Statistical consideration and data analysis methods

5.1 General considerations

5.1.1 Analysis Populations

Safety population was defined as the randomized subjects who had at-least one dose of treatment. This was defined for all the studies planned to be included in the pooled analyses.

The Intended to treat (ITT) population was defined as all subjects in safety population and one post baseline assessment of efficacy. This was considered to be the primary population for the analyses of efficacy and was defined for all the studies planned to be included in the pooled analyses.

Per protocol (PP) population was also defined as a subset of ITT population with no protocol deviations. As a general rule, this analysis population was only performed if there was more than 10% difference in the number of subjects in ITT & PP populations. It was defined for most of the studies included in the pooled analyses with the exception of [redacted] and GSKCH Clinical Study Report 206233, 2017.

This rule will be applicable to the pooled analyses as well however ITT analysis population will be considered as the main analysis population.

For this pooled study, the following populations consistent to majority of the studies will be defined:

Randomized; Subjects randomized to at-least one treatment

Safety, ITT and PP populations are as per the definitions above.

5.1.2 Exclusion of Data from Analysis

All data recorded will be included to be pooled where possible. The endpoints of interest include the AOB over 12h and maximum incisal BF at each time point (0, 0.5, 1, 3, 6, 9 and 12h), with any others being excluded from analysis.

Any protocol violations will be excluded from the PP population at the blinded data review stage.

5.1.3 Handling of Dropouts and Missing Data

In general, missing data will not be imputed.

However, for the calculation of AUC will be linearly interpolated between successive measurements with valid readings. Missing readings will be ignored, and interpolation will be made between pre and post the missing values, if necessary. In the case of more than one missing value or if the 12-hour value is missing, the AOB will be set to missing. The same will be true for all other time points (1,3, 6 and 9-hour) calculations.

For study GSKCH Clinical Study Report L3510566, 2008, only 1 h timepoint data is available. In this scenario, if 1h timepoint or baseline is missing then AOB will be set to missing.

5.1.4 Sample size information

Table 5-1 below summarizes the sample size information from the selected studies

Table 5-1 Sample size information for the selected studies

Study	Primary/ Exploratory Variable	Primary Timepoint	Treatment Difference+ (lbs)	Variability Estimate (SD – lbs)	Study Ref	Type I Error	Statistical Power
(GSKCH Clinical Study Report 203114, 2016)	AOB_{0-12}	12h	1.577	2.281	RH02443	5%	90%
CCI [redacted]	BF, AOB_{0-12}	12h	2.432	2.413	RH02035	5%	84.8%
CCI [redacted]	BF, AOB_{0-12}	12h	2.432	2.413	RH02035	5%	84.8%
CCI [redacted]	BF	12h	3.3^	5^	RH01686	5%	80%
(GSKCH Clinical Study Report 207545, 2017)	AOB_{0-12}	12h	2.3	2.83	RH02446 203114	5%	90%
(GSKCH Clinical Study Report 206233, 2017)	AOB_{0-12}	12h	2.01	1.929	203114	5%	81%
CCI [redacted]	BF, AUC	12h	N/A	N/A	N/A	N/A	N/A
CCI [redacted]	BF	12h	8.7	6.5	PCL BF2008-07	5%	95%
(GSKCH Clinical Study Report L3510566, 2008)	BF	12h	0.036g*	0.073g*	L2700375	5%	80%

+ difference between adhesive and no adhesive

^ difference between baseline and 12h

*sample size and statistical power was calculated based on food occlusion variable (primary objective for study L3510566)

For this study, no formal sample size calculation is performed. The pooled analyses of efficacy will be performed on all the subjects in the ITT population from all of the respective studies.

5.1.5 Group classification

A total of 3 different groups were identified for the purposes of the pooled sub-group analyses as shown in Table 5-2.

Table 5-2 Groups for the pooled analysis

	Kapur Score			DBT Score		
Denture fitting	Fair (<=4)	Good (5-7)	Very good (>7)			
Conditions of DBT score				Low (<7)	Medium (7-9)	High (>9)

5.1.6 Time points

All timepoints measured fit to 6 post baseline times 0.5, 1, 3, 6, 9 and12 hours.

5.1.7 Data structure and data selection

The focus of this work is to analyse the BF data at various timepoints, primary being 12 hours. The data from each of the studies will be mapped into a similar structure and pooled accordingly for analyses.

5.2 Criteria for evaluation

Since the primary focus of this pooled analysis is the BF data at 12 hours, study success will therefore be achieved if there is a statistically significant difference between the test adhesive and no adhesive for AOB 0-12h. Other analyses defined are secondary and exploratory.

5.3 Statistical Methods and Analytical Plan

5.3.1 Demographic and Baseline Characteristics

Subject disposition and demographics will be provided by study and overall.

5.3.2 Variables of interest

The primary efficacy variable of interest is BF AOB 0-12h. Other variables of interest are BF AOB at various timepoints 0.5, 1, 3, 6 and 9 h, raw mean BF and measurement within change from baseline and comparison between treatments are also assessed as part of the secondary objectives.

Exploratory variables of interest are Kapur index scores and DBTs to be assessed for impact on baseline BF values. Percentage change from maximum BF is also another exploratory variable of interest for this study.

5.3.3 Efficacy Variables

AOB will be calculated for each subject using BF measurements at pretreatment baseline, 0.5, 1, 3, 6, 9 and 12 hours.

The AOB will be calculated for the interval starting at the time (t0) of the baseline reading (y0) and ending at the time (tn+1) of the last valid reading (yn+1) using the trapezoidal method:

$$AOB = \frac{1}{2}\sum_{i=0}^{n}(t_{i+1} - t_i)(y_{i+1} + y_i) \text{ - } (y0 \text{ x } 12)$$

AOB is equivalent to the AUC above the pre-treatment baseline value and adjusts for any differences in pre-treatment baseline BF values between the treatment groups. The AOB was divided by 12 (or by the last available timepoint) so that the value was reported on the original BF scale.

Other variables will be described in more detail in the reporting and analysis plan.

5.4 Statistical methodology

The primary means of assessing the outcome of the study is the analysis of the change from baseline in BF as measured by $AOB_{0\text{-}12}$ for test adhesive compared to no adhesive.

The primary response variable is AOB over 12 hours for the incisal BF (lbs) (denoted by $AOB_{0\text{-}12}$). To calculate this variable, first the AUC is calculated from 0 to 12 hours using the trapezoid method; denoted as $AUC_{0\text{-}12}$. $AOB_{0\text{-}12}$ is defined as $(AUC_{0\text{-}12})/12$ minus baseline BF (lbs). This is also described in section 5.3.4.

An Analysis of Covariance (ANCOVA) model will be used to analyse $AOB_{0\text{-}12}$, with treatment, study and period as fixed effects; the covariates in this model are the subject level baseline and period level baseline minus subject level baseline. Subject will be included as a random effect. Pairwise treatment comparisons will be obtained as a difference in adjusted means and presented with 95% confidence intervals (CI) and associated p-values. Within treatment group estimates will also be calculated with their 95% CI's and p-values to assess the within group changes from baseline.

The analyses for secondary and exploratory variables will be defined in full in the reporting and analysis plan.

5.4.1 Summary data

The data at each timepoint will be summarized and presented in tabular and graphical format. The tables will summarise just the pooled data with some exception of sub group analyses exploratory objective where data for individual studies and pooled will be presented. The graphs will summarise by study and pooled. Further details will be documented in the RAP.

5.4.2 Data displays

5.4.2.1 Tables

The raw data will be summarized by visit just for the pooled data with the exception of exploratory sub-group analyses where data is summarised by study as well.
A summary of the results from the analysis will be presented to show the adjusted means (se) treatment difference, 95% CI and P-Value. This will be presented by study and pooled where specified. Further details will be documented in the RAP.

5.4.2.2 Plots

A plot over time for the AOB variables at various timepoints will be presented for individual studies as well as pooled analyses. Further details will be documented in the RAP.

6 Publication/Disclosure

This study meets GSK disclosure requirements as defined in policy POL-GSKF-408. Registration on a public clinical trial register is also required before initiation of the analysis.

7 References

Atassi M, Ling MR, Oneglia K, *et al.* A proof‐of‐principle bite force study using two experimental test denture adhesives and a currently marketed denture adhesive. Clin Exp Dent Res. 2020;6:266-73.

Axe A, Jain R, Varghese R, *et al.* Randomized clinical study comparing three experimental denture adhesives and fixodent® versus no adhesive. The Journal of clinical dentistry. 2018;29(4):69-74.

CCI [redacted]

GSKCH Clinical Study Report 203114, A proof of principle bite force study using two new test adhesives and a currently marketed denture adhesive. . GSK Data Held on File; 2016.

GSKCH Clinical Study Report 206233, A proof-of-principle bite force study using two new test adhesives and a currently marketed denture adhesive. . GSK Data Held on File; 2017.

GSKCH Clinical Study Report 207545, A bite force study assessing two currently marketed denture adhesive products compared to no-adhesive control. . GSK Data Held on File; 2017.

GSKCH Clinical Study Report L3510566, A study of denture adhesives in well-fitting dentures. . GSK Data Held on File; 2008.

CCI [redacted]

CCI

GSKCH Clinical Study Report RH02625, A proof-of-principal bite force study using three new test adhesives and a commercially available denture adhesive. . GSK Data Held on File; 2015.

CCI

Jose A, Varghese R, Roohpour N, *et al.* A randomized proof-of-principle bite force study of two experimental denture adhesives and a commercially available adhesive. International Journal of Prosthodontics. 2018;31(4).

CCI

Munoz CA, Gendreau L, Shanga G, *et al.* A clinical study to evaluate denture adhesive use in well-fitting dentures. Journal of Prosthodontics. 2012;21:123-9.

CCI

Varghese R, Gossweiler AG, Burnett GR, *et al.* A randomised bite force study assessing two currently marketed denture adhesive products compared with no - adhesive control. Clin Exp Dent Res. 2019;5:276-83. doi: 10.1002/cre2.182.

CCI

8 Appendices

8.1 Abbreviations

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

Table 8-1 Abbreviations

AE	Adverse event
ANCOVA	Analysis of Covariance
AOB	Area Over Baseline
AUC	Area Under Curve
BF	Bite Force
CI	Confidence Interval
CMC	Carboxymethylcellulose
DBTs	Denture Bearing Tissues
GSK CH	GlaxoSmithKline Consumer Healthcare
h	Hour
ITT	Intended to treatment
Lbs	Pounds
MA	Maleic Anhydride
PMV	Poly Vinyl Methyl
PP	Per Protocol
RAP	Reporting analysis plan

Signature Page for 213380 TMF-22823 v1.0

Reason for signing: Approved	Name: PPD Role: A Date of signature: 29-Jun-2020 09:51:06 GMT+0000

Reason for signing: Approved	Name: PPD Role: A Date of signature: 30-Jun-2020 11:54:15 GMT+0000

Signature Page for TMF-22823 v1.0

CLINICAL STUDY REPORT APPENDIX

11 APPENDICES

11.5 Documentation of Statistical Methods

STATISTICAL REPORTING AND ANALYSIS PLAN

A Post-hoc Pooled Analysis of GSK CH Clinical Data Investigating the Efficacy of Denture Adhesive creams containing PMV/MA &CMC on Denture Retention and Bite Force

Protocol Number: 213380

Phase: N/A

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	06-Nov-2020	Not applicable (N/A)

Table of contents

List of tables

Abbreviation

Abbreviation	Term
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AOB	Area Over Baseline
AUC	Area Under the Curve
BF	Bite Force
CI	Confidence Interval
DBTs	Denture Bearing Tissues
GSK CH	GlaxoSmithKline Consumer Healthcare
ITT	Intended-To-Treat
lbs	Pounds
N/A	Not Applicable
PMV/MA&CMC	Poly Methyl Vinyl / Maleic Anhydride and Carboxymethylcellulose
PP	Per Protocol
SD	Standard Deviation
SE	Standard Error

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 Protocol 213380, version 1.0 dated 02-Jul-2020.

1 Summary of Key Protocol Information

Denture adhesive are a well-known adjuvant to improve denture retention, comfort and to reduce the ingress of food particles under the denture. They function through formation of a seal between the denture and oral soft tissues and thus provide a firm hold for dentures. Improved retention facilitates increased incisal bite force (BF) and improves the chewing ability of denture wearers which can improve denture function.

There are a number of recognized methods which have been used to demonstrate the clinical efficacy of a denture adhesive. These include the Kapur Index (Kapur, 1967) and measurement of the maximum incisal BF until denture dislodgement (Howell and Manly, 1948) to measure denture retention and stability, denture dislodgement (Tarbet et al, 1980) to measure denture movement in function, and masticatory performance (Kapur, 1967) an indicator of chewing efficiency.

Data on the efficacy of denture adhesive creams containing the same adhesive ingredient, a combination of poly methyl vinyl / maleic anhydride and carboxymethylcellulose (PMV/MA&CMC), on denture hold and BF improvement exists for individual GlaxoSmithKline Consumer Healthcare (GSK CH) studies.

The aim of this pooled analysis study is to aggregate individual subject level data from GSK CH BF studies on denture adhesive creams containing 30% PMV/MA & 24% CMC to reinforce the current claim sets (denture hold and BF improvements over 12-hour period), which will be evaluated as primary and secondary objectives in this study and to unlock new claims.

This study will summarize all GSK CH available clinical data investigating denture adhesive creams with the same adhesive material that are considered similar to the currently marketed product. Nine BF studies have been identified in which formulations varied on flavorings/preservatives, vitamin E and colorants, but these characteristics would not be expected to materially impact the mode of action and the efficacy of the products.

1.1 Study Design

The studies included in this pooled analysis have the criteria such as:

- Clinical studies conducted by GSK CH, including:
  a. Access to study protocols, study reports, and
  b. Access to anonymized individual information sources/ study data
- Study design and subject inclusion criteria in agreement with pre-defined study selection criteria:
  a. Subject eligibility based on study inclusion criteria:

1. Completely edentulous maxillary arch
2. Well-made complete dentures according to the design and construction criteria used in GSK studies (GSKCH Clinical Study Report L3510566, 2008; CCI [redacted]
3. Qualifying maxillary incisal BF readings (without adhesive) less than or equal to 9 lbs at the Screening and subsequent pre-treatment baseline bites

b. Raw BF data available

c. Comparable treatment (30% PMV/MA & 24% CMC denture adhesive creams) CCI [redacted] and variants CCI [redacted]

Listed in Table 1-1 are the 9 clinical studies, selected based on the criteria identified above, which assessed the efficacy of 30% PMV/MA & 24% CMC denture adhesives in improving denture retention and BF.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan Text, 06 Nov 2020

Table 1-1 Overview of Studies Selected for Inclusion in Pooled Analysis

GSK Study	(GSKCH Clinical Study Report L3510566, 2008)	CCI	CCI	(GSKCH Clinical Study Report 206233, 2017)	(GSKCH Clinical Study Report 207545, 2017)	(GSKCH Clinical Study Report 203114, 2016)	CCI	CCI	CCI
Study period	Mar2008-Apr2008	Oct2014-Jan2015	Jun2014-Aug2014	Mar2017-Apr2017	Feb2017-May2017	Oct2015-Feb2016	Nov2013-Dec2013	Jan2013-Jan2013	Oct2009-Oct2009
Study Location	University of Buffalo (NY)	OHRI (Indianapolis)	TKL Research Inc. (NJ)	TKL Research Inc. (NJ)	OHRI (Indianapolis)	OHRI (Indianapolis)	University of Buffalo (NY)	University of Buffalo (NY)	GSK Sensory Research Area (NJ)
Product application.	denture adhesives were applied to the dentures as per product label instructions								
Treatment groups Test No Adhesive	30% PMV/MA & 24% CMC No Adhesive						30% PMV/MA & 24% CMC N/A		
Time points	1h	0.5, 1, 3, 6, 9, 12h						0.5, 1, 3, 6, 12h	
Endpoints Primary Secondary Exploratory	BF	BF, AOB_{0-12}	BF, AOB_{0-12}	AOB_{0-12} AOB_{0-9}	AOB_{0-12} AOB_{0-9}	AOB_{0-12} AOB_{0-9}	BF AOB_{0-12}	BF, AUC	BF

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan Text, 06 Nov 2020

GSK Study	(GSKCH Clinical Study Report L3510566, 2008)	(CCI [redacted]	[redacted]	(GSKCH Clinical Study Report 206233, 2017)	(GSKCH Clinical Study Report 207545, 2017)	(GSKCH Clinical Study Report 203114, 2016)	(CCI [redacted]	[redacted]	[redacted]
No. randomized subjects (N=xx)	37	48	45	23	44	48	22	42	13
ITT population (N=xx)	37	48	45	23	44	48	22	42	13
Gender (%Male/ Female)	51.4/48.6	41.7/58.3	31.1/68.9	21.7/78.3	40.9/59.1	39.6/60.4	40.9/59.1	45.2/54.8	30.8/69.2

These studies included subjects aged >18 years, in good general and mental health, with completely edentulous maxillary arch and using a well-made, moderately well-fitting dentures (except for GSKCH Clinical Study Report PCLBF2009-09, 2009 where Kapur Index was not considered).

All studies were single-center, examiner-blind, up to 4 treatments, randomized, crossover group (with exception of studies GSKCH Clinical Study Report RH01686, 2013 and GSKCH Clinical Study Report PCLBF2009-09, 2009 which were parallel and monadic group, respectively). Overall, these studies have been selected for similar subject eligibility criteria, endpoints and the use of the same interventional product. Only studies with Kapur score (retention ≥2 and stability ≥2) and denture bearing tissues (DBTs) Score (GSKCH Clinical Study Report 203114, 2016; GSKCH Clinical Study Report 206233, 2017; GSKCH Clinical Study Report 207545, 2017; GSKCH Clinical Study Report L3510566, 2008; CCI [redacted] will be included in the respective sub-group analyses (as described in the exploratory objectives).

In all studies, subjects entered the screening visit during which eligibility for the study was determined. The subject populations included male and non-pregnant, non-lactating female subjects at least 18 years of age with certain inclusion criteria as determined by an appropriately qualified clinical examiner.

Before any study procedures, denture cleansing was performed (upper and lower dentures, where necessary) by suitably qualified site staff in order to thoroughly clean all traces of denture fixative, plaque and particulates/debris. Prior to all BF measures, any lower denture (partial or complete) was fully stabilized by the investigator using a marketed denture adhesive. At Screening, subjects were instructed on BF system training tasks in order to obtain triplicate BF measurements (training bites) without denture adhesive as pre-treatment baseline. Only subjects able to complete the 4 'qualifying' bites as required per eligibility/adherence for continuation in the study (2 bites being reproducible (±2lb) and all 4 to be less than or equal to 9 lbs) were enrolled.

Eligible subjects were then randomly assigned to one of intervention products (30% PMV/MA & 24% CMC denture adhesive creams), or a no adhesive negative control arm (except for CCI [redacted] where 'no adhesive' arm was not included) and allocated study treatment for a 12-hour period.

In all these included studies, the maximum incisal BF until denture dislodgement was measured before and after application of the denture adhesive. The endpoints evaluated varied between these studies, in some direct comparison of BF between treatments or compared to baseline were made, in others, where BF measurements were performed at multiple time points after adhesive application, the Area Under the Curve (AUC) was calculated as the integrated BF over the time span of interest. In other studies, the Area Over Baseline (AOB) was calculated as the AUC minus the baseline BF integrated over the same time span.

Studies GSKCH Clinical Study Report 206233, 2017 and GSKCH Clinical Study Report 207545, 2017 also included assessments of adhesive ooze, flavor/ after-taste, texture and assess ease of removal, ease of extrusion of the product from the tube; study GSKCH Clinical Study Report 203114, 2016 also included questionnaires for flavor, texture, ease of removal and oral tolerance; GSKCH Clinical Study Report L3510566, 2008 also included food occlusion evaluation (as primary) and masticatory efficacy (as secondary), none of which will be included in this pooled analysis given that they are not measures of denture hold and improvement in BF.

A single population was defined for each study for all safety, baseline and demographic summaries, as well as for the analysis of efficacy measures. These variables were originally analyzed individually and have not previously been pooled and analyzed together. In this study, pooled data from safety population will not be analyzed because this study will focus on efficacy and information on Adverse Events/safety profile can be obtained from single studies.

1.2 Study Objectives

Study objectives and endpoints are defined in Table 1-2:

Table 1-2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PMV/MA & 24% CMC denture adhesive to no adhesive over 12 hours	AOB over 12 hours
Secondary Objectives	**Secondary Endpoints**
To compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PMV/MA & 24% CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 9 hours	AOB up to 0.5, 1, 3, 6 and 9 hours
To compare and evaluate maximum incisal BF made with 30% PMV/MA & 24% CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 12 h	Raw mean BF measurement between adhesive and no adhesive at 0.5, 1, 3, 6, 9 and 12 hours
To compare and evaluate maximum incisal BF made with 30% PMV/MA & 24% CMC denture adhesive and no adhesive to baseline over 12 h	Within-treatment change from baseline in raw BF measurement up to 0.5, 1, 3, 6, 9 and 12 hours

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
To compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PMV/MA & 24% CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 12 hours, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF	AOB up to 0.5, 1, 3, 6, 9 and 12 hours in 3 categories: Kapur score (Clinically Fair 4, clinically Good 5-7, clinically very good >7) DBT score (Poor <7, satisfactory 7-9, good >9) Baseline BF measurements (Baseline BF ≤2.5 pounds (lbs), Baseline BF >2.5 lbs)
To compare and evaluate maximum BF made with 30% PMV/MA & 24% CMC denture adhesive to no adhesive over multiple measure time points from 0.5 to 12 h, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF	Raw mean BF measurement between adhesive and no adhesive at 0.5, 1, 3, 6, 9 and 12 hours in 3 categories: Kapur score (Clinically Fair 4, clinically Good 5-7, clinically very good >7) DBT score (Poor <7, satisfactory 7-9, good >9) Baseline BF measurements (Baseline BF ≤2.5 lbs, Baseline BF >2.5 lbs)
To compare and evaluate maximum BF made with 30% PMV/MA & 24% CMC denture adhesive and no adhesive to baseline over multiple measure time points from 0.5 to 12 h, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF	Within-treatment change from baseline in raw BF measurement up to 0.5, 1, 3, 6, 9 and 12 hours in 3 categories: Kapur score (Clinically Fair 4, clinically Good 5-7, clinically very good >7) DBT score (Poor <7, satisfactory 7-9, good >9) Baseline BF measurements (Baseline BF ≤2.5 lbs, Baseline BF >2.5 lbs)
To evaluate the baseline BF with respect to the maximum observed BF	Percentage changes of baseline BF value from the maximum BF force measurement at any given post baseline timepoint
To evaluate the effect of retention, stability and conditions of DBTs on baseline BF	Baseline BF including Kapur Index and DBT in the model to be assessed
To evaluate the relative BF at all measure time points with respect to the maximum observed BF	Percentage changes of BF value at 0.5, 1, 3, 6, 9 and 12 h from the maximum BF force measurement

The objectives listed above will be analyzed for the pooled data only. In order to consider the study successful there should be a statistically significant difference and a difference of greater than 2 lbs between the 30% PMV/MA & 24% CMC adhesive creams compared with the negative control in maximum incisal BF over 12-hours period.

Having reviewed the planned treatment differences in previous studies (respective sample size) included in this pooled analysis, it seems that an approximate average of 2 lbs treatment difference is considered to be an appropriate treatment difference value.

1.3 Treatments

A total of 30 different denture adhesive were identified across the 9 studies included in this pooled analysis.

For the purposes of pooled analysis study treatments will be further synergised into 2 groups as shown in below Table 1-3.

Table 1-3 Treatment Groups for Pooled Analyses

GSK Study	Treatments Groups in Individual Studies	Grouping for Pooled Analysis [1]	
		Test Adhesive	No Adhesive
GSKCH Clinical Study Report L3510566, 2008	SPG Original (Batch number = CCI)	-	-
	SPG Free (Batch number = CCI)	X	-
	SPG Comfort Seal Strips (Batch number = CCI)	-	-
	No Adhesive	-	X
CCI	Test adhesive: new mineral oil formulation of Super Poligrip® Denture Adhesive Cream CCI	-	-
	Positive control adhesive: Super Poligrip® Denture Adhesive Cream, Original, USA CCI	X	-
	No Adhesive	-	X
CCI	Test denture adhesive: experimental denture adhesive cream with a new mineral oil formulation CCI	-	-
	Positive control denture adhesive: Super Poligrip® Original Denture Adhesive Cream, USA (CCI)	X	-
	No Adhesive	-	X

GSK Study	Treatments Groups in Individual Studies	Grouping for Pooled Analysis [1]	
		Test Adhesive	No Adhesive
GSKCH Clinical Study Report 206233, 2017	Test Adhesive 1: Prototype cream denture adhesive containing a new water insoluble, heat-resistant polyvinyl acetate (PVA) polymer and a new solvent system (CCI)	-	-
	Test Adhesive 2: Prototype cream denture adhesive containing a new water insoluble, heat-resistant PVA polymer and a new solvent system (CCI)	-	-
	Positive Control Adhesive: Super Poligrip Free Adhesive Cream (USA marketplace) CCI	X	-
	Negative Control: No Adhesive	-	X
GSKCH Clinical Study Report 207545, 2017	Test Adhesive: Protefix® Denture Adhesive, Crème Mint (Germany marketplace)	-	-
	Reference Adhesive: Super Poligrip Free Adhesive Cream (USA marketplace) CCI	X	-
	Negative Control: No Adhesive	-	X
GSKCH Clinical Study Report 203114, 2016	Test adhesive 1 CCI	-	-
	Test adhesive 2 CCI	-	-
	Super Poligrip® Free Adhesive Cream (USA) (CCI CCI	X	-
	Negative Control: No Adhesive	-	X
CCI	Test adhesive 1: CMC/HPMC/Konjac (CCI)	-	-
	Test adhesive 2: CMC/Xanthan/HPMC/Konjac CCI	-	-
	Poligrip Super Wernets Denture Fixative Powder (UK Marketplace – CCI)	-	-

GSK Study	Treatments Groups in Individual Studies	Grouping for Pooled Analysis [1]	
		Test Adhesive	No Adhesive
	Super Poligrip Original Denture Adhesive Cream (USA Marketplace – CCI	X	-
CCI	Test adhesive G1: CMC/Xanthan Gum 1	-	-
	Test adhesive G2: CMC/Xanthan Gum 2	-	-
	Test adhesive G3: CMC/Xanthan Gum 3	-	-
	Positive control denture adhesive: Super Poligrip Original (US)	X	-
CCI	Poligrip Gum Care Free Denture Adhesive (CCI)	X	-

[1] X = Treatments included in corresponding treatment group for pooled analysis; - = Treatment not included in pooled analysis.

The treatment groups will be re-derived for this study, as described in Table 1-3. In total, Test Adhesive group will consist of data from 9 denture adhesives tested in individual studies, while No Adhesive group will consist of data collected from 6 studies.

1.4 Sample Size Calculation

The sample size information from the selected studies are defined in Table 1-4:

Table 1-4 Sample Size Information for the Selected Studies

Study	Primary/ Exploratory Variable	Primary Timepoint	Treatment Difference+ (lbs)	Variability Estimate (SD – lbs)	Study Ref	Type I Error	Statistical Power
GSKCH Clinical Study Report 203114, 2016	AOB_{0-12}	12h	1.577	2.281	RH02443	5%	90%
CCI	BF, AOB_{0-12}	12h	2.432	2.413	RH02035	5%	84.8%
CCI	BF, AOB_{0-12}	12h	2.432	2.413	RH02035	5%	84.8%

Study	Primary/ Exploratory Variable	Primary Timepoint	Treatment Difference+ (lbs)	Variability Estimate (SD – lbs)	Study Ref	Type I Error	Statistical Power
CCI [redacted]	BF	12h	3.3^	5^	RH01686	5%	80%
GSKCH Clinical Study Report 207545, 2017	AOB_{0-12}	12h	2.3	2.83	RH02446 203114	5%	90%
GSKCH Clinical Study Report 206233, 2017	AOB_{0-12}	12h	2.01	1.929	203114	5%	81%
CCI [redacted]	BF, AUC	12h	N/A	N/A	N/A	N/A	N/A
CCI [redacted]	BF	12h	8.7	6.5	PCL BF2008-07	5%	95%
GSKCH Clinical Study Report L3510566, 2008	BF	12h	0.036g*	0.073g*	L2700375	5%	80%

+ difference between adhesive and no adhesive

^ difference between baseline and 12h

*sample size and statistical power was calculated based on food occlusion variable (primary objective for study L3510566)

For this study, no formal sample size calculation is performed. The pooled analyses of efficacy will be performed on all the subjects in the Intended-To-Treat (ITT) population from all of the respective studies.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned for this study.

2.2 Final Analyses

Final analysis will be performed on pooled data from each of the individual studies included.

3 Considerations for Data Analyses and Data Handling Conventions

3.1 Baseline Definition

For analysis of incisal BF, as measured by AOB:

- Subject level baseline is defined as the mean of subject's non-missing pre-treatment assessments across periods within a subject.
- Period level baseline is defined as the latest assessment with a non-missing value before the first administration of study treatments for the relevant period.

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

3.2 Subgroups/Stratifications

This pooled analysis will also explore the efficacy of the denture adhesives on subgroup populations. A total of 3 different groups were identified for the purposes of the pooled subgroup analyses:

- Denture fitting assessed by Kapur Score:
  - Fair – ≤ 4;
  - Good – 5-7 inclusive;
  - Very good – > 7;
- Conditions of DBTs score:
  - Low – < 7;
  - Medium – 7-9 inclusive;
  - High – > 9;
- Baseline BF measurements:
  - Baseline BF measurement ≤ 2.5 lbs;
  - Baseline BF measurement > 2.5 lbs;

3.3 Centers Pools

Center pooling is not applicable for this pooled analysis.

3.4 Time Points and Visit Windows

Incisal BF measurements are taken at different time points in individual studies, as described in Table 1-1. The analysis of incisal BF will be based on 6 post baseline time points: 0.5, 1, 3, 6, 9 and 12 hours. Studies with no data collected at particular time points will not be included in the analysis.

4 Data Analysis

Data analysis will be performed by Syneos Health with oversight from GSK CH. The statistical analysis software used will be SAS version 9.4 or higher.

Data from each study was anonymized and shared with Syneos Health to perform the analyses. Efficacy data for each study will be pooled and analyzed together. Analyses will focus on the 12 hours period because it is the longest time point in these studies and considered to be a scientifically valid endpoint to inform on potential efficacy.

Subject data listing is not applicable for this pooled analysis and is included in the individual clinical study report.

4.1 Populations for Analysis

4.1.1 Subject Disposition

Subject disposition will be summarized considering all the 9 studies together (pooled data) at first, by treatment groups defined for pooled analysis (Table 1.3) and for all combined treatment groups (Overall).

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized.

The number of subjects screened and randomized will be presented in Table 14.1.1.1. The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized will be displayed. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of randomized subjects who complete and discontinue the study, broken down by reason for discontinuation, by treatment group and overall will also be displayed. The percentages will be based on the number of subjects randomized.

Table 14.1.1.1 will also present the number and percentage of subjects in each of the defined analysis populations by treatment group and overall. Percentages will be based on the number of subjects randomized.

In addition, subject disposition will be summarized separately for individual 9 studies.

For the 7 individual crossover studies (GSKCH Clinical Study Report 203114, 2016; CCI [redacted] GSKCH Clinical Study Report 207545, 2017; GSKCH Clinical Study Report 206233, 2017; GSKCH Clinical Study Report L3510566, 2008) the number of subjects screened, randomized, the number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized and number and percentage of randomized subjects who complete and discontinue the study, broken down by reason for discontinuation will be presented in Table 14.1.1.2 by treatment sequence group and period for each individual study.

Disposition data for the 2 individual studies conducted as monadic and parallel [CCI [redacted]]) will be summarized in Table 14.1.1.3 by treatment group.

4.1.2 Protocol Deviations

Protocol deviations data will be analyzed for pooled data only with respect to the important protocol deviations leading to exclusion from Per Protocol (PP) population. For one study enrolled in this pooled analysis (CCI [redacted]), PP population is not defined and data for protocol deviations is not collected.

The number and percentage of subjects with at least one important protocol deviation, important protocol deviations leading to exclusion from the PP population with reasons for deviations will be presented by treatment group and Overall (Table 14.1.2) for pooled data only.

4.1.3 Analysis Populations

The analysis populations defined for this pooled analysis study are presented in Table 4-1.

Table 4-1 Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Randomized	Comprise all subjects randomized to at least one treatment in the individual studies.	Disposition, Protocol Deviations
Safety	Comprise all randomized subjects who had at least one dose of treatment. This population will be based on the treatment the subject actually received.	Disposition, Demographic and Baseline Characteristics
ITT	Comprise all randomized subjects who are in the safety population and have at least one post baseline assessment of efficacy. This population will be based on the treatment arm to which the subject was randomized.	Disposition, Demographic and Baseline Characteristics, Efficacy Analyses
PP	Comprise all subjects in the ITT population who fully comply with all study procedures and restrictions and who do not have any important protocol deviations that could confound the interpretation of analysis conducted on ITT.	Disposition

NOTES:
Please refer to Attachment 1: List of Data Displays which details the population to be used for each displays being generated.
PP Population was defined for most of the studies included in the pooled analyses with the exception of CCI [redacted]

The primary population for assessment of efficacy will be the ITT population. As a general rule, PP analysis is to be performed on primary objective if there is more than 10% difference in the number of subjects between the PP and ITT populations.

For this pooled analysis, since the individual study data is already available and it is observed that the difference in the number of subjects between the PP and ITT population is less than 1%, hence PP analysis on primary objective as planned will not be performed.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum and maximum for continuous variables, and frequency count [n] and percentage [%] of subjects for categorical variables) will be presented for demographic variables. These variables include age, sex, race and ethnicity.

For GSKCH Clinical Study Report L3510566, 2008, the race data was collected in different way, compared to other studies. In order to summarize race data from GSKCH Clinical Study Report L3510566, 2008, it will be mapped as described in Table 4-2.

Table 4-2 Race Mapping Rule for L3510566

Original Race Category	New Race Category
Asian	Multiple *Asian is considered as either Asian - Central/South Asian Heritage, Asian - East Asian Heritage, Asian - Japanese Heritage and Asian - South East Asian Heritage*
Black	African American/African Heritage
Caucasian	White - White/Caucasian/European Heritage
Hispanic	Multiple *Hispanic is considered as either White/Caucasian/European Heritage and White - Arabic/North African Heritage*
Other	Other

Ethnicity data is not collected for 3 of the individual studies (CCI [redacted] GSKCH Clinical Study Report L3510566, 2008; CCI [redacted]. Ethnicity will be summarized only for individual studies with ethnicity data collected and will not be summarized on pooled data.

Demographic data will be summarized for pooled data (by treatment group and overall) and individual studies (by overall only) for Safety population (Table 14.1.3.1) and ITT population (Table 14.1.3.2).

4.2.2 General Medical History

N/A

4.2.3 Other Baseline Characteristics

Other baseline characteristics defined for this pooled analysis are denture fitting as assessed by Kapur Score, Conditions of DBTs score and baseline BF measurements.

Kapur Score

The Kapur Index (Olshan Modification) (Kapur, 1967; Olshan et al, 1992) is an assessment used to examine the denture (maxillary and mandibular) for retention and stability. The score obtained was used as inclusion criteria in GSK CH studies and it will be used in this pooled analysis for one of sub groups analysis, as described in Section 3.2.

Retention:

The examiner attempted to unseat the maxillary and mandibular denture by applying an opposing vertical force at the canine/lateral incisor region of the denture. The examiner scored retention as 0-5 using the following criteria:

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

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

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

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

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

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

Stability:

The examiner attempted to rock the seated dentures by placing alternate horizontal force at the cuspid and contralateral molar regions of the maxillary and mandibular dentures. The examiner scored denture stability as 0-4 using the following criteria:

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

3 = Good – when denture base has very slight rocking on its supporting structure under pressure

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

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

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

The sum score is the total score for both upper and lower dentures. Maxillary and mandibular dentures are scored separately for retention and stability criteria and only maxillary (upper) scores are used in BF studies.

For the purposes of this analysis and considering the data available (inclusion criteria for each study: Kapur score retention ≥2 and stability ≥2) the combined retention and stability score for the maxillary denture alone will be rated as described in Section 3.2.

DBTs:

The DBTs (Kapur, 1967) was assessed by the investigator at screening and recorded for the maxillary edentulous arch only. There were no eligibility requirements associated with this measure in GSK studies. It will be used as stratification factor in this pooled analysis for one of the sub groups analysis, as described in Section 3.2.

Ridge Shape – (for both Maxillary and Mandibular)

1 = Flat

2 = V-shaped

3 = Shaped between U & 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*

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

The sum score is the total score for both upper and lower dentures. Maxillary and mandibular dentures are scored separately, and only maxillary scores will be evaluated in this pooled analysis as described in Section 3.2.

Baseline BF Measurements:

Baseline BF measurements will be derived as described in Section 3.1. Baseline BF measurements will be evaluated and will be used as stratification factor in this pooled analysis for one of the sub groups analysis, as described in Section 3.2.

Data for Kapur Score is not collected for CCI [redacted]. Data for DBTs score is not collected for CCI [redacted]. Data from both studies will not be included in summary table of other baseline characteristics.

For the above listed baseline characteristics the number (n) and percentage (%) by treatment group and overall will be presented in Table 14.1.4 based on pooled data for the ITT population.

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

4.3.1 Study Product Compliance and Exposure

N/A

4.3.2 Prior and Concomitant Medication

N/A

4.4 Analysis of Efficacy

The ITT population will be considered as primary population for primary, secondary and exploratory analysis.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary objective is to compare and evaluate the maximum incisal BF until maxillary denture dislodgement of 30% PMV/MA & 24% CMC denture adhesive (as defined in Table 1-3) to no adhesive over 12 hours, $AOB_{0\text{-}12}$.

The primary means of assessing the outcome of the pooled analysis is the analysis of the change from baseline in BF as measured by $AOB_{0\text{-}12}$ for test adhesive compared to no adhesive.

The primary response variable is AOB over 12 hours for the incisal BF (lbs) (denoted by $AOB_{0\text{-}12}$). The AOB will be calculated for the interval starting at the time (t_0) of the baseline reading (y_0) and ending at the time (t_{n+1}) of the last valid reading (y_{n+1}) using the trapezoidal method:

$$AOB_{0-12} = \frac{1}{2}\sum_{i=0}^{n}(t_{i+1} - t_i)(y_{i+1} - y_i) - (y_0 \; x \; 12)$$

AOB is equivalent to the AUC above the pre-treatment baseline value and adjusts for any differences in pre-treatment baseline BF values between the treatment groups. The AOB will be divided by 12 so that the value was reported on the original BF (lbs) scale.

For each individual study, incisal BF measurement are taken at different time points, as described by Table 1-1.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated, hence the study will be excluded from the summary and statistical analysis of the primary endpoint $AOB_{0\text{-}12}$.

Descriptive statistics (n, missing, mean, SD, standard error [SE], median, minimum, and maximum values) of $AOB_{0\text{-}12}$ by treatment arm for pooled data will be presented for the ITT population (Table 14.2.2.1).

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

An Analysis of Covariance (ANCOVA) model will be used to analyze $AOB_{0\text{-}12}$, with treatment, study and period as fixed effects. The covariates in this model are the subject level baseline and period level baseline minus subject level baseline. Subject will be included as a random effect. Pairwise treatment comparisons will be obtained as a difference in adjusted means and presented with 95% confidence intervals (CI) and associated p-values. Within treatment group estimates will also be calculated with their 95% CIs and p-values to assess the within group changes from baseline.

The null hypothesis for the primary endpoint is that there is no difference in the mean BF AOB at 12 hours between the test adhesive and no adhesive.

- $H_0: \mu_1 = \mu_2$

The alternative hypothesis for the primary endpoint is that there is difference in the mean BF AOB at 12 hours between the test adhesive and no adhesive.

- $H_0: \mu_1 \neq \mu_2$

All studies included in this pooled analysis are crossover design with the exception of CCI [redacted] being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of the primary endpoint $AOB_{0\text{-}12}$.

Results from the statistical analysis of $AOB_{0\text{-}12}$ including treatment comparisons, 95% CIs and associated p-value based on pooled data will be presented for ITT population (Table 14.2.3.1).

In addition, forest plot with adjusted mean and corresponding 95% CIs obtained from ANCOVA model will be presented by treatment group presenting both pooled and individual study data in Figure 14.2.3.1 for ITT population.

The assumption of normality and homogeneity of variance in the ANCOVA model will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Sign Rank test).

4.4.1.3 Supportive Analyses

As a general rule, PP analysis is to be performed on primary objective if there is more than 10% difference in the number of subjects between the PP and ITT populations. For this pooled analysis, since the individual study data is already available and it is observed that the difference in the number of subjects between the PP and ITT population is less than 1%, hence PP analysis on primary objective as planned will not be performed.

4.4.2 Secondary Efficacy Variables

The secondary efficacy variables defined in this pooled analysis are:

- AOB up to 0.5, 1, 3, 6 and 9 hours.
- Raw mean BF measurement between adhesive and no adhesive at 0.5, 1, 3, 6, 9 and 12 hours.
- Within-treatment change from baseline in raw BF measurement up to 0.5, 1, 3, 6, 9 and 12 hours.

For all statistical analysis described in subsections below, the assumption of normality and homogeneity of variance in the ANCOVA models will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Sign Rank test).

4.4.2.1 AOB up to 0.5, 1, 3, 6 and 9 Hours

Secondary key efficacy variable for assessment of change from baseline in BF over 0.5, 1, 3, 6 and 9 hours after application is $AOB_{0\text{-}t}$ (where t is 0.5, 1, 3, 6 and 9 hours BF measurements). $AOB_{0\text{-}t}$ will be derived following the same methodology as the primary efficacy variable.

The $AOB_{0\text{-}t}$ will be calculated for the interval starting at the time (t_0) of the baseline reading (y_0) and ending at the time (t_{n+1}) of the last valid reading (y_{n+1}) using the trapezoidal method:

$$AOB_{0-t} = \frac{1}{2}\sum_{i=0}^{n}(t_{i+1} - t_i)(y_{i+1} - y_i) - (y_0 \; x \; t)$$

Where t is the incisal BF assessment at 0.5, 1, 3, 6 and 9 hours, respectively.

AOB is equivalent to the AUC above the pre-treatment baseline value and adjusts for any differences in pre-treatment baseline BF values between the treatment groups. The AOB will be divided by the ending time of the last valid reading (t) so that the value will be reported on the original BF (lbs) scale.

$AOB_{0\text{-}t}$ will be analyzed using same ANCOVA model as the primary efficacy variable. For more details, see Section 4.4.1.2.

Similarly, to analysis of primary efficacy variable, $AOB_{0\text{-}t}$ will be summarized and analyzed based on pooled data.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated hence the study will be excluded from the summary and statistical analysis of AOB up to 0.5, 3, 6 and 9 hours.

All studies included in this pooled analysis are crossover design with the exception of CCI [redacted] being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of $AOB_{0\text{-}t}$.

4.4.2.2 Raw Mean BF Measurement Between Adhesive and No Adhesive at 0.5, 1, 3, 6, 9 and 12 Hours

Raw mean incisal BF measurements over time (up to 0.5, 1, 3, 6, 9 and 12 hours post-baseline) will be analyzed to compare and evaluate the maximum BF made with test adhesive against no adhesive.

Raw mean incisal BF measurements will be summarized and analyzed based on pooled data, and using the same ANCOVA model as the primary efficacy variable (for more details, see Section 4.4.1.2) and including only the studies with available raw incisal BF data, as shown in Table 1-1.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated hence the study will be excluded from the summary and statistical analysis of raw mean BF measurements at 0.5, 3, 6, 9 and 12 hours.

All studies included in this pooled analysis are crossover design with the exception of CCI [redacted] being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of the raw mean BF measurements over time.

4.4.2.3 Within-Treatment Change from Baseline in Raw BF

Within-treatment change from baseline in raw incisal BF over time (up to 0.5, 1, 3, 6, 9 and 12 hours post-baseline) will be analyzed to compare and evaluate the maximum BF made with test adhesive against no adhesive.

Within-treatment change from baseline in raw incisal BF over time will be summarized and analyzed based on pooled data, and using the same ANCOVA model as the primary efficacy

variable (for more details, see Section 4.4.1.2) and including only the studies with available raw incisal BF data, as shown in Table 1-1.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated hence the study will be excluded from the summary and statistical analysis of within-treatment change from baseline in raw incisal BF at 0.5, 3, 6, 9 and 12 hours.

All studies included in this pooled analysis are crossover design with the exception of CCI being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of within-treatment change from baseline in raw incisal BF over time.

4.4.3 Exploratory Efficacy Variables

The exploratory efficacy variables defined in this pooled analysis are:

- AOB up to 0.5, 1, 3, 6, 9 and 1 hours in 3 categories.
- Raw mean BF measurements between adhesive and no adhesive at 0.5, 1, 3, 6, 9 and 12 hours in 3 categories.
- Within-treatment change from baseline in raw BF measurement up to 0.5, 1, 3, 6, 9 and 12 hours in 3 categories.
- Percentage change of baseline BF measurement from the maximum BF measurement at any post-baseline time point.
- Baseline BF measurements including Kapur Index and DBTs scores in the model to be assessed.
- Percentage changes of BF measurement at 0.5, 1, 3, 6, 9 and 12 hours from the maximum BF measurement.

For all statistical analysis described in subsections below, the assumption of normality and homogeneity of variance in the Analysis of Variance (ANOVA) and ANCOVA models will be investigated. Violation of this assumption will be overcome using a suitable data transformation or a non-parametric technique (e.g. Wilcoxon Sign Rank test).

4.4.3.1 AOB up to 0.5, 1, 3, 6, 9 and 12 Hours in 3 Categories

AOB up to 0.5, 1, 3, 6, 9 and 12 hours (denoted by $AOB_{0\text{-}t}$) will be derived following the same methodology as described in Section 4.4.1.1 and Section 4.4.2.1.

$AOB_{0\text{-}t}$ will be summarized and analyzed by 3 subgroups (as defined in Section 3.2) based on pooled data and for each individual study with available raw incisal BF data.

Same ANCOVA model as the primary efficacy variable (described in Section 4.4.1.2) based on 3 subgroup populations will be used to compare and evaluate AOB of test denture adhesive to

no adhesive, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs score and baseline BF.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated hence the study will be excluded from the summary and statistical analysis of AOB up to 0.5, 3, 6, 9 and 12 hours.

All studies included in this pooled analysis are crossover design with the exception of CCI [redacted] being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of $AOB_{0\text{-}t}$.

4.4.3.2 Raw Mean BF Measurement Between Adhesive and No Adhesive at 0.5, 1, 3, 6, 9 and 12 Hours in 3 Categories

Raw mean incisal BF measurements at 0.5, 1, 3, 6, 9 and 12 hours will be summarized and analyzed by 3 subgroups (as defined in Section 3.2) based on pooled data and for each individual study with available raw incisal BF data.

Same ANCOVA model as the primary efficacy variable (described in Section 4.4.1.2) based on 3 subgroup populations will be used to compare and evaluate the raw mean incisal BF measurements over time (up to 0.5, 1, 3, 6, 9 and 12 hours post-baseline) of test denture adhesive to no adhesive, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs score and baseline BF.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated hence the study will be excluded from the summary and statistical analysis of raw mean BF measurements at 0.5, 3, 6, 9 and 12 hours.

All studies included in this pooled analysis are crossover design with the exception of CCI [redacted] being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of the raw mean BF measurements over time.

4.4.3.3 Within-Treatment Change from Baseline in Raw BF Measurement up to 0.5, 1, 3, 6, 9 and 12 Hours in 3 Categories

Within-treatment change from baseline in raw incisal BF at 0.5, 1, 3, 6, 9 and 12 hours will be summarized and analyzed by 3 subgroups (as defined in Section 3.2) based on pooled data and for each individual study with available raw incisal BF data.

Same ANCOVA model as the primary efficacy variable (described in Section 4.4.1.2) based on 3 subgroup populations will be used to compare and evaluate the maximum BF made with test

adhesive against no adhesive, within categories based on the modification of Kapur Index score, conditions of the maxillary DBTs and baseline BF.

For GSKCH Clinical Study Report L3510566, 2008, only one post-baseline incisal BF assessment at 1 hour was evaluated hence the study will be excluded from the summary and statistical analysis of within-treatment change from baseline in raw incisal BF at 0.5, 3, 6, 9 and 12 hours.

All studies included in this pooled analysis are crossover design with the exception of CCI being parallel and monadic study designs, respectively. Due to the difference in study designs, the study period effect cannot be evaluated as per the planned statistical analyses and hence these two listed studies will be excluded from the summary and statistical analysis of within-treatment change from baseline in raw incisal BF over time.

4.4.3.4 Percentage Change of Baseline BF Measurement from the Maximum BF Measurement

To evaluate the baseline BF with respect to the maximum observed BF, percentage change of baseline BF measurement from the maximum observed BF measurement will be summarized. Summaries will be presented for pooled data only. Available data from all individual studies will be included in summaries.

To derive the percentage change of baseline BF from the maximum BF measurement, the first step would be to calculate mean BF at each time point (baseline, 0.5, 1, 3, 6, 9 and 12 hours) by treatment group. The next step would be to identify the maximum mean post-baseline BF measurement (BF_{max}).

The percentage change of baseline BF from the maximum BF measurement will be calculated as follows:

$$\%\ Change = \left(\frac{BF - BF_{baseline}}{BF_{max} - BF_{baseline}}\right) * 100$$

Where, BF is the mean BF measurement at 0.5, 1, 3, 6, 9 and 12 hours post-baseline and $BF_{baseline}$, is the mean baseline BF measurement.

4.4.3.5 Baseline BF Measurements Including Kapur Index and DBTs Scores in the Model to be Assessed

To evaluate the effect of retention, stability as assessed by Kapur Index and conditions of DBTs on baseline BF, the baseline BF measurement will be analyzed including raw Kapur Index and DBTs scores in the model based on pooled data only. Available data from all individual studies will be included in analysis.

An ANOVA model will be used to evaluate the effect of retention, stability and conditions of DBTs on baseline BF measurements.

The model will include raw Kapur Index score and raw DBTs score as fixed effects and subject as random effect. The hypothesis tests for significance of fixed effects (Kapur Index and DBTs raw scores) will be performed to assess the effect on baseline BF measurements.

Data for Kapur Score is not collected for CCI [redacted] and data for DBTs score is not collected for CCI [redacted], hence these two listed studies will be excluded from the summary and statistical analysis of baseline BF measurements including Kapur Index and DBTs scores.

4.4.3.6 Percentage Changes of BF Measurement at 0.5, 1, 3, 6, 9 and 12 Hours from the Maximum BF Measurement

To evaluate the relative BF at all measured time points with respect to the maximum observed BF, the percentage changes of BF measurements at 0.5, 1, 3, 6, 9 and 12 hours post-baseline from the maximum BF measurement will be summarized. Summaries will be presented for pooled data only. Available data from all individual studies will be included in summaries.

To derive the percentage change of BF measurements at all post-baseline time points from the maximum BF measurement, the first step would be to calculate mean BF at each time point (baseline, 0.5, 1, 3, 6, 9 and 12 hours) by treatment group. The next step would be to identify the maximum post-baseline BF measurement (BF_{max}).

The percentage change of BF from the maximum BF measurement will be calculated as follows:

$$\%\ Change = \left(\frac{BF}{BF_{max}}\right) * 100$$

Where, BF is the mean BF measurement at 0.5, 1, 3, 6, 9 and 12 hours post-baseline.

4.4.4 Handling of Missing Values/Censoring/Discontinuations

For calculation of AOB, linear interpolation will be used in the case of missing values. In calculation of AOB, AUC will be linearly interpolated between successive measurements with valid readings. Missing readings will be ignored, and interpolation will be made between pre and post the missing values, if necessary. If more than one of the assessments during the 12-hour period is missing or if the 12-hour value is missing, the $AOB_{0\text{-}12}$ will be set to missing. The same missing data handling rule will be applied to the calculation of AOB over 0.5, 1, 3, 6 and 9 hours.

For study GSKCH Clinical Study Report L3510566, 2008, only 1-hour time point data is available. In this scenario, if 1-hour time point or baseline BF measurement is missing then AOB will be set to missing.

Other missing data will not be replaced or imputed. Subjects who dropped out individual studies will be included in analyses up to the point of discontinuation.

4.5 Analysis of Secondary and Exploratory Objectives

The ITT population will be considered as primary population for secondary and exploratory analyses. Supportive analyses are not planned for secondary and exploratory objectives.

4.5.1 Efficacy (Secondary)

4.5.1.1 AOB up to 0.5, 1, 3, 6 and 9 Hours

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum values) of change from baseline in BF as measured by AOB for 0.5, 1, 3, 6 and 9 hours will be presented based on pooled data by treatment arm (Table 14.2.2.1) for the ITT population.

Results from the statistical analysis of $AOB_{0\text{-}0.5}$, $AOB_{0\text{-}1}$, $AOB_{0\text{-}3}$, $AOB_{0\text{-}6}$, $AOB_{0\text{-}9}$ and $AOB_{0\text{-}12}$ including treatment comparisons, 95% CIs and associated p-value based on pooled data will be presented (Table 14.2.3.1) for ITT population, based on pooled data.

4.5.1.2 Raw Mean BF Measurement Between Adhesive and No Adhesive at 0.5, 1, 3, 6, 9 and 12 Hours

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum values) of raw mean BF measurements at 0.5, 1, 3, 6, 9 and 12 hours will be presented based on pooled data by treatment arm (Table 14.2.4.1) for the ITT population.

Results from the statistical analysis of raw mean BF measurements at 0.5, 1, 3, 6, 9 and 12 hours including treatment comparisons, 95% CIs and associated p-values based on pooled data will be presented (Table 14.2.4.2) for the ITT population.

Mean incisal BF by treatment group will be plotted over time for pooled data (Figure 14.2.4.1) and for each individual study (Figure 14.2.4.2) for the ITT population.

4.5.1.3 Within-Treatment Change from Baseline in Raw BF

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum values) of the within-treatment change from baseline in raw BF measurements at 0.5, 1, 3, 6, 9 and 12 hours will be presented based on pooled data by treatment arm (Table 14.2.4.1) for the ITT population.

Results from the statistical analysis of within-treatment change from baseline in raw mean BF measurements at 0.5, 1, 3, 6, 9 and 12 hours including within-treatment 95% CIs and associated p-values based on pooled data will be presented (Table 14.2.5.1) for the ITT population.

Within-treatment change from baseline in incisal BF by treatment group will be plotted over time for pooled data (Figure 14.2.5.1) and for each individual study (Figure 14.2.5.2) for the ITT population.

4.5.2 Efficacy (Exploratory)

4.5.2.1 AOB up to 0.5, 1, 3, 6, 9 and 12 Hours in 3 Categories

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum values) of $AOB_{0\text{-}t}$ (up to 0.5, 1, 3, 6, 9 and 12 hours post-baseline), by treatment group for pooled data will be presented for the ITT population by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7) in Table 14.2.6.1, by DBTs score (Low – < 7; Medium – 7-9; High – > 9) in Table 14.2.6.3 and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Table 14.2.6.5.

Results from the statistical analysis of $AOB_{0\text{-}t}$ (up to 0.5, 1, 3, 6, 9 and 12 hours post-baseline) including treatment comparisons, 95% CIs and associated p-value based on pooled data will be presented for ITT population by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7) in Table 14.2.6.2, by DBTs score (Low – < 7; Medium – 7-9; High – > 9) in Table 14.2.6.4 and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Table 14.2.6.6.

Mean incisal BF by treatment group will be plotted over time for pooled data by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7), by DBTs score (Low – < 7; Medium – 7-9; High – > 9) and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Figure 14.2.6.1 for the ITT population.

4.5.2.2 Raw Mean BF Measurement Between Adhesive and No Adhesive at 0.5, 1, 3, 6, 9 and 12 Hours in 3 Categories

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum values) of raw mean BF measurements at 0.5, 1, 3, 6, 9 and 12 hours by treatment group for pooled data will be presented for the ITT population by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7) in Table 14.2.7.1, by DBTs score (Low – < 7; Medium – 7-9; High – > 9) in Table 14.2.7.3 and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Table 14.2.7.5.

Results from the statistical analysis of raw mean BF measurements at 0.5, 1, 3, 6, 9 and 12 hours including treatment comparisons, 95% CIs and associated p-values based on pooled data will be presented for the ITT population by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7) in Table 14.2.7.2, by DBTs score (Low – < 7; Medium – 7-9; High – > 9) in Table 14.2.7.4 and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Table 14.2.7.6.

Mean incisal BF by treatment group will be plotted over time for pooled data by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7), by DBTs score (Low – < 7; Medium – 7-9; High – > 9) and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Figure 14.2.6.1 for the ITT population.

4.5.2.3 Within-Treatment Change from Baseline in Raw BF Measurement up to 0.5, 1, 3, 6, 9 and 12 Hours in 3 Categories

Descriptive statistics (n, missing, mean, SD, SE, median, minimum, and maximum values) of the within-treatment change from baseline in raw BF measurements at 0.5, 1, 3, 6, 9 and 12 hours by treatment group for pooled data will be presented for the ITT population by Kapur

Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7) in Table 14.2.7.1, by DBTs score (Low – < 7; Medium – 7-9; High – > 9) in Table 14.2.7.3 and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Table 14.2.7.5.

Results from the statistical analysis of within-treatment change from baseline in raw mean BF measurements at 0.5, 1, 3, 6, 9 and 12 hours including within-treatment 95% CIs and associated p-values based on pooled data will be presented for the ITT population by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7) in Table 14.2.8.1, by DBTs score (Low – < 7; Medium – 7-9; High – > 9) in Table 14.2.8.2 and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Table 14.2.8.3.

Within-treatment change from baseline in incisal BF by treatment group will be plotted over time for pooled data by Kapur Index score (Fair – ≤ 4; Good – 5-7; Very Good – > 7), by DBTs score (Low – < 7; Medium – 7-9; High – > 9) and by baseline BF measurement (≤ 2.5 lbs; > 2.5 lbs) in Figure 14.2.8.1 for the ITT population.

4.5.2.4 Percentage Change of Baseline BF Measurement from the Maximum BF Measurement

Percentage change of baseline BF measurement from the maximum BF measurement will be summarized descriptively (n, missing, mean, SD, SE, median, minimum, and maximum values) based on the pooled data by time point (0.5, 1, 3, 6, 9 and 12 hours post-baseline) in Table 14.2.4.1 for the ITT population. Mean percentage change of baseline BF measurements from the maximum BF measurements at 0.5, 1, 3, 6, 9 and 12 hours will be presented in Table 14.2.9.1 for the ITT population.

4.5.2.5 Baseline BF Measurements Including Kapur Index and DBTs Scores in the Model to be Assessed

Results from the statistical analysis of baseline BF measurements including raw Kapur Index scores and DBTs score in the model will be presented based on pooled data for the ITT population (Table 14.2.10.1).

4.5.2.6 Percentage Changes of BF Measurement at 0.5, 1, 3, 6, 9 and 12 hours from the Maximum BF Measurement

Percent change of BF measurement from the maximum BF measurement at all time points (0.5, 1, 3, 6, 9 and 12 hours post-baseline) will be summarized descriptively (n, missing, mean, SD, SE, median, minimum, and maximum values) based on the pooled data by time point (0.5, 1, 3, 6, 9 and hours post-baseline) in Table 14.2.4.1 for the ITT population. Mean percentage change of BF measurement from the maximum BF measurement at 0.5, 1, 3, 6, 9 and 12 hours will be presented in Table 14.2.11.1 for the ITT population.

4.6 Analysis of Safety

Safety analysis is not applicable for this pooled analysis as the objectives of this analysis is to investigate the maximum incisal BF until maxillary denture dislodgement of test denture adhesive to no adhesive. The individual safety data can be obtained from individual clinical study reports.

4.6.1 Adverse Events and Serious Adverse Events

N/A

4.6.2 Other Safety Variables

N/A

4.7 Analysis of Other Variables

N/A

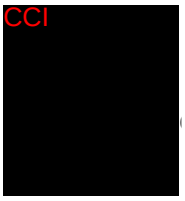
5 Changes to the Protocol Defined Statistical Analysis Plan

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

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
5.1.1 Analysis Populations It was defined for most of the studies included in the pooled analyses with the exception of GSKCH Clinical Study Report PCLBF2009-09, 2009 and GSKCH Clinical Study Report 206233, 2017.	4.1.3 Analysis Populations PP Population was defined for most of the studies included in the pooled analyses with the exception of GSKCH Clinical Study Report PCLBF2009-09, 2009.	Reference to GSKCH Clinical Study Report 206233, 2017 in the Protocol is not correct. For this study, PP population is defined.

Attachment 1: List of Data Displays



Table, Figure and Listing Shells

A Post-hoc Pooled Analysis of GSK CH Clinical Data Investigating the Efficacy of Denture Adhesive creams containing PMV/MA &CMC on Denture Retention and Bite Force

Protocol Number: 213380

Phase: N/A

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Document History

Document	Version Date	Summary of Changes
Original Analysis Plan Shells	06-Nov-2020	Not applicable (N/A)

General Notes for Tables, Figures and Listings

This section provides guidance and specifications for the planned TFLs.

- The treatment labels for the column headings, for the pooled tables only, will be as follows:
  - Test Adhesive
  - No Adhesive
- For displaying summary statistics, the following decimal place rules should be applied where x is the precision of the raw data:

  x: minimum and maximum

  x + 1: mean (or LS Mean), median, percentiles, quartiles, and confidence intervals

  x + 2: standard deviation, standard error

  No rounding of AOB will be applied to the numeric value in the datasets, for display purposes of derived AOB x will be regarded as 3 decimal places.
- P-values are displayed as 0.xxxx (4 digits after decimal), if p-value is less than 0.0001 display <0.0001.
- Percentages should be displayed as xx.x (1 digit after decimal). If all subjects are included, 100% will be presented, if none then no percentage value will be displayed.
- Unless otherwise specified in the table footnote, percentages will be based on the number of subjects in the analysis population, for the relevant sequence/treatment group, regardless of time point.
- Update the status of the outputs as or ‘Draft’ or ‘Final’ depending on status of TFL delivery.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.1.1.1
Subject Disposition
All Screened Subjects

Analysis Population: All Screened Subjects (N = xxx)

	Test Adhesive n (%)	No Adhesive n (%)	Overall n (%)
Subjects screened			xxx
Subjects not randomized			xxx (xx.x)
Did not meet study criteria			xxx (xx.x)
Adverse events			xxx (xx.x)
Lost to follow-up			xxx (xx.x)
Protocol violation			xxx (xx.x)
Withdrawal of consent			xxx (xx.x)
Other			xxx (xx.x)
Subjects randomized	xxx	xxx	xxx
Completed study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Did not complete study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Did not meet study criteria	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adverse events	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Protocol violation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Withdrawal of consent	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Safety population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ITT Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PP Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

For the category "Subjects not randomized", percentages are calculated using the number of screened subjects as the denominator.
For all categories under “Subjects randomized”, percentages are calculated using number of subjects’ randomized as the denominator.

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program file name: xxxxxx Source: Dataset

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Programming Note:
1. This table will be produced on pooled data only.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.1.1.2
Subject Disposition by Treatment Sequence and Period
All Screened Subjects

Analysis Population: All Screened Subjects (N = xxx)
Study: 203114

	Sequence 1 n (%)	Sequence 2 n (%)	---	Sequence X n (%)	Overall n (%)
Subjects screened					xxx
Subjects not randomized					xxx (xx.x)
Did not meet study criteria					xxx (xx.x)
Adverse events					xxx (xx.x)
Lost to follow-up					xxx (xx.x)
Protocol violation					xxx (xx.x)
Withdrawal of consent					xxx (xx.x)
Other					xxx (xx.x)
Subjects randomized	xxx	xxx	---	xxx	xxx
Period X					
Started period	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Completed	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Did not complete	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Did not meet study criteria	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Adverse events	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Protocol violation	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Withdrawal of consent	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	---	xxx (xx.x)	xxx (xx.x)
---	---	---	---	---	---

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

	Sequence 1 n (%)	Sequence 2 n (%)	--- 	Sequence X n (%)	Overall n (%)
Safety population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ITT Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PP Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

For the category "Subjects not randomized", percentages are calculated using the number of screened subjects as the denominator.
For the category "Started period", percentages are calculated using the number of subjects randomized as the denominator. For the category "Completed" and all categories under "Did not complete", percentages are calculated using number of subjects starting that period as the denominator.
Study L3510566 is presented by Overall only.
Treatment Legend:
203114: A = Super Poligrip Free Adhesive Cream (USA); B = Test adhesive 1 (CCI); C = Test adhesive 2 (CCI); D = No Adhesive.
CCI : A = No Adhesive; B = Control Adhesive: Super Poligrip Denture Adhesive Cream, Original, USA CCI); C = Test Adhesive: eral Oil Formulation (CCI .
CCI : A = Test Adhesive: al Oil Formulation CCI ; B = No Adhesive; C = Positive Control Adhesive: Super Poligrip Original e Adhesive Cream, USA CCI).
CCI : A = Test adhesive C/Konjac - CCI ; B = Test adhesive 2: CMC/Xanthan/HPMC/Konjac - CCI ; C = Poligrip Super Wernets Fixative Powder - CCI ; D = Super Poli ginal Denture Adhesive Cream - USA Marketplace CCI
207545: A = Protefix Denture Adhesive, Creme Mint (Germany marketplace); B = No Adhesive; C = Super Poligrip Free Adhesive Cream (USA marketplace).
A = Test Adhesive 2 -CCI ; B = Super Poligrip Free Adhesive Cream (USA marketplace); C = No Adhesive; D = Test Adhesive 1 -CCI .

Program Run Date: DDMMMYYYY:HH:MM
Page x of y
Program file name: xxxxxx
Source: Dataset
Programming Notes:
1. The table will continue with other crossover individual studies: CCI , **207545, 206223** and **L3510566.**
2. Present individual studies as follows:
- **203114**: Study is conducted as 4 periods 4 treatment/sequences study. Thus, present 4 sequence columns + Overall, with the following labels: Sequence labels: Sequence 1 = "A/C/B/D"; Sequence 2 = "B/A/D/C"; Sequence 3 = "C/D/A/B"; Sequence 4 = "D/B/C/A".
Period X" panels 4 times for each of the 4 periods.
- CCI Study is conducted as 3 periods 3 treatments 6 sequences study. Thus, present 6 sequence columns + Overall, with the g labels: Sequence labels: Sequence 1 = "A/B/C"; Sequence 2 = "A/C/B"; Sequence 3 = "B/A/C"; Sequence 4 = "B/C/A"; Sequence 5 = "C/A/B"; Sequence 6 = "C/B/A.
Period X" panels 3 times for each of the 3 periods.
- CCI Study is conducted as 3 periods 3 treatments 6 sequences study. Thus, present 6 sequence columns + Overall, with the g labels: Sequence labels: Sequence 1 = "A/B/C"; Sequence 2 = "A/C/B"; Sequence 3 = "B/A/C"; Sequence 4 = "B/C/A"; Sequence 5 = "C/A/B"; Sequence 6 = "C/B/A.
Repeat "Period X" panels 3 times for each of the 3 periods.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

	Sequence 1 n (%)	Sequence 2 n (%)	---	Sequence X n (%)	Overall n (%)

- CCI Study is conducted as 4 periods 4 treatment/sequences study. Thus, present 4 sequence columns + Overall, with the following Sequence labels: Sequence 1 = "A/D/C/B"; Sequence 2 = "B/D/C/A"; Sequence 3 = "C/A/D/B"; Sequence 4 = "D/C/B/A".
  Repeat "Period X" panels 4 times for each of the 4 periods.
- **207545**: Study is conducted as 3 periods 3 treatments 6 sequences study. Thus, present 6 sequence columns + Overall, with the following labels: Sequence labels: Sequence 1 = "A/B/C"; Sequence 2 = "A/C/B"; Sequence 3 = "B/A/C"; Sequence 4 = "B/C/A"; Sequence 5 = "C/A/B"; Sequence 6 = "C/B/A.
  Repeat "Period X" panels 3 times for each of the 3 periods.
- **206233**: Study is conducted as 4 periods 4 treatment/sequences study. Thus, present 4 sequence columns + Overall, with the following labels: Sequence labels: Sequence 1 = "A/B/D/C"; Sequence 2 = "B/C/A/D"; Sequence 3 = "C/D/B/A"; Sequence 4 = "D/A/C/B".
  Repeat "Period X" panels 4 times for each of the 4 periods.
- **L3510566**: Study is conducted as 4 periods 4 treatment study with 16 sequences. Thus, present only Overall.
  Repeat "Period X" panels 4 times for each of the 4 periods.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.1.1.3
Subject Disposition by Treatment Group
All Screened Subjects

Analysi i : All Screened Subjects (N = xxx)
Study: CCI -CO

	Treatment Group 1 n (%)	Treatment Group 2 n (%)	--- n (%)	Treatment Group X n (%)	Overall n (%)
Subjects screened					xxx
Subjects not randomized					xxx (xx.x)
Did not meet study criteria					xxx (xx.x)
Adverse events					xxx (xx.x)
Lost to follow-up					xxx (xx.x)
Protocol violation					xxx (xx.x)
Withdrawal of consent					xxx (xx.x)
Other					xxx (xx.x)
Subjects randomized	xxx	xxx	xxx	xxx	xxx
Completed study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Did not complete study	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Did not meet study criteria	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Adverse events	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Lost to follow-up	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Protocol violation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Withdrawal of consent	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Safety population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ITT Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
PP Population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

For all categories under "Subjects not randomized", percentages are calculated using the number of screened subjects as the denominator. For all categories under "Subjects randomized", percentages are calculated using number of subjects' randomized as the denominator.

Program Run Date: DDMMMYYYY:HH:MM Page x of y

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Program file name: xxxxxx
Source: Dataset

Programming Notes:

1. The table will continue CCI study.
2. [illegible] idual studi[illegible]ollows:
   - CCI CCI Study is conducted as monadic (one treatment). Thus, present only Overall column and use the following label: "Poligrip [illegible] Denture Adhesive (CCI
   - CCI Study is conducted as 4 parallel study. Thus, present 4 treatment columns + Overall, with the following labels: t Group 1 = "Test Adhesive 1: CMC/Xanthan Gum 1"; Treatment Group 2 = "Test Adhesive 2: CMC/Xanthan Gum 2"; Treatment Group 3 = "Test Adhesive 3: CMC/Xanthan Gum 3"; Treatment Group 4 = "Positive Control: Super Poligrip Original (US)".

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.1.2
Incidence of Important Protocol Deviations
All Randomized Subjects

Analysis Population: All Randomized Subjects (N = xxx)

	Test Adhesive (N = xxx) n (%)	No Adhesive (N = xxx) n (%)	Overall (N = xxx) n (%)
Subjects with at least one important protocol deviation	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Important protocol deviations leading to exclusion from Per Protocol population	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Deviation reason 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Deviation reason 2	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
---	---	---	---

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program file name: xxxxxx Source: Dataset
Programming Note:
1. This table will be produced on po ly.
2. PP population is not defined for CCI , respectively, no data for Important Protocol Deviations is collected for these studies.

Table 14.1.3.1
Demographic Characteristics
Safety Population

Study: Pooled
Analysis Population: Safety (N = xxx)

	Test Adhesive (N = xxx)	No Adhesive (N = xxx)	Overall (N = xxx)
Sex [n (%)]			
Male	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Female	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Race [n (%)]			
African American/African Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
American Indian or Alaskan Native	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Asian - Central/South Asian Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Asian - East Asian Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Asian - Japanese Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Asian - South East Asian Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Native Hawaiian or Other Pacific Islander	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
White - Arabic/North African Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
White - White/Caucasian/European Heritage	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Multiple	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Ethnicity [n (%)]			
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Age (years)			
n	xx	xx	xx
Mean	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Program Run Date: DDMMMYYYY:HH:MM
Program: xxxxxx.sas
Page x of y
Source: Dataset

Programming Notes:

1. The table will continue with individual studies: **203114,** CCI **, 207545, 206233,** CCI and **L3510566.**
2. Present summaries for pooled data at first.
3. For individual studies, present only "Overall" column. Do not present summaries by treatment/sequence.
4. The categories for all the races as given on the individual study eCRF pages (except for study L3510566) will be displayed. For study L3510566, present the mapped races, as described in RAP text. In case more than one Race is ticked, present them in "Multiple" race and count such subjects in this categ
5. "Ethnicity" on 4, CCI , 207545 and 206223. Do not present "Ethnicity" for pooled data, CCI L3510566 and CCI .
6. or **Table 14.1.**
   - Title: Table 14.1.3.2 Demographic Characteristics
   - Population: ITT Population
   - Additional Notes:
     - Retrieve subjects included in ITT population.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.1.4
Other Baseline Characteristic
ITT Population

Analysis Population: ITT (N = xxx)

	Test Adhesive (N = xxx) n (%)	No Adhesive (N = xxx) n (%)	Overall (N = xxx) n (%)
Kapur Score			
Fair (<=4)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Good (5-7)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Very Good (>7)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DBTs Score			
Low (<7)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Medium (7-9)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
High (>9)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Baseline BF Measurement (lbs)			
<= 2.5	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
> 2.5	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

DBTs = Denture Bearing Tissues; BF = Bite Force; lbs = Pound.
Summary statistics of other baseline characteristics are based on data from 7 studies (203114, CCI , 207545, 206233 and L3510566).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program file name: xxxxxx Source: Dataset
Programming Note:
1. This table will be produced on pooled data only.
2. mented in RAP Text, the following individual studies are included in the summaries: 7 studies (203114, CCI , CCI , 207545, 206233 and L3510566).

Table 14.2.2.1
Summary of Area Over Baseline (lbs) by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

Endpoint	Statistic	Test Adhesive (N = xxx)	No Adhesive (N = xxx)
AOB 0-12*	n	xx	xx
	Missing	xx	xx
	Mean	x.xx	x.xx
	SD	x.xxx	x.xxx
	SE	x.xxx	x.xxx
	Median	x.xx	x.xx
	Minimum	x.x	x.x
	Maximum	x.x	x.x
AOB 0-0.5	n	xx	xx
	Missing	xx	xx
	Mean	x.xx	x.xx
	SD	x.xxx	x.xxx
	SE	x.xxx	x.xxx
	Median	x.xx	x.xx
	Minimum	x.x	x.x
	Maximum	x.x	x.x
---	---	---	---

* indicates the primary endpoint.
AOB = Area Over Baseline; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
Higher values of AOB demonstrate a stronger bite force over time.
Summary statistics of AOB0-12 are based on data from 6 studies (203114, CCI 207545 and 206233).
Summary statistics of AOB0-0.5 are based on data from 6 studies (203114 CCI, 207545 and 206233).
Summary statistics of AOB0-1 are based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Summary statistics of AOB0-3 are based on data from 6 studies (203114, CCI, 207545 and 206233).
Summary statistics of AOB0-6 are based on data from 6 studies (203114, CCI, 207545 and 206233).
Summary statistics of AOB0-9 are based on data from 6 studies (203114, CCI, 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Program: xxxxxx.sas Source: Dataset

Programming Notes:

1. Table will continue with AOB 0-0.5, AOB0-1, AOB 0-3, AOB 0-6 and AOB 0-9.
2. Use the following order: AOB0-12, AOB0-0.5, AOB0-1, AOB0-3, AOB0-6, AOB0-9.
3. As documented in RAP Text, t tudies are included in the summaries:
   AOB0-12: 6 studies (203114, CCI 207545 and 206233).
   AOB0-0.5: 6 studies (203114 CCI , 207545 and 206233).
   AOB0-1: 7 studies (203114, CCI 207545, 206233 and L3510566).
   AOB0-3: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-6: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-9: 6 studies (203114, CCI , 207545 and 206233).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.3.1
Statistical Analysis of Area Over Baseline (lbs) by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

Endpoint	Treatment Group	n	Adjusted Mean (SE) [1]	95% CI [1]	p-value [1]	Comparison with No Adhesive		
						Adjusted Mean Difference (SE) [1]	95% CI [1]	p-value [1]
AOB 0-12*	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx			
AOB 0-0.5	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx			
---	---	---	---	---	---	---	---	---

* indicates the primary endpoint.
AOB = Area Over Baseline; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates and subject as a random effect.
Adjusted Mean Difference is calculated as Test Adhesive minus No Adhesive ference favors Test Adhesive.
Statistical analysis of AOB0-12 is based on data from 6 studies (203114, CCI 207545 and 206233).
Statistical analysis of AOB0-0.5 is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of AOB0-1 is based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Statistical analysis of AOB0-3 is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of AOB0-6 is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of AOB0-9 is based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Table will continue with AOB 0-1, AOB 0-3, AOB 0-6 and AOB 0-9.
2. Use the following order: AOB0-12, AOB0-0.5, AOB0-1, AOB0-3, AOB0-6, AOB0-9.
3. As documented in RAP Text, the following individual studies are included in the statistical analysis of AOB:

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

AOB0-12: 6 studies (203114, CCI 207545 and 206233).
AOB0-0.5: 6 studies (203114, CCI , 207545 and 206233).
AOB0-1: 7 studies (203114, CCI 207545, 206233, and L3510566).
AOB0-3: 6 studies (203114, CCI , 207545 and 206233).
AOB0-6: 6 studies (203114, CCI , 207545 and 206233).
AOB0-9: 6 studies (203114, CCI , 207545 and 206233).

Table 14.2.4.1
Summary of Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

BF Measurement	Statistic	Test Adhesive (N = xxx) Observed Value	Change from Baseline	Percentage Change of Baseline from the Maximum [1]	Percentage Change from Maximum [2]	No Adhesive (N = xxx) Observed Value	Change from Baseline	Percentage Change of Baseline from the Maximum [1]	Percentage Change from Maximum [2]
Baseline	n	xx				xx			
	Missing	xx				xx			
	Mean	x.xx				x.xx			
	SD	x.xxx				x.xxx			
	SE	x.xxx				x.xxx			
	Median	x.xx				x.xx			
	Minimum	x.x				x.x			
	Maximum	x.x				x.x			
0.5h	n	xx	xx	xx	xx	xx	xx	xx	xx
	Missing	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	SD	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
	SE	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
	Median	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x	x.x	x.x	x.x	x.x	x.x
---	---	---	---	---	---	---	---	---	---

BF = Bite Force; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
[1] Percentage change of baseline from the maximum is defined as: [(observed bite force – baseline bite force) / (maximum bite force / baseline bite force)] * 100.

[2] Percentage change from the maximum is defined as: [observed bite force / maximum bite force] * 100.
Maximum bite force is defined as the highest bite force measurement observed assessments.
Summary of Bite Force at Baseline are based on data from 7 studies (2031 CCI , 207545, 206233 and L3510566).
Summary of Bite Force at 0.5h are based on data from 6 studies (203114 CCI 7545 and 206233).
Summary of Bite Force at 1h are based on data from 7 studies (203114, CCI , 207545, 206233 and L3510566).
Summary of Bite Force at 3h are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary of Bite Force at 6h are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary of Bite Force at 9h are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary of Bite Force at 12h are based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Table will continue with mean BF measurements at 1h, 3h, 6h, 9h and 12h.
2. Use the following order: Baseline, 0.5h, 1h, 3h, 6h, 9h, 12h.
3. As documented in RAP Text, the udies are included in the summaries:
   Baseline: 7 studies (2031 CCI , 207545, 206233 and L3510566).
   0.5h: 6 studies (203114 CCI 7545 and 206233).
   1h: 7 studies (203114, CCI 207545, 206233 and L3510566).
   3h: 6 studies (203114, CCI , 207545 and 206233).
   6h: 6 studies (203114, CCI , 207545 and 206233).
   9h: 6 studies (203114, CCI 207545 and 206233).
   12h: 6 studies (203114, CCI , 207545 and 206233).

Protocol 213380 Draft/Final

Table 14.2.4.2
Statistical Analysis of Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

BF Measurement	Treatment Group	n	Adjusted Mean (SE) [1]	Comparison with No Adhesive		
				Adjusted Mean Difference (SE) [1]	95% CI [1]	p-value [1]
0.5 h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)			
1h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)			
---	---	---	---	---	---	---

BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates and subject as a random effect.
Adjusted Mean Difference is calculated as Test Adhesive minus No Adhesive suc ence favors Test Adhesive.
Statistical analysis of BF at 0.5h is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of BF at 1h is based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Statistical analysis of BF at 3h is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of BF at 6h is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of BF at 9h is based on data from 6 studies (203114, CCI 207545 and 206233).
Statistical analysis of BF at 12h is based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Table will continue with BF measurements at 3h, 6h, 9h and 12h.
2. Use the following order: 0.5h, 1h, 3h, 6h, 9h, 12h.
3. As documented in RAP Text, the ies are included in the statistical analysis of raw mean BF:
BF at 0.5h: 6 studies (203114, CCI , 207545 and 206233).
BF at 1h: 7 studies (203114, CCI 207545, 206233, and L3510566).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

BF at 3h: 6 studies (203114, CCI , 207545 and 206233).
BF at 6h: 6 studies (203114, CCI , 207545 and 206233).
BF at 9h: 6 studies (203114, CCI 207545 and 206233).
BF at 12h: 6 studies (203114, CCI , 207545 and 206233).

Protocol 213380 Draft/Final

Table 14.2.5.1
Statistical Analysis of Within-Treatment Change from Baseline in Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

Time Point	Treatment Group	n	Adjusted Mean (SE) [1]	95% CI [1]	p-value [1]
0.5 h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
1 h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
---	---	---	---	---	---

BF = Bite force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates and subject as a random effect.
Adjusted Mean Difference is calculated as Test Adhesive minus No Adhesive such that a positive difference favors Test Adhes
ic ysis of within treatment change from baseline in BF (lbs) at 0.5h is based on data from 6 studies (203114, CCI , CCI , CCI , 207545 and 206233).
ic ysis of within treatment change from baseline in BF (lbs) at 1h is based on data from 7 studies (203114, CCI , CCI , 207545, 206233 and L3510566).
ical analysis of within treatment change from baseline in BF (lbs) at 3h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ical analysis of within treatment change from baseline in BF (lbs) at 6h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ical analysis of within treatment change from baseline in BF (lbs) at 9h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ysis of within treatment change from baseline in BF (lbs) at 12h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Programming Notes:

1. Table will continue with within-treatment change from baseline in BF at 3 h, 6 h, 9 h and 12 h.
2. Use the following order: 0.5 h, 1 h, 3 h, 6 h, 9 h, 12 h.
3. As documented in RAP Text, the following individual studies are included sis of raw mean BF:
   - Within treatment change from baseline in BF at 0.5h: 6 studies (203114, CCI , 207545 and 206233).
   - Within treatment change from baseline in BF at 1h: 7 studies (203114, CCI 207545, 206233, and L3510566).
   - Within treatment change from baseline in BF at 3h: 6 studies (203114, CCI , 207545 and 206233).
   - Within treatment change from baseline in BF at 6h: 6 studies (203114, CCI , 207545 and 206233).
   - Within treatment change from baseline in BF at 9h: 6 studies (203114, CCI 207545 and 206233).
   - Within treatment change from baseline in BF at 12h: 6 studies (203114, CCI , 207545 and 206233).

Table 14.2.6.1
Summary of Area Over Baseline (lbs) by Treatment Group and Kapur Index Score
ITT Population

Study: Pooled
Subgroup: Fair (<=4)
Analysis Population: ITT (N = xxx)

Endpoint	Statistic	Test Adhesive (N = xxx)	No Adhesive (N = xxx)
AOB 0-12	n	xx	xx
	Missing	xx	xx
	Mean	x.xx	x.xx
	SD	x.xxx	x.xxx
	SE	x.xxx	x.xxx
	Median	x.xx	x.xx
	Minimum	x.x	x.x
	Maximum	x.x	x.x
AOB 0-0.5	n	xx	xx
	Missing	xx	xx
	Mean	x.xx	x.xx
	SD	x.xxx	x.xxx
	SE	x.xxx	x.xxx
	Median	x.xx	x.xx
	Minimum	x.x	x.x
	Maximum	x.x	x.x
---	---	---	---

AOB = Area Over Baseline; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
Higher values of AOB demonstrate a stronger bite force over time.
Summary statistics of AOB0-12 are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary statistics of AOB0-0.5 are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary statistics of AOB0-1 are based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Summary statistics of AOB0-3 are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary statistics of AOB0-6 are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary statistics of AOB0-9 are based on data from 6 studies (203114, CCI , 207545 and 206233).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Program Run Date: DDMMMYYYY:HH:MM
Program: xxxxxx.sas
Page x of y
Source: Dataset

Programming Notes:

1. Table will continue with AOB 0-0.5, AOB0-1, AOB 0-3, AOB 0-6 and AOB 0-9.
2. Use the following order: AOB0-12, AOB0-0.5, AOB0-1, AOB0-3, AOB0-6, AOB0-9.
3. Table will continue with Kapur Index Score categories "Good (5-7)" and "Very Good (>7).
4. Table will present summaries both for pooled data and individual studies. Start with pooled data and indicate Study as "Pooled". Then continue with individual studies. For presentation of individual studies, use the following treatment column labels:
   - Super Poligrip Free Adhesive Cream (USA); Test adhesive 1 (CCI); Test adhesive 2 (CCI No Adhesive.
   - CCI No Adhesive; Positive Control Adhesive: Super Poligrip Denture Adhesive Cream, Original, USA (CCI Test : New Mineral Oil Formulation (CCI
   - CCI Test Adhesive: New Mineral Oi tion (CCI No Adhesive; Positive Control Adhesive: Super Poligrip Denture Adhesive Cream, USA (CCI
   - CCI Test adhesive 1: CMC/HPMC/Kon CCI Test adhesive 2: CMC/Xanthan/HPMC/Konjac - CCI rnets Denture Fixative Powder - CCI ligrip Original Denture Adhesive Cream – USA Mar CCI
   - **207545**: Protefix Denture Adhesive, Creme Mint (Germany marketplace); No Adhesive; Super Poligrip Free Adhesive Cream (USA marketplace).
   - **206223**: Test Adhesive 2 - CCI Super Poligrip Free Adhesive Cream (USA marketplace); No Adhesive; Test Adhesive 1 6.
   - CCI **-09**: Poligrip Gum Care Free Denture Adhesive (CCI
   - CCI "Test Adhesive 1: CMC/Xanthan Gum 1"; "Test Adhesive 2: CMC/Xanthan Gum 2"; "Test Adhesive 3: CMC/Xanthan Gum 3"; Positive Control: Super Poligrip Original (US)".
   - **L3510566**: SPG Original denture adhesive (CCI SPG Free (CCI SPG Comfort Seal Strips (CCI), No adhesive.
5. As documented in RAP Text, t tudies are included in the summaries:
   AOB0-12: 6 studies (203114, CCI 207545 and 206233).
   AOB0-0.5: 6 studies (203114 CCI , 207545 and 206233).
   AOB0-1: 7 studies (203114, CCI , 207545, 206233 and L3510566).
   AOB0-3: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-6: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-9: 6 studies (203114, CCI , 207545 and 206233).
6. Repeat for **Table 14.2.6.3**:
   - Title: Table 14.2.6.3 Summary of Area Over Baseline (lbs) by Treatment Group and DBTs Score
   - Population: ITT Population
   - Additional Notes:
     - DBTs groups are: "Low (<7)", "Medium (7-9)", High (>9)".
     - Update first footnote to: AOB = Area Over Baseline; DBTs = Denture Bearing Tissues; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
7. Repeat for **Table 14.2.6.5**:
   - Title: Table 14.2.6.5 Summary of Area Over Baseline (lbs) by Treatment Group and Baseline Bite Force Measurement
   - Population: ITT Population
   - Additional Notes:

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

- Baseline BF Measurement groups are: "<= 2.5 lbs", "> 2.5 lbs".
- Update first footnote to: AOB = Area Over Baseline; BF = Bite Force; SD = Standard Deviation; SE = Standard Error; lbs = Pound.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.6.2
Statistical Analysis of Area Over Baseline (lbs) by Treatment Group and Kapur Index Score
ITT Population

Subgroup: Fair (<=4)
Analysis Population: ITT (N = xxx)

Endpoint	Treatment Group	n	Adjusted Mean (SE) [1]	95% CI [1]	p-value [1]	Comparison with No Adhesive		
						Adjusted Mean Difference (SE) [1]	95% CI [1]	p-value [1]
AOB 0-12	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx			
AOB 0-0.5	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx			
---	---	---	---	---	---	---	---	---

AOB = Area Over Baseline; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates and subject as a random effect.
Adjusted Mean Difference is calculated as Test Adhesive minus No Adhesive ference favors Test Adhesive.
Statistical analysis of AOB0-12 is based on data from 6 studies (203114, CCI 207545 and 206233).
Statistical analysis of AOB0-0.5 is based on data from 6 studies (203114 CCI , 207545 and 206233).
Statistical analysis of AOB0-1 is based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Statistical analysis of AOB0-3 is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of AOB0-6 is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of AOB0-9 is based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Table will continue with AOB 0-1, AOB 0-3, AOB 0-6 and AOB 0-9.

2. Use the following order: AOB0-12, AOB0-0.5, AOB0-1, AOB0-3, AOB0-6, AOB0-9.
3. Table will continue with Kapur Index Score categories "Good (5-7)" and "Very Good (>7).
4. As documented in RAP Text, th tudies are included in the statistical analysis of AOB:
   AOB0-12: 6 studies (203114, CCI 207545 and 206233).
   AOB0-0.5: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-1: 7 studies (203114, CCI 207545, 206233, and L3510566).
   AOB0-3: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-6: 6 studies (203114, CCI , 207545 and 206233).
   AOB0-9: 6 studies (203114, CCI , 207545 and 206233).
5. Repeat for **Table 14.2.6.4:**
   - Title: Table 14.2.6.4 Statistical Analysis of Area Over Baseline (lbs) by Treatment Group and DBTs Score
   - Population: ITT Population
   - Additional Notes:
     - DBTs groups are: "Low (<7)", "Medium (7-9)", High (>9)".
     - Update first footnote to: AOB = Area Over Baseline; DBTs = Denture Bearing Tissues; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
6. Repeat for **Table 14.2.6.6:**
   - Title: Table 14.2.6.6 Statistical Analysis of Area Over Baseline (lbs) by Treatment Group and Baseline Bite Force Measurement
   - Population: ITT Population
   - Additional Notes:
     - Baseline BF Measurement groups are: "<= 2.5 lbs", "> 2.5 lbs".
     - Update first footnote to: AOB = Area Over Baseline; BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.7.1
Summary of Raw Mean Bite Force (lbs) Over Time by Treatment Group and Kapur Index Score
ITT Population

Study: Pooled
Subgroup: Fair (<=4)
Analysis Population: ITT (N = xxx)

BF Measurement	Statistic	Test Adhesive (N = xxx)		No Adhesive (N = xxx)	
		Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline	n	xx		xx	
	Missing	xx		xx	
	Mean	x.xx		x.xx	
	SD	x.xxx		x.xxx	
	SE	x.xxx		x.xxx	
	Median	x.xx		x.xx	
	Minimum	x.x		x.x	
	Maximum	x.x		x.x	
0.5h	n	xx	xx	xx	xx
	Missing	xx	xx	xx	xx
	Mean	x.xx	x.xx	x.xx	x.xx
	SD	x.xxx	x.xxx	x.xxx	x.xxx
	SE	x.xxx	x.xxx	x.xxx	x.xxx
	Median	x.xx	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x	x.x
---	---	---	---	---	---

BF = Bite Force; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
Summary of Bite Force at Baseline are based on data from 7 studies (2031 02035, 207545, 206233 and L3510566).
Summary of Bite Force at 0.5h are based on data from 6 studies (203114 CCI , 207545 and 206233).
Summary of Bite Force at 1h are based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Summary of Bite Force at 3h are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary of Bite Force at 6h are based on data from 6 studies (203114, CCI , 207545 and 206233).
Summary of Bite Force at 9h are based on data from 6 studies (203114, CCI , 207545 and 206233).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Summary of Bite Force at 12 h are based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM
Program: xxxxxx.sas
Page x of y
Source: Dataset

Programming Notes:

1. Table will continue with mean BF measurements at 1h, 3h, 6h, 9h and 12h.
2. Use the following order: Baseline, 0.5h, 1h, 3h, 6h, 9h, 12h.
3. Table will continue with Kapur Index Score categories "Good (5-7)" and "Very Good (>7).
4. Table will present summaries both for pooled data and individual studies. Start with pooled data and indicate Study as "Pooled". Then continue with individual studies. For presentation of individual studies, use the following treatment column labels:
   - **203114** Super Poligrip Free Adhesive Cream (USA); Test adhesive 1 (CCI Test adhesive 2 (CCI No Adhesive.
   - CCI No Adhesive; Positive Control Adhesive: Super Poligrip Denture Adhesive Cream, Original, USA (CCI Test : New Mineral Oil Formulation (CCI
   - CCI Test Adhesive: New Mineral Oi tion (CCI No Adhesive; Positive Control Adhesive: Super Poligrip Denture Adhesive Cream, USA (CCI
   - CCI : Test adhesive 1: CMC/HPMC/Konjac - CCI Test adhesive 2: CMC/Xanthan/HPMC/Konjac - CCI ernets Denture Fixative Powder - IB0048; ligrip Original Denture Adhesive Cream – USA Mar CCI
   - **207545**: Protefix Denture Adhesive, Creme Mint (Germany marketplace); No Adhesive; Super Poligrip Free Adhesive Cream (USA marketplace).
   - **206223** t Adhesive 2 - CCI Super Poligrip Free Adhesive Cream (USA marketplace); No Adhesive; Test Adhesive 1 CCI
   - CCI **9**: Poligrip Gum Care Free Denture Adhesive (CCI
   - CCI "Test Adhesive 1: CMC/Xanthan Gum 1"; "Test Adhesive 2: CMC/Xanthan Gum 2"; "Test Adhesive 3: CMC/Xanthan Gum itive Control: Super Poligrip Original (US)".
   - **L3510566**: SPG Original denture adhesive (CCI), SPG Free (CCI), SPG Comfort Seal Strips (CCI), No adhesive.
5. As documented in RAP Text, th udies are included in the summaries:
   Baseline: 7 studies (2031 CCI , 207545, 206233 and L3510566).
   0.5h: 6 studies (203114 CCI , 207545 and 206233).
   1h: 7 studies (203114, CCI , 207545, 206233 and L3510566).
   3h: 6 studies (203114, CCI , 207545 and 206233).
   6h: 6 studies (203114, CCI , 207545 and 206233).
   9h: 6 studies (203114, CCI , 207545 and 206233).
   12h: 6 studies (203114, CCI , 207545 and 206233).
6. Repeat for **Table 14.2.7**.
   - Title: Table 14.2.7.3 Summary of Raw Mean Bite Force (lbs) Over Time by Treatment Group and DBTs Score
   - Population: ITT Population
   - Additional Notes:
     - DBTs groups are: "Low (<7)", "Medium (7-9)", High (>9)".
     - Update first footnote to: DBTs = Denture Bearing Tissues; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
7. Repeat for **Table 14.2.7.5**:
   - Title: Table 14.2.7.5 Summary of Raw Mean Bite Force (lbs) Over Time by Treatment Group and Baseline Bite Force Measurement
   - Population: ITT Population

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

- Additional Notes:
  - Baseline BF Measurement groups are: "<= 2.5 lbs", "> 2.5 lbs".
  - Update first footnote to: BF = Bite Force; SD = Standard Deviation; SE = Standard Error; lbs = Pound.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.7.2
Statistical Analysis of Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group and Kapur Index Score
ITT Population

Subgroup: Fair (<=4)
Analysis Population: ITT (N = xxx)

BF Measurement	Treatment Group	n	Adjusted Mean (SE) [1]	Comparison with No Adhesive		
				Adjusted Mean Difference (SE) [1]	95% CI [1]	p-value [1]
0.5 h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)			
1h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)			
---	---	---	---	---	---	---

BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates and subject as a random effect.
Adjusted Mean Difference is calculated as Test Adhesive minus No Adhesive su ence favors Test Adhesive.
Statistical analysis of BF at 0.5h is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of BF at 1h is based on data from 7 studies (203114, CCI 207545, 206233 and L3510566).
Statistical analysis of BF at 3h is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of BF at 6h is based on data from 6 studies (203114, CCI , 207545 and 206233).
Statistical analysis of BF at 9h is based on data from 6 studies (203114, CCI 207545 and 206233).
Statistical analysis of BF at 12h is based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Table will continue with BF measurements at 3h, 6h, 9h and 12h.
2. Use the following order: 0.5h, 1h, 3h, 6h, 9h, 12h.
3. Table will continue with Kapur Index Score categories "Good (5-7)" and "Very Good (>7).

4. As documented in RAP Text, the f ies are included in the statistical analysis of raw mean BF:
   BF at 0.5h: 6 studies (203114, CCI , 207545 and 206233).
   BF at 1h: 7 studies (203114, CCI 207545, 206233, and L3510566).
   BF at 3h: 6 studies (203114, CCI , 207545 and 206233).
   BF at 6h: 6 studies (203114, CCI , 207545 and 206233).
   BF at 9h: 6 studies (203114, CCI 207545 and 206233).
   BF at 12h: 6 studies (203114, CCI , 207545 and 206233).
5. Repeat for **Table 14.2.7.4:**
   - Title: Table 14.2.7.4 Statistical Analysis of Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group and DBTs Score
   - Population: ITT Population
   - Additional Notes:
     - DBTs groups are: "Low (<7)", "Medium (7-9)", High (>9)".
     - Update first footnote to: DBTs = Denture Bearing Tissues; BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
6. Repeat for **Table 14.2.7.6:**
   - Title: Table 14.2.7.6 Statistical Analysis of Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group and Baseline Bite Force Measurement
   - Population: ITT Population
   - Additional Notes:
     - Baseline BF Measurement groups are: "<= 2.5 lbs", "> 2.5 lbs".
     - Update first footnote to: BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.

Protocol 213380 Draft/Final

Table 14.2.8.1
Statistical Analysis of Within-Treatment Change from Baseline in Raw Mean Bite Force (lbs) Measurements Over Time
by Treatment Group and Kapur Index Score
ITT Population

Subgroup: Fair (<=4)
Analysis Population: ITT (N = xxx)

Time Point	Treatment Group	n	Adjusted Mean (SE) [1]	95% CI [1]	p-value [1]
0.5 h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
1h	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx
---	---	---	---	---	---

BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates and subject as a random effect.
Adjusted Mean Difference is calculated as Test Adhesive minus No Adhesive such that a positive difference favors Test Adhesi
ysis of within treatment change from baseline in BF (lbs) at 0.5h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ysis of within treatment change from baseline in BF (lbs) at 1h is based on data from 7 studies (203114, CCI , CCI , 207545, 206233 and L3510566).
ical analysis of within treatment change from baseline in BF (lbs) at 3h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ical analysis of within treatment change from baseline in BF (lbs) at 6h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ical analysis of within treatment change from baseline in BF (lbs) at 9h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).
ysis of within treatment change from baseline in BF (lbs) at 12h is based on data from 6 studies (203114, CCI , CCI , 207545 and 206233).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset

Programming Notes:

1. Table will continue with within-treatment change from baseline in BF at 3h, 6h, 9h and 12h.
2. Use the following order: 0.5h, 1h, 3h, 6h, 9h, 12h.
3. Table will continue with Kapur Index Score categories "Good (5-7)" and "Very Good (>7).
4. As documented in RAP Text, the following individual studies are included in the statistical analysis of raw mean BF:
   Within treatment change from baseline in BF at 0.5h: 6 studies (203114, CCI , 207545 and 206233).
   Within treatment change from baseline in BF at 1h: 7 studies (203114, CCI 207545, 206233, and L3510566).
   Within treatment change from baseline in BF at 3h: 6 studies (203114, CCI , 207545 and 206233).
   Within treatment change from baseline in BF at 6h: 6 studies (203114, CCI , 207545 and 206233).
   Within treatment change from baseline in BF at 9h: 6 studies (203114, CCI 207545 and 206233).
   Within treatment change from baseline in BF at 12h: 6 studies (203114, CCI , 207545 and 206233).
5. Repeat for **Table 14.2.8.2:**
   - Title: Table 14.2.8.2 Statistical Analysis of Within-Treatment Change from Baseline in Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group and DBTs Score
   - Population: ITT Population
   - Additional Notes:
     - DBTs groups are: "Low (<7)", "Medium (7-9)", High (>9)".
     - Update first footnote to: DBTs = Denture Bearing Tissues; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
6. Repeat for **Table 14.2.8.3:**
   - Title: Table 14.2.8.3 Statistical Analysis of Within-Treatment Change from Baseline in Raw Mean Bite Force (lbs) Measurements Over Time by Treatment Group and Baseline Bite Force Measurement
   - Population: ITT Population
   - Additional Notes:
     - Baseline BF Measurement groups are: "<= 2.5 lbs", "> 2.5 lbs".
     - Update first footnote to: BF = Bite Force; CI = Confidence Interval; SE = Standard Error; lbs = Pound.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.9.1
Mean Percentage Change of Baseline Bite Force (lbs) from the Maximum Bite Force Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

Time Point	Test Adhesive (N = xxx)		No Adhesive (N = xxx)	
	Mean Bite Force	Percentage Change	Mean Bite Force	Percentage Change
0.5 h	x.xx	x.xx	x.xx	x.xx
1 h	x.xx	x.xx	x.xx	x.xx
3 h	x.xx	x.xx	x.xx	x.xx
6 h	x.xx	x.xx	x.xx	x.xx
9 h	x.xx	x.xx	x.xx	x.xx
12 h	x.xx	x.xx	x.xx	x.xx

lbs = Pound.
The percentage change of baseline bite force from the maximum bite force is derived based on mean bite force measurements at each time point and is defined as: [(observed bite force – baseline bite force) / (maximum bite force - baseline bite force)] * 100.
Maximum bite force is defined as the highest mean bite force measurement observed at any of post-baseline assessments.
Higher values indicate stronger bite force compared to baseline with respect to the maximum observed bite force.
Mean perc te force from the 5, 3, 6 and 12 hours is derived based on data from 8 studies (203114, CCI , 207545, 206233, CCI).
hour is derived based on data from 9 studies (203114, CCI , CCI , 207545, 206233, CCI and L3510566).
seline bi imum bite force at 9 hours is derived based on data from 6 studies (203114, CCI , 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Use the following order: 0.5h, 1h, 3h, 6h, 9h, 12h.
2. As documented in RAP Text, the following individual studies are included in the summaries:

0.5h: 8 studies (203114, CCI , 207545, 206233 CCI).
1h: 9 studies (203114, CCI 207545, 206233, CCI L3510566).
3h: 8 studies (203114, CCI , 207545, 206233, CCI).
6h: 8 studies (203114, CCI , 207545, 206233, CCI).
9h: 6 studies (203114, CCI 207545 and 20623
12h: 8 studies (203114, CCI , 207545, 206233, CCI).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.10.1
Statistical Analysis of Bite Force (lbs) Measurements at Baseline Including Kapur Index Score and DBTs Score in the Model
ITT Population

Analysis Population: ITT (N = xxx)

Parameter	Effect	p-value [1]
Baseline BF (lbs)	Kapur Index Score	0.xxxx
	DBTs Score	0.xxxx

BF = Bite Force; DBTs = Denture Bearing Tissues; lbs = Pound.
[1] Analysis was performed using ANOVA model with raw Kapur Index Score and raw DBTs Score as fixed effects and subject as a random effect. The presented p-values are from Type 3 tests of fixed effects.
Statistical analysis of bite force measurements at baseline is based on data from 7 studies (203114, CCI [redacted], 207545, 206233, and L3510566).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. [redacted]oled data. As documented in RAP Text, the analysis table will be based on 7 individual studies (203114, CCI [redacted], 207545, 206233, and L3510566).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Protocol 213380 Draft/Final

Table 14.2.11.1
Mean Percentage Change of Bite Force (lbs) from the Maximum Bite Force Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)

Time Point	Test Adhesive (N = xxx)		No Adhesive (N = xxx)	
	Mean Bite Force	Percentage Change	Mean Bite Force	Percentage Change
0.5 h	x.xx	x.xx	x.xx	x.xx
1 h	x.xx	x.xx	x.xx	x.xx
3 h	x.xx	x.xx	x.xx	x.xx
6 h	x.xx	x.xx	x.xx	x.xx
9 h	x.xx	x.xx	x.xx	x.xx
12 h	x.xx	x.xx	x.xx	x.xx

lbs = Pound.
The percentage change of bite force from the maximum bite force is derived based on mean bite force measurements at each time point and is defined as: [observed bite force / maximum bite force] * 100.
Maximum bite force is defined as the highest mean bite force measurement observed at any of post-baseline assessments.
Summary s ge of bite force fr ce at 0.5, 3, 6 and 12 hours are based on data from 8 studies (203114, CCI , 207545, 206233, CCI).
ge of bit ce at 1 hour are based on data from 9 studies (203114, CCI , 207545, 206233, CCI L3510566).
cent change of bit bite force at 9 hours are based on data from 6 studies (203114, CCI , 207545 and 206233).

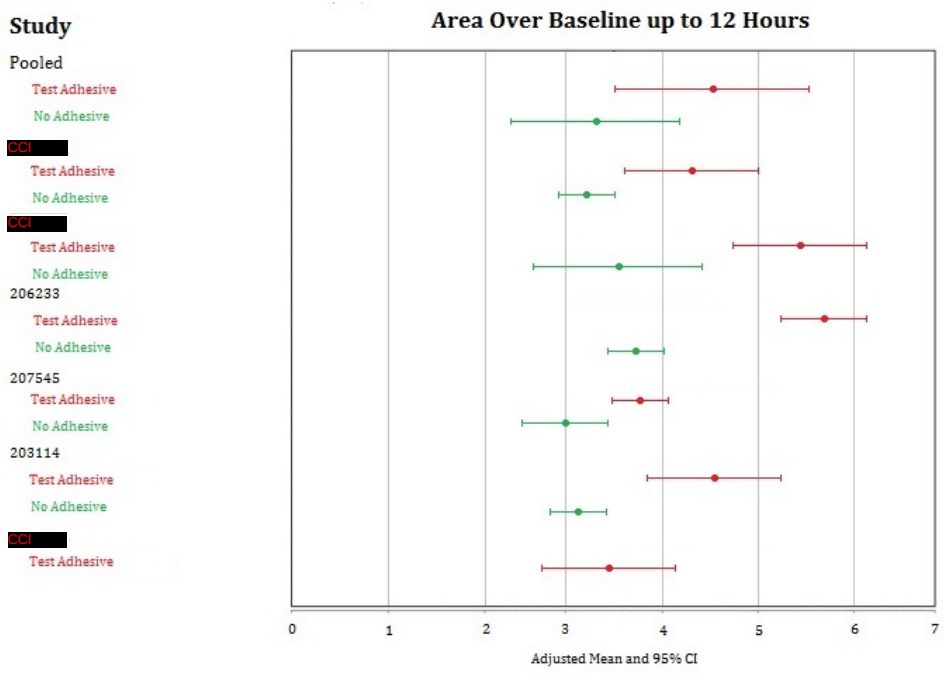
Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:

1. Use the following order: 0.5h, 1h, 3h, 6h, 9h, 12h.
2. As documented in RAP Text, the following individual studies are included in the summaries:

0.5h: 8 studies (203114, CCI , 207545, 206233 CCI).
1h: 9 studies (203114, CCI 207545, 206233, CCI L3510566).
3h: 8 studies (203114, CCI , 207545, 206233, CCI .
6h: 8 studies (203114, CCI , 207545, 206233, CCI).
9h: 6 studies (203114, CCI 207545 and 20623
12h: 8 studies (203114, CCI , 207545, 206233, CCI).

Figure 14.2.3.1
Forest Plot for Area Over Baseline (lbs) up to 12 Hours by Treatment
ITT Population

Analysis Population: ITT (N = xxx)



Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

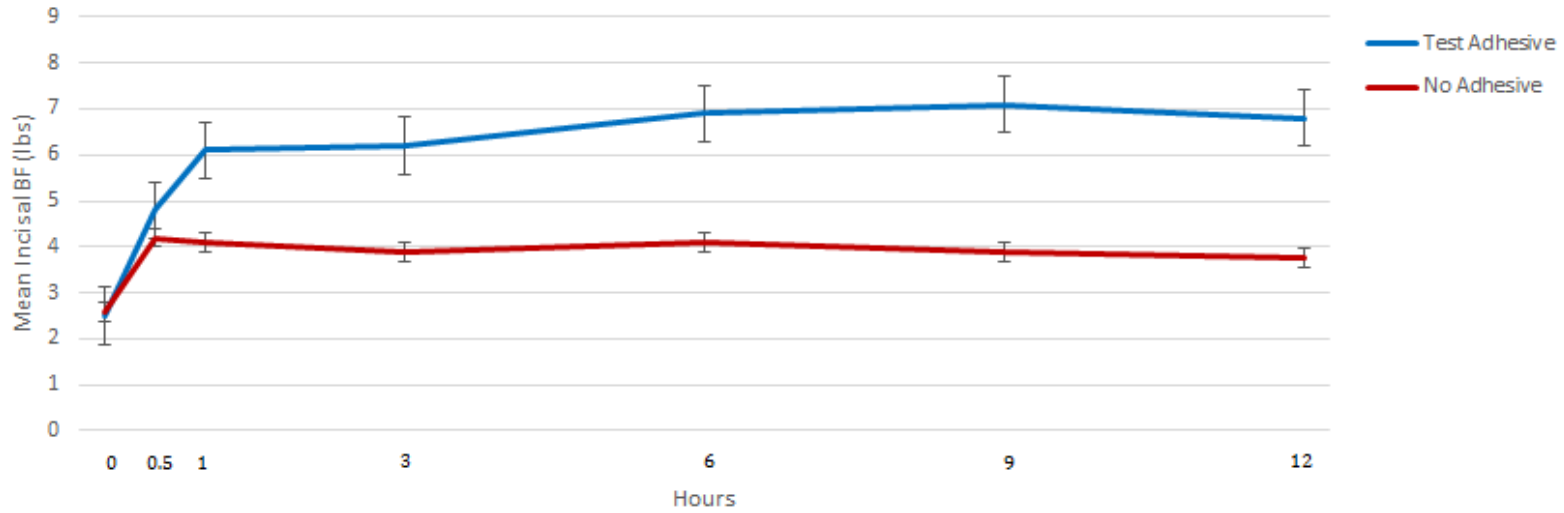
AOB = Area Over Baseline; CI = Confidence Interval; lbs = Pound.
Higher values of AOB demonstrate a stronger bite force over time.
Adjusted Mean and 95% CI are from ANCOVA model with treatment, study and period as fixed effects, subject level baseline and period level baseline minus subject level baseline as covariates a fect.
Forest plot is based on data from 6 studies (203114, CCI , 207545 and 206233).
Individual studies treatment legend:
CCI : Test Adhesive = Super Poligrip Denture Adhesive Cream, Original, USA (CCI); No Adhesive = No Adhesive.
CCI : Test Adhesive = Super Poligrip Original Denture Adhesive Cream, USA (CCI); No Adhesive = No Adhesive.
: Test Adhesive = Super Poligrip Free Adhesive Cream (USA marketplace); sive = No Adhesive.
207545: Test Adhesive = Super Poligrip Free Adhesive Cream (USA marketplace); No Adhesive = No Adhesive.
203114: Test adhesive = Super Poligrip Free Adhesive Cream (USA); No Adhesive = Adhesive.
CCI : Test Adhesive = Super Poligrip Original Denture Adhesive Cream - USA marketplace CCI .

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Forest plot will be based both on pooled data and individual data. Present them in the same order as shown in mock plot.
2. Take Adjusted Mean and 95% CI from ANCOVA model used in Table 14.2.3.1.
3. Present treatments in 3 colors: with red the active adhesive mapped to "Test Adhesive" for pooled data; with green: no adhesive; with blue color all active adhesive that are not used in pooled analysis.

Protocol 213380 Draft/Final

Figure 14.2.4.1
Mean Incisal Bite Force (lbs) Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)
Study: 203114



BF = Bite Force; lbs = Pound.
Mean incisal BF (lbs) measurements for each treatment group is presented on y-axis. Time points (Hours) are presented on x-axis. Individual standard error boundaries are presented in bars.

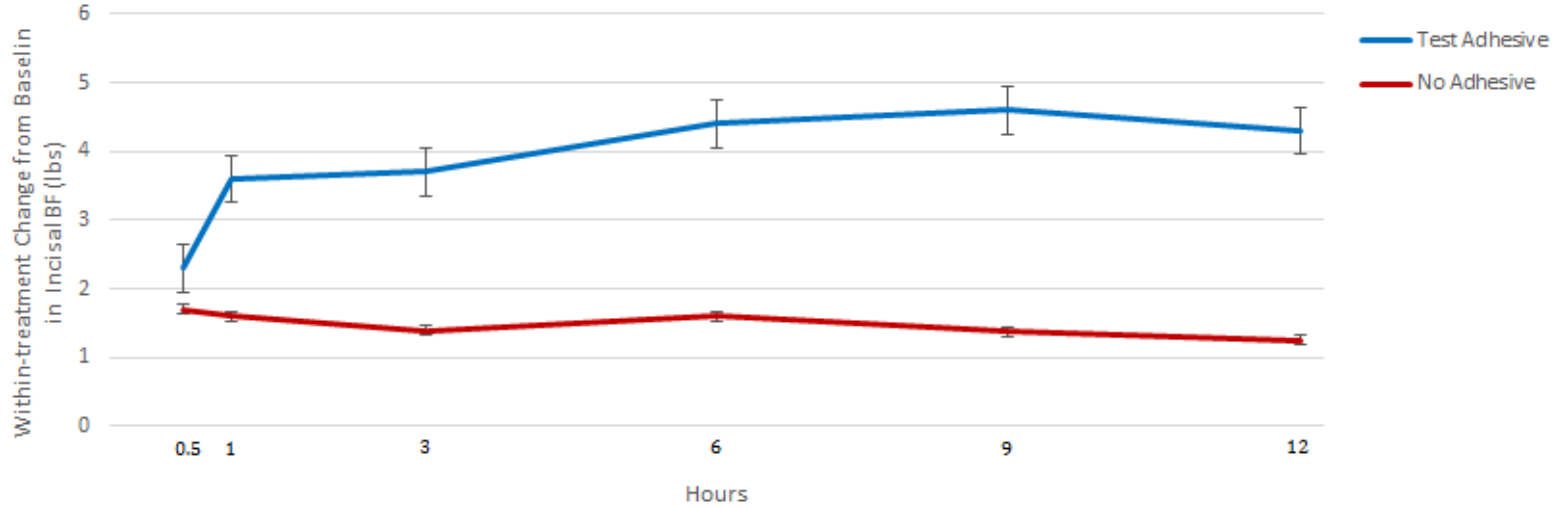
Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

1. Start y-axis from 0. Stagger means.
2. This figure will be produced on pooled data only. Thus, do not present "Study" line.
3. Repeat for **Figure 14.2.4.2:**
   - Title: Figure 14.2.4.2 Mean Incisal Bite Force (lbs) Over Time by Treatment Group and Study
   - Population: ITT Population
   - Additional Notes:
     - Present individual studies – i.e. 1 graph with 9 different plots for each study.
     - Present study line with corresponding study number in the graph, as shown above with red color.
     - For individual studies, present all treatments, as follows:
       - Super Poligrip Free Adhesive Cream (USA); Test adhesive 1 ([redacted] Test adhesive 2 ([redacted] sive.
       - [redacted] No Adhesive; Positive Control Adhesive: Super Poligrip Den sive Cream, Origina [redacted] Test : New Mineral Oil Formulation ([redacted]
       - [redacted] Test Adhesive: New Mineral Oi on [redacted]); No Adhesive; Positive Control Adhesive: Super Poligrip Denture Adhesive Cream, USA ([redacted]
       - [redacted] Test adhesive 1: CMC/HPMC/Ko [redacted]; Test adhesive 2: CMC/Xanthan/HPMC/Konjac - [redacted] Poligrip rnets Denture Fixative Powder - [redacted] per Poligrip Original Denture Adhesive Cream arketplace [redacted]
       - rotefix Denture Adhesive, Creme Mint (Germany marketplace); No Adhesive; Super Poligrip Free Adhesive Cream rketplace).
       - [redacted] Test Adhesive 2 - [redacted]; Super Poligrip Free Adhesive Cream (USA marketplace); No Adhesive; Test Adhesive 1 6.
       - [redacted] **-09**: Poligrip Gum Care Free Denture Adhesive ([redacted]
       - [redacted] "Test Adhesive 1: CMC/Xanthan Gum 1"; "Test Ad CMC/Xanthan Gum 2"; "Test Adhesive 3: CMC/Xanthan Gum itive Control: Super Poligrip Ori US)".
       - **L3510566**: SPG Original denture adhesive ([redacted]), SPG Free ([redacted]), SPG Comfort Seal Strips ([redacted]), No adhesive.
     - For individual studies, present the following time points:
       - 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - **9-09**: 0 (Baseline), 0.5, 1, 3, 6, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 12 hours post-baseline.
       - : 0 (Baseline), 1 hour post-baseline.

Figure 14.2.5.1
Within-Treatment Change from Baseline in Incisal Bite Force (lbs) Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)
Study: 203114



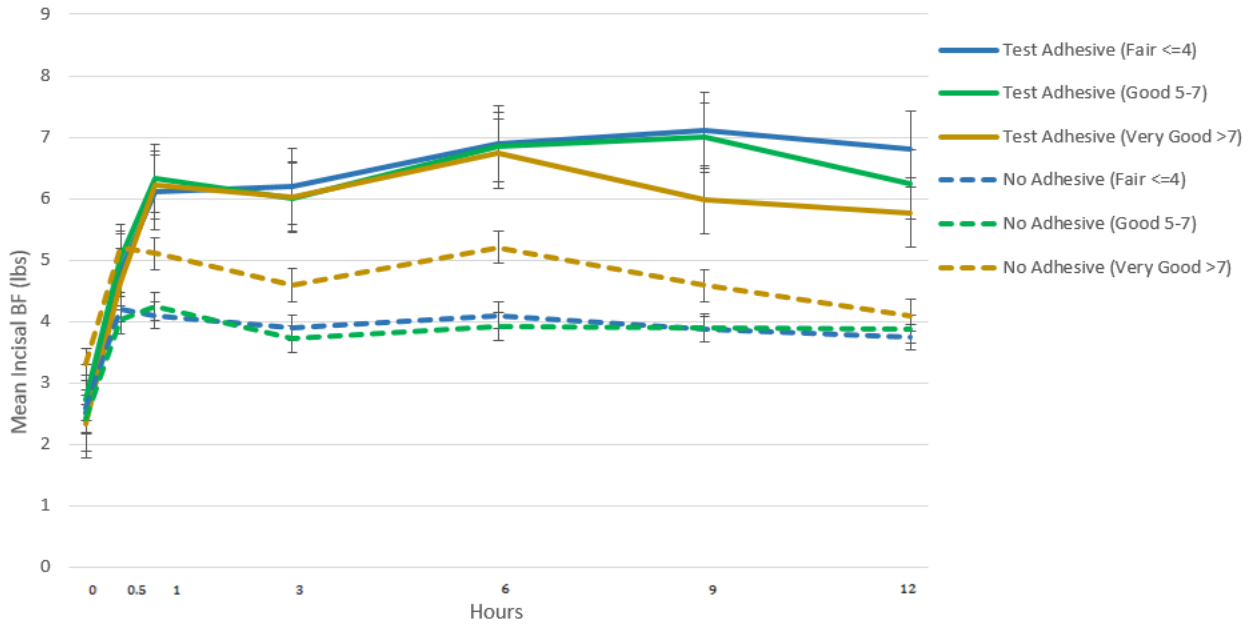
BF = Bite Force; lbs = Pound.
Within-treatment change from baseline in incisal BF (lbs) measurements for each treatment group is presented on y-axis. Time points (Hours) are presented on x-axis. Individual standard error boundaries are presented in bars.

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Start y-axis from 0. Stagger means.

2. This figure will be produced on pooled data only. Thus, do not present "Study" line.
3. Repeat for **Figure 14.2.5.2:**
   - Title: Figure 14.2.5.2 Within-Treatment Change from Baseline in Incisal Bite Force (lbs) Over Time by Treatment Group and Study
   - Population: ITT Population
   - Additional Notes:
     - Present individual studies – i.e. 1 graph with 9 different plots for each study.
     - Present study line with corresponding study number in the graph, as shown above with red color.
     - For individual studies, present all treatments, as follows:
       - **203114**: Super Poligrip Free Adhesive Cream (USA); Test adhesive 1 ([redacted] Test adhesive 2 ([redacted] sive.
       - **RH02446**: No Adhesive; Positive Control Adhesive: Super Poligrip Den sive Cream, Origina [redacted] Test : New Mineral Oil Formulation ([redacted]
       - [redacted] Test Adhesive: New Mineral Oi on ([redacted] No Adhesive; Positive Control Adhesive: Super Poligrip Denture Adhesive Cream, USA ([redacted]
       - [redacted] Test adhesive 1: CMC/HPMC/Ko [redacted] Test adhesive 2: CMC/Xanthan/HPMC/Konjac - [redacted] Poligrip rnets Denture Fixative Powder - IB er Poligrip Original Denture Adhesive Cream arketplace [redacted]
       - rotefix Denture Adhesive, Creme Mint (Germany marketplace); No Adhesive; Super Poligrip Free Adhesive Cream rketplace).
       - [redacted] Test Adhesive 2 - [redacted] Super Poligrip Free Adhesive Cream (USA marketplace); No Adhesive; Test Adhesive 1 6.
       - [redacted] **-09**: Poligrip Gum Care Free Denture Adhesive ([redacted]
       - [redacted] "Test Adhesive 1: CMC/Xanthan Gum 1"; "Test Ad CMC/Xanthan Gum 2"; "Test Adhesive 3: CMC/Xanthan Gum itive Control: Super Poligrip Ori)".
       - **L3510566**: SPG Original denture adhesive ([redacted] SPG Free ([redacted] SPG Comfort Seal Strips ([redacted] No adhesive.
     - For individual studies, present the following time points:
       - 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] (Baseline), 0.5, 1, 3, 6, 9, 12 hours post-baseline.
       - [redacted] **-09**: 0 (Baseline), 0.5, 1, 3, 6, 12 hours post-baseline.
       - [redacted] 0 (Baseline), 0.5, 1, 3, 6, 12 hours post-baseline.
       - : 0 (Baseline), 1 hour post-baseline.

Figure 14.2.6.1
Mean Incisal Bite Force (lbs) Over Time by Treatment Group and Subgroup
ITT Population

Subgroup: Kapur Index Score
Analysis Population: ITT (N = xxx)



BF = Bite Force; DBTs = Denture Bearing Tissues; lbs = Pound.
Mean incisal BF (lbs) measurements for each treatment group by subgroup category is presented on y-axis. Time points (Hours) are presented on x-axis. Individual standard error boundaries are presented in bars.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

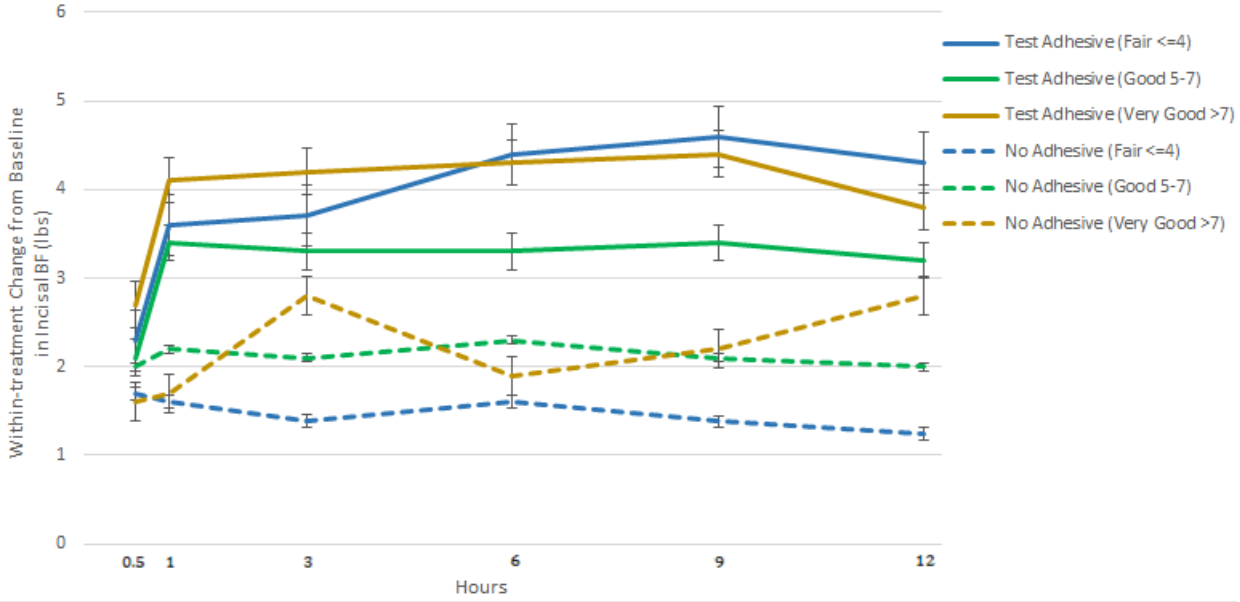
Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset

Programming Notes:

1. Start y-axis from 0. Stagger means.
2. This figure will be produced on pooled data only.
3. The figure will continue with DBTs Score and baseline BF measurements subgroups (i.e. 1 graph with 3 different plots for each subgroup).
4. Groups for DBTs Score are: "Low (<7)", "Medium (7-9)", High (>9)". Groups for baseline BF measurements are: (<= 2.5 lbs; > 2.5 lbs).

Figure 14.2.8.1
Within-Treatment Change from Baseline in Incisal Bite Force (lbs) Over Time by Treatment Group and Subgroup
ITT Population

Subgroup: Kapur Index Score
Analysis Population: ITT (N = xxx)



BF = Bite Force; DBTs = Denture Bearing Tissues; lbs = Pound.
Within-treatment change from baseline in incisal BF (lbs) measurements for each treatment group by subgroup category is presented on y-axis.
Time points (Hours) are presented on x-axis. Individual standard error boundaries are presented in bars.

Program Run Date: DDMMMYYYY:HH:MM Page x of y

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Program: xxxxxx.sas Source: Dataset

Programming Notes:

1. Start y-axis from 0. Stagger means.
2. This figure will be produced on pooled data only.
3. The figure will continue with DBTs Score and baseline BF measurements subgroups (i.e. 1 graph with 3 different plots for each subgroup).
4. Groups for DBTs Score are: "Low (<7)", "Medium (7-9)", High (>9)". Groups for baseline BF measurements are: (<= 2.5 lbs; > 2.5 lbs).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Final Version 1.0 Statistical Reporting and Analysis Plan TFL Shells, 06 Nov 2020

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells, 21 Apr 2021

Protocol 213380 Draft/Final

Table 14.2.2.2
Summary of Area Over Baseline (lbs) Over 12 Hours by Treatment Group for Non-crossover Studies
ITT Population

Analysis Population: ITT (N = xxx)

Endpoint	Statistic	Test Adhesive (N = xxx)	No Adhesive (N = xxx)
AOB 0-12	n	xx	xx
	Missing	xx	xx
	Mean	x.xx	x.xx
	SD	x.xxx	x.xxx
	SE	x.xxx	x.xxx
	Median	x.xx	x.xx
	Minimum	x.x	x.x
	Maximum	x.x	x.x

AOB = Area Over Baseline; SD = Standard Deviation; SE = Standard Error; lbs = Pound.
Higher values of AOB demonstrate a stronger bite force over time.
Summary statistics are based on data from 2 studies CCI

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Note:
1. Use data for CCI and CCI (i.e. non-crossover studies) only to produce this table.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells, 21 Apr 2021

Protocol 213380 Draft/Final

Table 14.2.3.2
Statistical Analysis of Area Over Baseline (lbs) Over 12 Hours by Treatment Group Including All Studies
ITT Population

Analysis Population: ITT (N = xxx)

Endpoint	Treatment Group	n	Adjusted Mean (SE) [1]	95% CI [1]	p-value [1]	Comparison with No Adhesive		
						Adjusted Mean Difference (SE) [1]	95% CI [1]	p-value [1]
AOB 0-12	Test Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx	xx.xx (xx.xxx)	(x.xx, x.xx)	0.xxxx
	No Adhesive (N = xx)	xx	x.xx (x.xxx)	(x.xx, x.xx)	0.xxxx			

AOB = Area Over Baseline; CI = Confidence Interval; SE = Standard Error; lbs = Pound.
[1] Analysis was performed using ANCOVA model with treatment and study as fixed effects and pre-treatment bite force measurement as covariate.
Adjusted Mean Difference is calculated as Test Adhesive minus [redacted]ositive difference
Statistical analysis is based on data from 8 studies (203114, CCI [redacted], 207545, 206233, CCI [redacted]).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Note:
1. Use data for all 8 studies with AOB0-12 derived, as indicated in footnotes.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells, 21 Apr 2021

Protocol 213380 Draft/Final

Table 14.2.4.3
Summary of Time to Maximum Bite Force (lbs)
ITT Population

Analysis Population: ITT (N = xxx)

	Test Adhesive (N = xxx)	No Adhesive (N = xxx)
Time Point [n (%)]		
Baseline	xxx (xx.x)	xxx (xx.x)
0.5 h	xxx (xx.x)	xxx (xx.x)
1 h	xxx (xx.x)	xxx (xx.x)
3 h	xxx (xx.x)	xxx (xx.x)
6 h	xxx (xx.x)	xxx (xx.x)
9 h	xxx (xx.x)	xxx (xx.x)
12 h	xxx (xx.x)	xxx (xx.x)
Hours		
n	xx	xx
Missing	xx	xx
Mean	x.xx	x.xx
SD	x.xxx	x.xxx
SE	x.xxx	x.xxx
Median	x.xx	x.xx
Minimum	x.x	x.x
Maximum	x.x	x.x

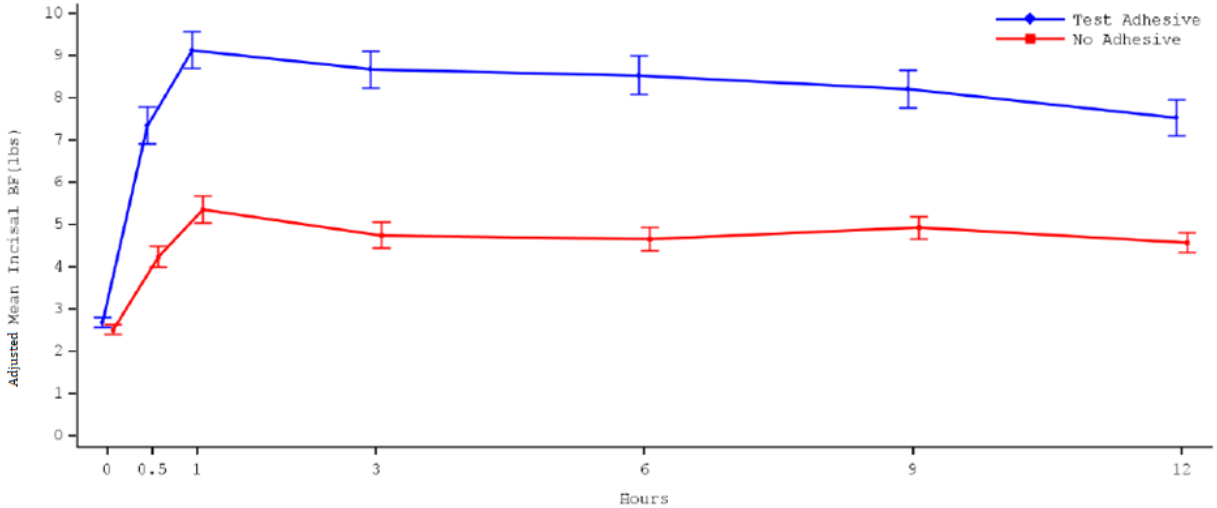
SD = Standard Deviation; SE = Standard Error; lbs = Pound.
Summary o orce (lbs) at Baseline, 0.5h, 3h, 6h, 9h and 12h is based on data from 6 crossover individual studies (203114, CCI , 207545 and 206233).
rce (lbs) at 1h time point is based on data from 7 crossover individual studies (203114, CCI CCI , 207545, 206233 and L3510566).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells #2, 10 Jun 2021

Figure 14.2.4.3
Adjusted Mean Incisal Bite Force (lbs) Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)



BF = Bite Force; lbs = Pound.
Adjusted mean incisal BF (lbs) measurements for each treatment group are presented on y-axis. Adjusted means BF is derived based on Table 14.2.4.2. Raw mean baseline BF is presented at time 0. Time points (Hours) are presented on x-axis. Standard error boundaries are presented in bars.
Bite Force at 0.5h, 3h, 6h, 9h and 12h is based on data from 6 crossover individual studies (203114, CCI [redacted], 207545 and 206233).
Bite Force at 1h time point is based on data from 7 crossover individual studies (203114, CCI [redacted], 207545, 206233 and L3510566).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset

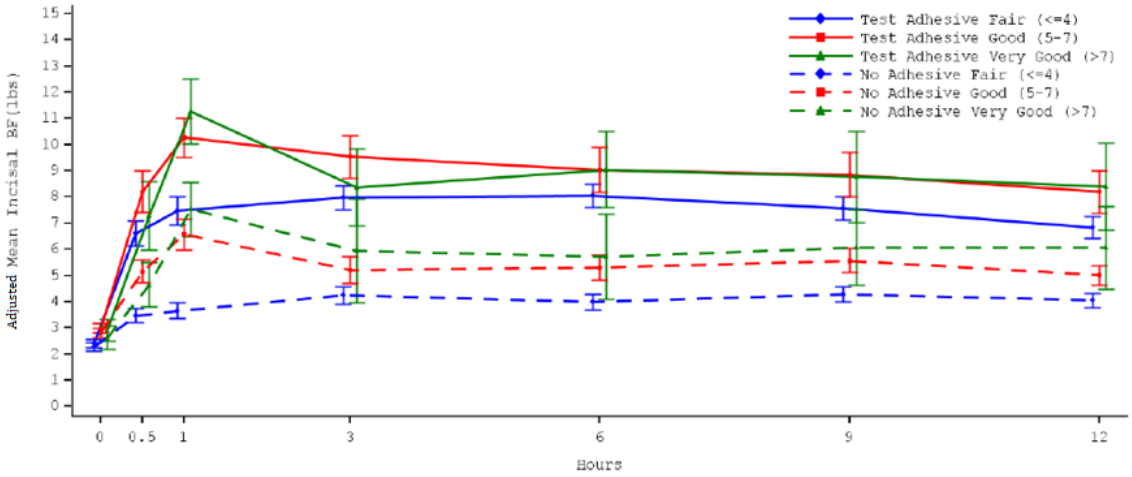
Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells #2, 10 Jun 2021

Programming Notes:

1. Start y-axis from 0. Stagger means.
2. This figure will be produced on pooled data only.
3. Do not present horizontal lines.

Figure 14.2.6.2
Adjusted Mean Incisal Bite Force (lbs) Over Time by Treatment Group and Subgroup
ITT Population

Subgroup: Kapur Index Score
Analysis Population: ITT (N = xxx)



BF = Bite Force; DBTs = Denture Bearing Tissues; lbs = Pound.
Adjusted mean incisal BF (lbs) measurements for each treatment group are presented on y-axis. Adjusted means BF is derived based on Tables 14.2.7.2, 14.2.7.4 and 14.2.7.6. Raw mean baseline BF is presented at time 0. Time points (Hours) are presented on x-axis. Standard error boundaries are presented in bars.
Bite Force at 0.5h, 3h, 6h, 9h and 12h is based on data from 6 crossover individual studies (203114, CCI [redacted], 207545 and 206233).
Bite Force at 1h time point is based on data from 7 crossover individual studies (203114, CCI [redacted], 207545, 206233 and L3510566).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells #2, 10 Jun 2021

Programming Notes:

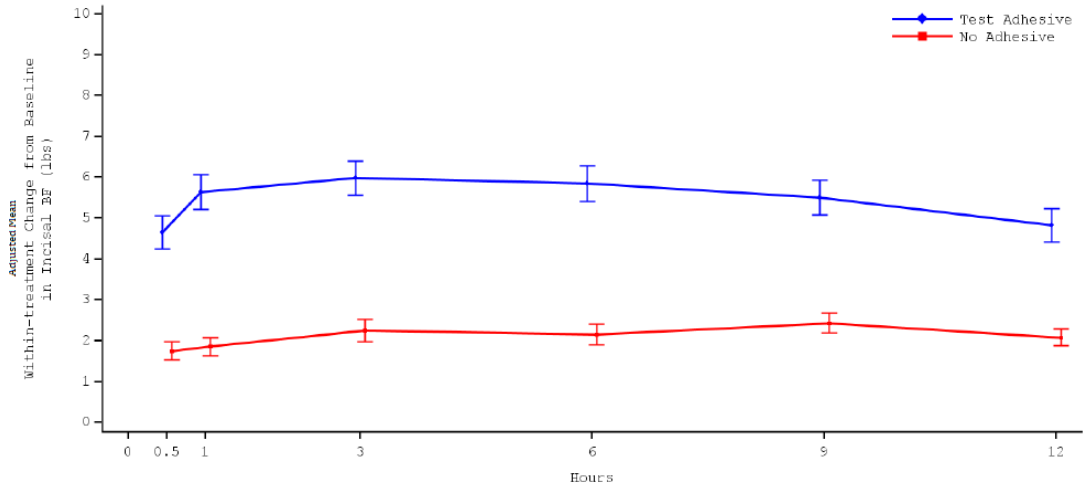
1. Start y-axis from 0. Stagger means.
2. This figure will be produced on pooled data only.
3. Do not present horizontal lines.
4. The figure will continue with DBTs Score and baseline BF measurements subgroups (i.e. 1 graph with 3 different plots for each subgroup).
5. Groups for DBTs Score are: "Poor (<7)", "Satisfactory (7-9)", Good (>9)". Groups for baseline BF measurements are: (<= 2.5 lbs; > 2.5 lbs).

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells #3, 15 Jun 2021

Protocol 213380 Draft/Final

Figure 14.2.5.3
Adjusted Mean Within-Treatment Change from Baseline in Incisal Bite Force (lbs) Over Time by Treatment Group
ITT Population

Analysis Population: ITT (N = xxx)



BF = Bite Force; lbs = Pound.
Adjusted mean within-treatment change from baseline in incisal BF (lbs) measurements for each treatment group are presented on y-axis and is derived based on Table 14.2.5.1. Standard error boundaries are presented
The graph is based on data from 6 crossover individual studies (203114, CCI , 207545 and 206233).

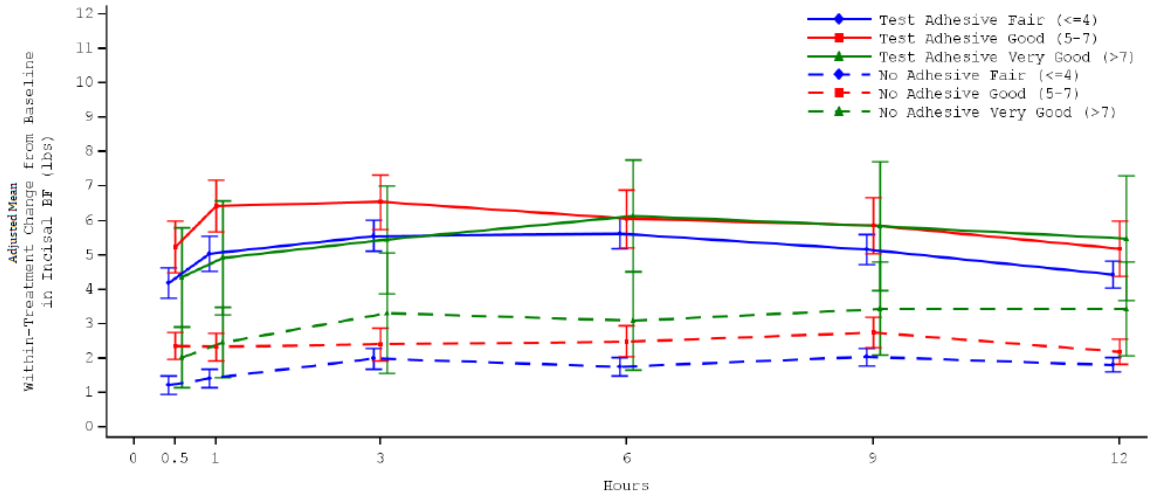
Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Start y-axis from 0. Stagger means.
2. Do not present horizontal lines.

Denture Adhesive (30% PMV/MA & 24% CMC denture adhesive creams)
213380
Additional Statistical Reporting and Analysis TFL Shells #3, 15 Jun 2021

Protocol 213380 Draft/Final

Figure 14.2.8.2
Adjusted Mean Within-Treatment Change from Baseline in Incisal Bite Force (lbs) Over Time by Treatment Group and Subgroup
ITT Population

Subgroup: Kapur Index Score
Analysis Population: ITT (N = xxx)



BF = Bite Force; lbs = Pound.
Adjusted mean within-treatment change from baseline in incisal BF (lbs) measurements for each treatment group are presented on y-axis and is derived based on Tables 14.2.8.1, 14.2.8.2 and 14.2.8.3. Time points (Hours) are presented on x-axis. Standard error boundaries are presented in bars.
The graph is based on data from 6 crossover individual studies (203114, CCI [redacted], 207545 and 206233).

Program Run Date: DDMMMYYYY:HH:MM Page x of y
Program: xxxxxx.sas Source: Dataset
Programming Notes:
1. Start y-axis from 0. Stagger means.

2. This figure will be produced on pooled data only.
3. Do not present horizontal lines.
4. The figure will continue with DBTs Score and baseline BF measurements subgroups (i.e. 1 graph with 3 different plots for each subgroup).
5. Groups for DBTs Score are: "Poor (<7)", "Satisfactory (7-9)", Good (>9)". Groups for baseline BF measurements are: (<= 2.5 lbs; > 2.5 lbs).