CONFIDENTIAL

STATISTICAL ANALYSIS PLAN FOR PROTOCOL 205202

A Method Development Clinical Study to Investigate the Efficacy of the Different Frequencies of Use of a Denture Cleanser

BIOSTATISTICS DEPARTMENT

GLAXOSMITHKLINE CONSUMER HEALTHCARE

PPD

PPD

Timing of Amendment: ☐ Before un-blinding ☒ After un-blinding

Reason for Amendment: Comments received from the clinical site regarding the analysis and clarification of endpoints. Please note all amendments are captured within the SAP text. Please refer to the Objectives & Endpoints document in Statistical analysis plan area which included clarification on endpoints. For further information about on the endpoints clarification please refer to the following document:

CCI [redacted]

In this amended SAP, the endpoints as described in the protocol have been further clarified and therefore differ slightly from the approved clinical protocol. This change has been introduced in the amended SAP as clarification on the endpoints was needed to ensure an appropriate analysis. Endpoints have not been changed, but only clarified in more detail than in the protocol. No objectives have been changed and these remain as per the approved clinical protocol.

The originally approved SAP (version 2.0) available in phoenix is now redundant and this SAP covers all previous analyses and amendments.

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Glossary

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
CFE	Colony Forming Equivalence
CFU/mL	Colony Forming Unit per millilitre
CI	Confidence Interval
CRF	Case Report Form
GSKCH	GlaxoSmithKline Consumer Healthcare
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
OST	Oral Soft Tissue
PII	Personally Identifiable Information
PP	Per Protocol
REP	Repeatability Population
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAQ	Subject Assessment Questionnaire
SD	Standard Deviation
SOC	System Organ Class

1 Introduction

This document describes the statistical methods and data presentations to be used in the summary and analysis of the final data from Protocol 205202.

Typically, the Statistical Analysis Plan (SAP) is approved prior to database freeze. Due to the changes needed for reasons stated above, this SAP amendment will be approved post unblinding.

2 Objectives

Objective	**Endpoint**
Primary Objective	**Endpoint**
• To evaluate and compare the microbial count from Denture Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 7	• Change from baseline (Day 0 pre-treatment) in aerobic bacteria microbial count on Day 7 (post-treatment) from disc samples as measured by colony forming units (CFU/disc) • Change from baseline (Day 0 pre-treatment) in anaerobic bacteria microbial count on Day 7 (post-treatment) from disc samples as measured by colony forming units (CFU/disc) • Change from baseline (Day 0 pre-treatment) in candida microbial count on Day 7 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)
Secondary Objective	**Endpoint**
• To evaluate and compare the microbial count from Denture Disc Samples following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 3	• Change from baseline (Day 0 pre-treatment) in aerobic bacteria microbial count on Day 3 (post-treatment) from disc samples as measured by colony forming units (CFU/disc) • Change from baseline (Day 0 pre-treatment) in anaerobic bacteria microbial count on Day 3 (post-treatment) from disc samples as measured by colony forming units (CFU/disc) • Change from baseline (Day 0 pre-treatment) in candida microbial count on Day 3 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)

Objective	Endpoint
Exploratory Objectives	**Endpoint**
• To evaluate and compare the microbial count from the Denture Sonicate following daily use regimen of a denture cleanser compared to a single (once a week) use regimen on Day 7.	• Change from pre-prophylaxis (Day -1 pre-prophylaxis) in aerobic bacteria microbial count on Day 7 (post-treatment) from the denture sonicate as measured by colony forming units (CFU/denture) • Change from pre-prophylaxis (Day -1 pre-treatment) in anaerobic bacteria microbial count on Day 7 (post-treatment) from the denture sonicate as measured by colony forming units (CFU/denture) • Change from pre-prophylaxis (Day -1 pre-prophylaxis) in candida microbial count on Day 7 (post-treatment) from the denture sonicate as measured by colony forming units (CFU/denture)
• To evaluate and compare plaque levels following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from baseline (Day 0 pre-treatment) in plaque score in the maxillary dentures tissue fitting surface on day 3 and Day 7 (post treatment) • Change from baseline (Day 0 pre-treatment) in plaque score in the maxillary denture polished surfaces on Day 3 and Day 7 (post treatment) • Change from baseline (Day 0 pre-treatment) in plaque score in the maxillary denture teeth (includes facial/buccal and palatal) on Day 3 and Day 7 (post treatment) ** See plaque index details below this table*
• To evaluate and compare the microbial composition from the Disc Sample following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Percentage of microbial composition as assessed by qPCR at Baseline (Day 0, pre-treatment), Day 3 (post-treatment) and Day 7 (post-treatment).

Objective	Endpoint
• To evaluate and compare stain levels on the maxillary denture following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	• Change from baseline (Day 0 pre-treatment) in stain score in the maxillary dentures tissue fitting surface on Day 7 (post treatment) • Change from baseline (Day 0 pre-treatment) in stain score in the maxillary denture polished surfaces on Day 7 (post treatment) • Change from baseline (Day 0 pre-treatment) in stain score in the maxillary denture teeth (includes facial/buccal and palatal) on Day 7 (post treatment) ** See stain index details below this table*
• To evaluate and compare the subject assessment questionnaire following daily use regimen of a denture cleanser compared to a single (once a week) use regimen.	Counts and percentages of scores for each question by treatment

** Stain on the surfaces of the denture will be assessed by modification of the Denture Cleanser Index (Mylonas et al., 2014). The plaque on the denture will be measured by assessing the surfaces of the denture using the modification of the Clinical Categorization of Denture Cleanliness Index (Blair et al., 1995).*

3 Study Design

Overall Design
This is a single-center, 2 treatment period, examiner-blind, randomised, 7 day crossover study in adult volunteers with a complete maxillary denture. This is a method development study to investigate the changes in the microbial counts by disc sampling and denture sonicate, level of denture plaque, microbial composition and stain on the maxillary dentures after daily denture cleanser use versus dentures that are cleaned weekly.
Screening (Visit 1):
The following assessments will be conducted: • Written informed consent • Demographics • Medical history

- Dental History
- Current and concomitant medications
- Criteria for well-made dentures
- Oral Soft Tissue (OST) Examination – Edentulous
- Denture Bearing Tissue Score
- Denture Retention and Stability Assessment
- Inclusion/ Exclusion Criteria
- Subject Eligibility
- Pre-prophylaxis measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
  - Microbiology Sample (Denture Sonicate)
- Denture Prophylaxis & Dental Prophylaxis (if applicable)
- Post-prophylaxis measures
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event Check
- Dispense Diary Card

Treatment Period 1 (Visit 2) & Treatment Period 2 (Visit 6): Day 0

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Pre-treatment measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Treatment Randomisation (Visit 2 Only)
- Dispense Treatment Product/ Supplies
- Supervised Product Use
- Post-treatment measures:
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event and Incident Check

Treatment Period 1 (Visit 3) & Treatment Period 2 (Visit 7): Day 3

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Return Treatment Product/ Supplies
- Compliance Check including Diary Card
- Pre-treatment measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Supervised Product Use
- Post-treatment measures:
  - Plaque Assessment Post-Treatment
  - Microbiology Sample (Disc Sampling) Post-Treatment
- Adverse Event and Incident Check
- Re-dispense Treatment Product/ Supplies and Diary Card

Treatment Period 1 (Visit 4) & Treatment Period 2 (Visit 8): Day 7 and LSLV

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Return Treatment Product/ Supplies
- Compliance Check including Diary Card
- Pre-treatment measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Supervised Product Use
- Post-treatment measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
  - Microbiology Sample (Denture Sonicate)
- Adverse Event and Incident Check
- Denture Prophylaxis & Dental Prophylaxis (if applicable)

LSLV:

- Study Conclusion/ Medical Sign-off

Treatment Period 2 (Visit 5): Day -1

The following assessments will be conducted:

- Current and Concomitant Medications
- Subject Adherence
- OST examination – Edentulous
- Pre-prophylaxis measures:
  - Subject Assessment Questionnaire (SAQ)
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
  - Microbiology Sample (Denture Sonicate)
- Denture Prophylaxis & Dental Prophylaxis (if applicable)
- Post-prophylaxis measures:
  - Stain Assessment
  - Plaque Assessment
  - Microbiology Sample (Disc Sampling)
- Adverse Event and Incident Check
- Dispense Diary Card

3.1 Study Treatment Information

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

	Test Product 1 Daily use period Treatment Regimen 1	**Test Product 2 Weekly use period Treatment Regimen 2**
Product Name	Corega® Tabs Dental Weiss für Raucher German Marketed Product	Corega® Tabs Dental Weiss für Raucher German Marketed Product
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]

Dose	1 tablet per day.	1 tablet on Day 7 at the clinic.
Route of Administration	N/A	N/A
Dosing Instructions	**Supervised product use at site:** Soak dentures in cup of very warm water (150 millilitre [ml]) with 1 tablet for 15 minutes (mins). Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. **Home use:** *In the evening*: ○ **Upper arch:** Soak dentures in cup of very warm water (150 ml) with 1 tablet for 15 mins. Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. Overnight soak in 150 ml of water. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted). If the subjects have lower removable partial or complete dentures, the soaking of these	**Supervised product use at site:** Soak dentures in cup of very warm water (150 ml) with 1 tablet for 15 mins. Brush dentures for 30 seconds using the solution, rinse under running water for 10 seconds. **Home use:** *In the evening*: ○ **Upper arch:** Soak dentures in cup of very warm water (150 ml) for 15 mins. Brush dentures for 30 seconds using the water, rinse under running water for 10 seconds in the evening. Overnight soak in 150 ml of water. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted). If the subjects have lower removable partial or complete dentures, the soaking of these

	dentures should be done in a separate cup from the cup provided for soaking the upper denture. *In the morning*: ○ **Upper arch:** Cleaning of the upper denture is not permitted. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted).	dentures should be done in a separate cup from the cup provided for soaking the upper denture. *In the morning*: ○ **Upper arch:** Cleaning of the upper denture is not permitted. ○ **Lower arch:** The lower arch can be cleaned using the subjects' normal oral hygiene procedures. (Mouthwashes are not permitted).

For Treatment period 2 where subject is randomized to a weekly use, the supervised product use on site on Day 0 and Day 3 will be using water. The denture cleanser tablet will only be used on Day 7.

4 Sample Size Determination

Due to lack of appropriate data it was not possible to perform a formal sample size calculation. A total of 17 subjects were considered sufficient to assess the efficacy and safety of the treatments under investigation. Confidence intervals will be provided to aid precision of treatment estimate.

Approximately 30 healthy subjects will be screened to randomize at least 20 subjects. This will ensure that approximately 17 evaluable subjects will complete the entire study.

5 Data Considerations

5.1 Analysis Populations

Safety Population: Safety population will include subjects who are randomized and

received at least one dose of study product during the study. Safety population summaries will be presented by treatment received.

Intent-to-Treat (ITT) Population: All subjects who are randomized, received at least one dose of study treatment and have at least one post-baseline assessment of microbial count from disc sampling will be included in the ITT population.

ITT will be the primary population for the efficacy assessment. Summaries and analyses based on ITT population will be presented by treatment randomized.

Per-Protocol (PP) Population: PP population will include those subjects who are randomized and received at least one dose of study product and have at least one post baseline efficacy assessment and have no protocol deviation deemed to affect efficacy during the study.

The following will be taken into consideration when determining the protocol violations with the potential to affect efficacy assessment. The exact details of exclusion will be provided in the Review Listing Requirement Document prior to blinded data review meeting.

- Violation of inclusion exclusion criteria
- Significant non-compliance with the treatment
- Significant non-compliance with the study schedule e.g., with regards to durations. All the post treatment samples should be taken within +/- one day time window.
- Uses of prohibited treatment or medication before or during the study which is deemed to affect the assessment of efficacy.
- Significant deviation from planned time of an evaluation.
- Any other reason identified which may affect the assessment of efficacy.
- Bacteria count data will be checked to observe the outliers (mean > 3SD).

Violations deemed to affect efficacy will be identified between the Biostatistician and Clinical Research Director or designee, before breaking the study blind and will be documented in the Population Definition Document. These will be excluded from the PP analysis.

Repeatability (REP) Population: The Repeatability (REP) population will be defined as all subjects in the ITT who have a repeat stain and/or plaque assessment at any visit. This population will be used when performing the repeatability analysis.

5.2 Subgroups/Stratification

No subgroup or stratified analyses are planned.

5.3 Time Windows

The study schedule should be followed as per protocol. Deviations from the study schedule with respect to visit timings will be reviewed on a case-by-case basis to determine whether the data should be excluded from PP analysis. For details of time window allowance refer Review Listing Requirement Document.

6 Demographics and Baseline Characteristics

6.1 Subject Disposition

The subject disposition will include the number of screened subjects and the screen failures overall. The number and percentages of subjects, in the ITT, PP and safety population will be presented by period and treatment group. The number and percentages of subjects who completed the study and who discontinued along with reason for discontinuation will be presented.

Protocol violations leading to exclusion of data from per protocol analysis will be summarized.

6.2 Demographics and Baseline Characteristics

Descriptive statistics (n (number of subjects), mean, median, standard deviation (SD), minimum and maximum for the continuous variables and frequency and percentages for categorical variables) will be provided for demographic variables. The demographic data will include age, gender and race. The demographic will be provided using ITT, PP and Safety population.

7 Treatment Compliance and Concomitant Medications

7.1 Treatment Compliance

Treatment compliance will be reviewed during blinded data review and a listing will

be produced for evaluation of protocol violations only. Non-compliance for any missed and additional denture cleansing will be assessed on a subject by subject basis for each visits, i.e., visit 3 and 7; visit 4 and 8. The data which are regarded as influenced by treatment non-compliance will be excluded from PP analysis. Any subject and/or time point excluded from PP analysis will be clearly documented in population definition document.

7.2 Concomitant Medications

Concomitant medication data will not be presented in the study report. A listing of concomitant medications will be produced for evaluation of protocol violators only.

8 Efficacy Analysis

All the endpoints will be tested under the following general hypotheses.

H_0: There is no treatment difference between daily and weekly product use.

Alternative hypotheses will be -

H_1: There is a treatment difference between daily and weekly product use.

All the statistical analyses will be conducted using statistical software SAS version 9.2.

8.1 Primary Efficacy Analysis

8.1.1 Microbial count at Day 7 - microbiology culture of aerobic bacteria, anaerobic bacteria and candida from disc samples

The primary endpoints are as follows:

- Change from baseline (Day 0 pre-treatment) in aerobic bacteria microbial count on Day 7 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)
- Change from baseline (Day 0 pre-treatment) in anaerobic bacteria microbial count on Day 7 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)
- Change from baseline (Day 0 pre-treatment) in candida microbial count on Day 7 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)

Each microbial count endpoint (aerobic bacteria, anaerobic bacteria and candida,

expressed as CFU/disc) will be analysed separately.

The aerobic bacteria, anaerobic bacteria, candida will be log transformed (base 10) respectively prior to any analysis being performed (i.e., descriptive or statistical analyses). To be able to perform log transformation of zero values a constant (perhaps 1) will be added to all the values in the data prior to log transformation and will be checked for normality assumptions.

Changes in log (base 10) scale from baseline (pre-treatment assessment on Day 0) will be calculated on Day 7 for each of the microbial counts (aerobic bacteria, anaerobic bacteria and candida) separately from the denture disc samples.

This will be analyzed using an analysis of covariance (ANCOVA) model with treatment and period as fixed effects, subject-level (mean across treatment periods) and period-level baseline scores as covariates. To allow model estimates to be representative of the studied population, subject will be included into the model as a random effect. For each treatment group, adjusted means and 95% Confidence Intervals (CIs) and p-value will be calculated. CI and p-values will be calculated for the difference between the treatments as well.

Model assumptions will be investigated using probability plot (Q_Q plot), residual plot and if violated then non-parametric tests such as Wilcoxon Rank Sum test , Signed rank test and/or a rank ANCOVA will be used to investigate any treatment procedure differences.

8.2 Secondary Efficacy Analysis

8.2.1 Microbial count at Day 3 - microbiology culture of aerobic bacteria, anaerobic bacteria and candida from disc samples

The secondary endpoints are as follows:

- Change from baseline (Day 0 pre-treatment) in aerobic bacteria microbial count on Day 3 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)
- Change from baseline (Day 0 pre-treatment) in anaerobic bacteria microbial count on Day 3 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)

- Change from baseline (Day 0 pre-treatment) in candida microbial count on Day 3 (post-treatment) from disc samples as measured by colony forming units (CFU/disc)

These endpoints will be analysed using the same method as for each of the primary endpoints described in section 8.1.1. Also, similar rules for log transformation of the data or adding a constant will be applied to explore the normality assumptions of the data.

8.3 Exploratory Efficacy Analysis

8.3.1 Microbial count at Day 7 - microbiology culture of aerobic bacteria, anaerobic bacteria and candida from denture sonicate

The exploratory endpoints are as follows:

- Change from pre-prophylaxis (Day -1 pre-prophylaxis) in aerobic bacteria microbial count on Day 7 (post-treatment) from the denture sonicate as measured by colony forming units (CFU/denture)
- Change from pre-prophylaxis (Day -1 pre-prophylaxis) in anaerobic bacteria microbial count on Day 7 (post-treatment) from the denture sonicate as measured by colony forming units (CFU/denture)
- Change from pre-prophylaxis (Day -1 pre-prophylaxis) in candida microbial count on Day 7 (post-treatment) from the denture sonicate as measured by colony forming units (CFU/denture)

Each microbial count endpoint (aerobic bacteria, anaerobic bacteria, candida CFU) for the denture sonicate will be analysed separately.

The aerobic bacteria, anaerobic bacteria and candida will be log transformed (base 10) respectively prior to any analysis being performed (i.e., descriptive or statistical analyses). To be able to perform log transformation of zero values a constant (perhaps 1) will be added to all the values in the data prior to log transformation and will be checked for normality assumptions.

Changes in log (base 10) scale from baseline (pre-treatment assessment on Day 0) will be calculated on Day 7 for each of the microbial counts (aerobic bacteria, anaerobic bacteria and candida) separately from the denture disc samples.

This will be analyzed using an analysis of covariance (ANCOVA) model with treatment and period as fixed effects, subject-level (mean across treatment periods)

and period-level baseline scores as covariates. To allow model estimates to be representative of the studied population, subject will be included into the model as a random effect. For each treatment group, adjusted means and 95% Confidence Intervals (CIs) and p-value will be calculated. CI and p-values will be calculated for the difference between the treatments as well.

Model assumptions will be investigated using probability plot (Q_Q plot), residual plot and if violated then non-parametric tests such as Wilcoxon Rank Sum test , Signed rank test and/or a rank ANCOVA will be used to investigate any treatment procedure differences.

8.3.2 Denture Plaque levels at Day 7 and Day 3

The exploratory endpoints are as follows:

- Change from baseline (Day 0 pre-treatment) in plaque score in the maxillary dentures tissue fitting surface on Day 3 and Day 7 (post treatment)
- Change from baseline (Day 0 pre-treatment) in plaque score in the maxillary denture polished surfaces on Day 3 and Day 7 (post treatment)
- Change from baseline (Day 0 pre-treatment) in plaque score in the maxillary denture teeth (includes facial/buccal and palatal) on Day 3 and Day 7 (post treatment)

. The plaque on the denture will be measured by assessing the surfaces of the denture using the modification of the Clinical Categorization of Denture Cleanliness Index (Blair et al., 1995).

The change from baseline in plaque scores at Day 7 and Day 3 in the tissue fitting surface, polished surface and teeth of the maxillary dentures. Each endpoint will be analysed separately using an ANCOVA model with treatment and period as fixed effects, subject-level (mean across treatment periods) and period-level (period level minus subject level) pre-treatment (on Day 0) baseline scores as covariates. To allow model estimates to be representative of the studied population, subject will be included into the model as a random effect. For each treatment group, adjusted means and 95% Confidence Intervals (CIs) and p-value will be calculated. CI and p-values will be calculated for the difference between the treatments as well.

Model assumptions will be investigated respectively using probability plot (Q_Q plot) and residual plot and if violated then suitable transformation or non-parametric tests such as Wilcoxon Rank Sum test, Signed rank test and/or a rank ANCOVA will be used to investigate any treatment differences.

8.3.3 *Microbial Composition at Day 7 and Day 3 from disc samples – assessed by qPCR*

The exploratory endpoints are as follows:

- Percentage of microbial composition of disc samples as assessed by qPCR at Baseline (Day 0, pre-treatment), Day 3 (post treatment) and Day 7 (post treatment).

Molecular microbial data will consists of 8 oral species. Those will be *Candida* sp. (18S generic Candida primers), *Streptococcus* sp *(*using primers for *S. mitis, S. intermedius* and *S. oralis)*, *Actinomyces naeslundii, Veillonella dispar, Lactobacillus casei, Lactobacillus zeae*, *Rothia denticariosa* and *Fusobacterium nucleatum.* The sum off these 8 oral species will be considered as 100%.

No formal statistical analyses or summary statistics will be performed on this data. This data will only be graphically presented. A stacked bar chart will be presented using excel for baseline (Day 0 pre-treatment), Day 3 (post treatment) and Day 7 (post treatment) per treatment for all species

8.3.4 *Denture Stain levels at Day 7*

The endpoints to analyse the stain levels are as follows:

- Change from baseline (Day 0 pre-treatment) in stain score in the maxillary dentures tissue fitting surface on Day 7 (post treatment)

- Change from baseline (Day 0 pre-treatment) in stain score in the maxillary denture polished surfaces on Day 7 (post treatment)

- Change from baseline (Day 0 pre-treatment) in stain score in the maxillary denture teeth (includes facial/buccal and palatal) on Day 7 (post treatment)

Stain on the surfaces of the denture will be assessed by modification of the Denture Cleanser Index (Mylonas et al., 2014)

The change from baseline in stain scores at Day 7 in the tissue fitting surface, polished surface and teeth of the maxillary dentures. Each endpoint will be analysed separately using an ANCOVA model with treatment and period as fixed effects, subject-level (mean across treatment periods) and period-level (period level minus subject level) pre-treatment (on day 0) baseline scores as covariates. To allow model estimates to be representative of the studied population, subject will be included into

the model as a random effect. For each treatment group, adjusted means and 95% Confidence Intervals (CIs) and p-value will be calculated. CI and p-values will be calculated for the difference between the treatments as well.

Model assumptions will be investigated respectively using probability plot (Q_Q plot) and residual plot and if violated then suitable transformation or non-parametric tests such as Wilcoxon Rank Sum test, Signed rank test and/or a rank ANCOVA will be used to investigate any treatment differences.

8.3.5 *Analysis of Subject Assessment Questionnaire (SAQ) at Day 7*

The exploratory endpoint is to summarise counts and percentages of scores for each question by treatment

Frequency and percentages by treatment for each of the four questions for screening and Day 7 pre and post treatment will be used to summarize the SAQ data. Wilcoxon Signed rank test will be used to investigate any differences pre and post treatment application and differences between the two treatments.

8.4 Other Efficacy Analysis

8.4.1 Examiner Repeatability

At each visit, for a random sample of subjects, stain and plaque assessments will be repeated by the examiner. The repeat assessments will be compared to the original assessments for stain and plaque respectively and will not be used in any efficacy analysis.

The first and second assessments on each denture surface (tissue fitting surface, polished surface and teeth) at a given visit will be cross tabulated.

For the area and intensity assessments, a weighted kappa coefficient (κ), along with the 95% CI will be calculated to assess the intra-examiner reliability. Fleiss-Cohen weighted kappa will be calculated for the repeatability analysis for each denture surface (tissue fitting surface, polished surface and teeth) and overall. Reliability will be deemed

- Excellent if $\kappa > 0.75$
- Fair to good if $0.4 \leq \kappa \leq 0.75$
- Poor if $\kappa < 0.4$

All subjects who have repeatability data will be included in this analysis.

8.4.2 Other analysis

Data on microbial composition has also been collected for other visits and time points from denture disc samples, and from the denture sonicate samples which are not included in the endpoints analysis, this data will be plotted and is listed in the Appendix for TLFs Microbial composition has also been analysed by microbiome techniques. This data will be summarized as the number of unique OTU's per sample.

9 Safety Analysis

The safety profile of the study treatments will be assessed with respect to adverse events (AEs). Oral soft tissue (OST) abnormalities will be documented as AEs if they appear or worsen after the initial assessment.

All safety data will be reported for the Safety population as per actual treatment received. All subjects screened will be included in the listing of AEs.

All AEs will be reviewed by the Clinical Research Director or Designee prior to database freeze and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). During this review stage, AEs will be further categorized as oral or non-oral.

AEs will be regarded as treatment emergent if they occur on or after the start date and time of the first treatment use (as determined by start date and time from the EXPOSURE/dispensing panel; if this date is missing a suitable alternative will be used eg date and time of randomisation). All other AEs prior to this will be considered non-treatment emergent.

The following summary tables and listings will be presented by treatment group.

- Table of treatment emergent AEs by Oral/Non-Oral and Preferred Term
- Table of treatment emergent AEs by SOC and Preferred Term
- Table of Treatment emergent treatment related AEs by Oral/Non-Oral and Preferred Term
- Listing of all AEs (including Non-treatment emergent from All Subjects).

- Listing of serious AEs. (if there are none a null listing will be produced, if there are >5 treatment emergent SAEs a table will be produced by SOC and PT)
- Listing of incidents (if there are none a null listing will be produced)
- Table of Non Serious treatment emergent AEs by SOC and Preferred Term. (only produced if there are > 5 Non-SAEs)

No inferential analyses will be performed to compare treatments with respect to safety.

10 Interim Analysis

No interim analyses are planned for this study.

11 Topline Summary

Topline summary will not be presented for this study.

12 Changes to Planned Analysis

Clarifications to the endpoints for each objective and there analyses along with log transformation rules for the data where appropriate has been added to this SAP.

13 References

None.

Appendix 1 Study Schedule

Procedure/ Assessment	Treatment Period 1								Wash-out Period between Treatment Schedules (7 ± 3 Days)	Treatment Period 2							
	Visit 1 Screening		Visit 2		Visit 3		Visit 4			Visit 5		Visit 6		Visit 7		Visit 8	
	Day -1		Day 0		Day 3 (Day 0 + 3d) [±1d]		Day 7 (Day 0+ 7d) [±1d]			Day -1		Day 0		Day 3 (Day 0 + 3d) [±1d]		Day 7 (Day 0+ 7d) [±1d]	
	Pre prophy	Post prophy	Baseline (Pre-trt)	Post trt	Pre trt	Post trt	Pre trt	Post trt		Pre prophy	Post prophy	Baseline (Pre trt)	Post trt	Pre trt	Post trt	Pre trt	Post trt
Informed consent	X																
Demographics	X																
Medical History	X																
Dental History	X																
Current/Concomitant medication	X		X		X		X			X		X		X		X	
Criteria for well made dentures	X																
Oral Soft Tissue (OST) examination – edentulous	X[1]		X[2]		X[2]		X[2]			X[1]		X[2]		X[2]		X[2]	
Denture Bearing Tissue Score	X																
Denture Retention and Stability Assessment	X																
Inclusion /Exclusion Criteria	X																
Subject Eligibility	X																
Subject Adherence			X		X		X			X		X		X		X	
Subject Assessment Questionnaire (SAQ)	X						X	X		X						X	X
Stain Assessment	X	X	X		X		X	X		X	X	X		X		X	X
Plaque assessment	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

Procedure/ Assessment	Treatment Period 1								Wash-out Period between Treatment Schedules (7 ± 3 Days)	Treatment Period 2							
	Visit 1 Screening		Visit 2		Visit 3		Visit 4			Visit 5		Visit 6		Visit 7		Visit 8	
	Day -1		Day 0		Day 3 [±1d]		Day 7 [±1d]			Day -1		Day 0		Day 3 [±1d]		Day 7 [±1d]	
	Pre prophy	Post prophy	Baseline (Pre-trt)	Post trt	Pre trt	Post trt	Pre trt	Post trt		Pre prophy	Post prophy	Baseline (Pre trt)	Post trt	Pre trt	Post trt	Baseline (Pre-trt)	Post trt
Microbiology Sample (Disc Sampling)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Microbiology Sample (Denture Sonicate)	X							X		X							X
Denture Prophylaxis & Dental Prophylaxis (if applicable)	X							X[3]		X							X[3]
Dispense Diary Card		X									X						
Return Diary Card			X[4]		X[4]		X					X[4]		X[4]		X	
Compliance check					X		X							X		X	
Treatment Randomisation			X														
Dispense Treatment / Supplies[5]			X									X					
Return Treatment/ Supplies[5]					X[6]		X							X[6]		X	
Supervised Product Use[7]			X		X		X					X		X		X	
Adverse Events		X[8]	X		X		X			X		X		X		X	
Incidents			X		X		X			X		X		X		X	
Study Conclusion/ Medical Sign-off																	X

[1] OST is performed pre-prophylaxis.
[2] OST is performed pre-treatment.
[3] Final Prophylaxis/cleaning of dentures and teeth (if applicable) to remove stains and build up, post all assessments and questionnaire.
[4] Diary card brought back to the site for compliance check.
[5] Study treatment/ supplies will include the assigned treatment product , denture brush, measuring cylinder and timer.
[6] Study treatment/ supplies brought to the site for compliance check and supervised product use.
[7] For treatment period where subject is randomized to a weekly use, the supervised product use on Day 0 and Day 3 will be using water. The denture cleanser will only be used on Day 7.
[8] Adverse events will be collected from prophylaxis at the Screening visit.

Appendix 2 List of Tables, Figures & Listings

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Table 9.1.2.1	Protocol Violations Leading to Exclusion from Per Protocol Analyses by Treatment (ITT Population)		App3
Table 9.2.1.1	Subject Demographics (Safety Population)		Table 9.2.1.1
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Table 9.2.1.3	Subject Demographics (PP Population)		Table 9.2.1.1
Table 9.3.1.1.1	Summary of aerobic bacteria microbial count (CFU/disc) – by visit for Denture Disc Sample (ITT Population)		App3
Table 9.3.1.1.2	Summary of anaerobic bacteria microbial count (CFU/disc) by visit for Denture Disc Sample (ITT Population)		Table 9.3.1.1.1
Table 9.3.1.1.3	Summary of candida microbial count (CFU/disc) by visit for Denture Disc Sample (ITT Population)		Table 9.3.1.1.1

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Table 9.3.1.2.1	Statistical Analysis of Change from Baseline in aerobic bacteria microbial count (CFU/disc) on Day 3 (post treatment) and Day 7 (post treatment) - Denture Disc Sample (ITT Population)		App3
Table 9.3.1.2.2	Statistical Analysis of Change from Baseline in anaerobic bacteria microbial count (CFU/disc) on Day 3 (post treatment) and Day 7 (post treatment) - Denture Disc Sample (ITT Population)		Table 9.3.1.2.1
Table 9.3.1.2.3	Statistical Analysis of Change from Baseline in candida microbial count (CFU/disc) on Day 3 (post treatment) and Day 7 (post treatment) - Denture Disc Sample (ITT Population)		Table 9.3.1.2.1
Table 9.3.1.3.1	Summary of aerobic bacteria microbial count (CFU/denture) by visit for Denture Sonicate Sample (ITT Population)		Table 9.3.1.1.1
Table 9.3.1.3.2	Summary of anaerobic bacteria microbial count (CFU/disc) –by visit for Denture Sonicate Sample (ITT Population)		Table 9.3.1.1.1
Table 9.3.1.3.3	Summary of candida microbial count (CFU/denture) by visit for Denture Sonicate Sample (ITT Population)		Table 9.3.1.1.1

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Table 9.3.1.4.1	Statistical Analysis of Change from Baseline in aerobic bacteria microbial count (CFU/denture) on Day 7 (post treatment)- Denture Sonicate Sample (ITT Population)		Table 9.3.1.2.1
Table 9.3.1.4.2	Statistical Analysis of Change from Baseline in anaerobic bacteria microbial count (CFU/denture) on Day 7 (post treatment) - Denture Sonicate Sample (ITT Population)		Table 9.3.1.2.1
Table 9.3.1.4.3	Statistical Analysis of Change from Baseline in candida microbial count (CFU/denture) on Day 7 - Denture Sonicate Sample (ITT Population)		Table 9.3.1.2.1
Table 9.3.2.1.1	Summary of Plaque Scores in tissue fitting surfaces on by visit (ITT Population)		Table 9.3.1.1.1
Table 9.3.2.1.2	Summary of Plaque Scores in polished surfaces by visit (ITT Population)		Table 9.3.1.1.1
Table 9.3.2.1.3	Summary of Plaque Scores dentures teeth surface by visit (ITT Population)		Table 9.3.1.1.1
Table 9.3.2.2.1	Statistical Analysis of change from Baseline Plaque Scores in tissue fitting surfaces on Day 3 (pot-treatment) and Day 7 (post-treatment) (ITT Population)		Table 9.3.1.2.1

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Table 9.3.2.2.2	Statistical Analysis of change from Baseline Plaque Scores in polished surfaces on Day 3 (post-treatment) and Day 7 (post-treatment) (ITT Population)		Table 9.3.1.2.1
Table 9.3.2.2.3	Statistical Analysis of change from Baseline Plaque Scores in dentures teeth surfaces on Day 3 (post-treatment) and Day 7 (post-treatment) (ITT Population)		Table 9.3.1.2.1
Table 9.3.2.3.1	Repeatability Analysis of Plaque Scores in tissue fitting surfaces (ITT Population)		App 3
Table 9.3.2.3.2	Repeatability Analysis of Plaque Scores in polished surfaces (ITT Population)		Table 9.3.2.3.1
Table 9.3.2.3.3	Repeatability Analysis of Plaque Scores in dentures teeth surfaces (ITT Population)		Table 9.3.2.3.1
Table 9.3.3.1.1	Summary of Stain Scores in tissue fitting surfaces by visit (ITT Population)		Table 9.3.1.1.1
Table 9.3.3.1.2	Summary of Stain Scores in polished surfaces by visit (ITT Population)		Table 9.3.1.1.1

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Table 9.3.3.1.3	Summary of Stain Scores in dentures teeth surfaces by visit (ITT Population)		Table 9.3.1.1.1
Table 9.3.3.2.1	Statistical Analysis of change from Baseline Stain Scores in tissue fitting surface on Day 7 (post-treatment) (ITT Population)		Table 9.3.1.2.1
Table 9.3.3.2.1	Statistical Analysis of change from Baseline Stain Scores in maxillary dentures polished surfaces on Day 7 (ITT Population)		Table 9.3.1.2.1
Table 9.3.3.2.1	Statistical Analysis of change from Baseline Stain Scores in maxillary dentures tissue teeth on Day 7 (ITT Population)		Table 9.3.1.2.1
Table 9.3.3.3.1	Repeatability Analysis of Stain Level Scores in tissue fitting surfaces (ITT Population)		Table 9.3.2.3.1
Table 9.3.3.3.2	Repeatability Analysis of Stain Level Scores in polished surfaces (ITT Population)		Table 9.3.2.3.1
Table 9.3.3.3.3	Repeatability Analysis of Stain Level Scores in dentures teeth (ITT Population)		Table 9.3.2.3.1
Table 9.3.4.1	Summary of all Microbial species by Treatment and visit (ITT Population)		9.3.1.1.1

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Table 9.3.4.2	Summary of the OTU's from microbiome data (ITT population)		App 3
Table 9.3.5.1	Summary of Subject Assessment Questionnaire (SAQ) Data on Day 7 (ITT Population)		Table 9.3.1.1.1
Table 9.4.1	Listing of Adverse Events All Subjects Screened	X	App 3
Table 9.4.2	Treatment Emergent Adverse Events by Oral/Non-Oral and Preferred Term – Safety Population	X	App 3
Table 9.4.3	Treatment Emergent Treatment Related Adverse Events by Oral/Non-Oral and Preferred Term – Safety Population	X	9.4.2
Table 9.4.4	Treatment Emergent Adverse Events by SOC and Preferred Term – Safety Population	X	
Table 9.4.5*	Listing of Serious Adverse Events All Subjects Screened	X	
Table 9.4.6**	Listing of incidents	X	
Table 9.4.7***	Table of non-serious AEs by SOC and PT	X	
Listing 2.1	Randomization Information	X	App 3
Listing 2.2	OST Abnormalities	X	App 3

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Figure 9.1.1	Plot of Log 10 Raw Means ± SE of Aerobic bacteria microbial count (CFU/disc) for the Denture Disc Sample by Visit and Treatment (ITT Population)		App 3
Figure 9.1.2	Plot of Log 10 Raw Means ± SE of Anaerobic bacteria microbial count (CFU/disc) for the Denture Disc Sample by Visit and Treatment (ITT Population)		Figure 9.1.1
Figure 9.1.3	Plot of Log 10 Raw Means ± SE of Candida microbial count (CFU/disc) for the Denture Disc Sample by Visit and Treatment (ITT Population)		Figure 9.1.1
Figure 9.2.1	Plot of Log 10 Raw Means ± SE of Aerobic bacteria microbial count (CFU/denture) for the Denture Sonicate by Visit and Treatment (ITT Population)		Figure 9.1.1
Figure 9.2.2	Plot of Log 10 Raw Means ± SE of Anaerobic bacteria Count (CFU/denture) for the Denture Sonicate by Visit and Treatment (ITT Population)		Figure 9.1.1
Figure 9.2.3	Plot of Log 10 Raw Means ± SE of Candida microbial count (CFU/denture) for the Denture Sonicate by Visit and Treatment (ITT Population)		Figure 9.1.1
Figure 9.3.1	Raw mean plaque score in tissue fitting surfaces for Day 0 (pre-treatment) Day 3 and Day 7 by Visit and treatment (ITT population)		App 3

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Figure 9.3.2	Raw mean plaque score of polished surfaces by Visit and treatment (ITT population)		Figure 9.3.1
Figure 9.3.3	Raw mean plaque score of dentures teeth by Visit and treatment (ITT population)		Figure 9.3.1
Figure 9.4.1	Stacked Bar Chart of all Microbial species by Treatment for Day 0 (pre-treatment) Day 3 and Day 7 for the Denture Disc Sample (ITT Population)		App3
Figure 9.4.2	Stacked Bar Chart of all Microbial species by Visit and by Treatment for Denture Disc Sample (ITT Population).		Figure 9.4.1
Figure 9.4.3	Stacked Bar Chart of all Microbial species by Visit and by Treatment for Denture Sonicate sample (ITT Population).		Figure 9.4.1
Figure 9.5.1	Raw mean stain score of tissue fitting surfaces by Visit and by treatment (ITT population)		Figure 9.3.1
Figure 9.5.2	Raw mean stain score of polished surfaces by Visit and by treatment (ITT population)		Figure 9.3.1
Figure 9.5.3	Raw mean stain score of dentures teeth by Visit and by treatment (ITT population)		Figure 9.3.1
Figure 9.6	Bar chart for Mean +/- SE Subject Questionnaire Scores by Visit and Treatment (ITT Population)		App3

Table/ Listing/ Figure No.	Table/Listing/Figure Title (including population)	Standard	Template
Figure 9.7.1	Raw mean plaque score of tissue fitting surfaces in maxillary dentures at all pre-post treatment visits by treatment (ITT population)		Figure 9.3.1
Figure 9.7.2	Raw mean plaque score of polished surfaces in maxillary dentures at all pre-post treatment visits by treatment (ITT population)		Figure 9.3.1
Figure 9.7.3	Raw mean plaque score of teeth in maxillary dentures at all pre-post treatment visits by treatment (ITT population)		Figure 9.3.1
Figure 9.8.1	Raw mean stain score of tissue fitting surfaces in maxillary dentures at all pre-post treatment visits by treatment (ITT population)		Figure 9.3.1
Figure 9.8.2	Raw mean stain score of polished surfaces in maxillary dentures at all pre-post treatment visits by treatment (ITT population)		Figure 9.3.1
Figure 9.8.3	Raw mean stain score of teeth in maxillary dentures at all pre-post treatment visits by treatment (ITT population)		Figure 9.3.1

* If there are none, a null listing will be produced. If there are more than 5 SAEs a table will be produced by SOC and Preferred Term.
** If null produce a null listing.
*** Only produced if there are > 5 Non SAE's

Appendix 3 Templates for Tables, Figures & Listing

This is a guideline which will give the guidance of treatment labels and sequence labels that will be used for the table header and in the figures, listings and in the footnotes.

The treatment labels for the column heading will be as follow:

- Daily Use Tablet
- Weekly Use Tablet

The sequence group labels for the column heading will be as follow:

- TRT1-TRT2
- TRT2-TRT1

If required following footnote will be added in the outputs.

Corega Tabs Dental Weiss für Raucher - CCI (1 tablet/Day)- German Marketed Product
Corega Tabs Dental Weiss für Raucher - CCI (1 tablet at Day 7)- German Marketed Product

Protocol: 205202

Table 9.1.1.1
Subject Disposition by Treatment
All Subject Screened

Program Run Date:ddmonyyyy

(All Subject Screened N=XX)

	Daily use Tablet (N=XX)	Weekly Use Tablet (N=XX)	Overall(N=XX) n (%)
TOTAL NUMBER OF SUBJECTS SCREENED	xx (xx.x)	xx (xx.x)	xx (xx.x)
SUBJECTS NOT RANDOMIZED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT MEET STUDY CRITERIA	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADVERSE EVENTS	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC.	xx (xx.x)	xx (xx.x)	xx (xx.x)
SUBJECTS RANDOMIZED	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
PROTOCOL DEVIATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
WITHDRAWAL OF CONSENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
OTHER	xx (xx.x)	xx (xx.x)	xx (xx.x)
SAFETY POPULATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
INTENT TO TREAT POPULATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
PER PROTOCOL POPULATION	xx (xx.x)	xx (xx.x)	xx (xx.x)

Corega Tabs Dental Weiss für Raucher - CCI (1 tablet/day) – German Marketed Product
Corega Tabs Dental Weiss für Raucher - CCI (1 tablet at day 7) – German Marketed Product

Protocol: 205915 Program Run Date:ddmonyyyy

Table 9.1.1.2
Subject Disposition by Treatment Sequence and Period
All Subject Randomized

(All Subject Randomized N=XX)

	TRT1-TRT2 (N=XX) n (%)	TRT2-TRT1 (N=XX) n (%)	Overall (N=XX) n (%)
TOTAL NUMBER OF SUBJECTS SCREENED			xx (xx.x)
SUBJECTS NOT RANDOMIZED			xx (xx.x)
DID NOT MEET STUDY CRITERIA			xx (xx.x)
ADVERSE EVENTS			xx (xx.x)
ETC.			xx (xx.x)
SUBJECTS RANDOMIZED	XX	XX	xx (xx.x)
STARTED PERIOD 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED PERIOD 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE PERIOD 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
PROTOCOL DEVIATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
WITHDRAWAL OF CONSENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
OTHER	xx (xx.x)	xx (xx.x)	xx (xx.x)
WASHOUT PERIOD1			
STARTED PERIOD	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE	xx (xx.x)	xx (xx.x)	xx (xx.x)

	TRT1-TRT2 (N=XX) n (%)	TRT2-TRT1 (N=XX) n (%)	Overall (N=XX) n (%)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC...	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED PERIOD 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE PERIOD 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
PROTOCOL DEVIATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
WITHDRAWAL OF CONSENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
OTHER	xx (xx.x)	xx (xx.x)	xx (xx.x)
WASHOUT PERIOD2			xx (xx.x)
STARTED PERIOD	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC...	xx (xx.x)	xx (xx.x)	xx (xx.x)
STARTED PERIOD 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED PERIOD 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE PERIOD 3	xx (xx.x)	xx (xx.x)	xx (xx.x)

	TRT1-TRT2 (N=XX) n (%)	TRT2-TRT1 (N=XX) n (%)	Overall (N=XX) n (%)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
PROTOCOL DEVIATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
WITHDRAWAL OF CONSENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
OTHER	xx (xx.x)	xx (xx.x)	xx (xx.x)
WASHOUT PERIOD3			
STARTED PERIOD	xx (xx.x)	xx (xx.x)	xx (xx.x)
COMPLETED	xx (xx.x)	xx (xx.x)	xx (xx.x)
DID NOT COMPLETE	xx (xx.x)	xx (xx.x)	xx (xx.x)
ADVERSE EVENT	xx (xx.x)	xx (xx.x)	xx (xx.x)
LOST TO FOLLOW UP	xx (xx.x)	xx (xx.x)	xx (xx.x)
ETC...	xx (xx.x)	xx (xx.x)	xx (xx.x)
SAFETY POPULATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
INTENT TO TREAT POPULATION	xx (xx.x)	xx (xx.x)	xx (xx.x)
PER PROTOCOL POPULATION	xx (xx.x)	xx (xx.x)	xx (xx.x)

Corega Tabs Dental Weiss für Raucher - CCI (1 tablet/day) – German Marketed Product
Corega Tabs Dental Weiss für Raucher - CCI (1 tablet at day 7) – German Marketed Product

Protocol: 205202 Program Run Date:ddmonyyyy

Table 9.1.2.1
Protocol Violations Leading to Exclusion from Per Protocol Analyses
Intent to Treat Population

Study Population: Intent to Treat Population (N=XX)

	Daily Use Tablet (N=XX)		Weekly Use Tablet (N=XX)	
	n	(%)	n	(%)
NUMBER OF SUBJECTS EXCLUDED FROM PER PROTOCOL POPULATION	XX	(XX.X)	XX	(XX.X)
PROTOCOL VIOLATION 1	XX	(XX.X)	XX	(XX.X)
PROTOCOL VIOLATION 2	XX	(XX.X)	XX	(XX.X)
NUMBER OF SUBJECTS WITH AT LEAST ONE PROTOCOL VIOLATION AFFECTING OUTCOME	XX	(XX.X)	XX	(XX.X)
PROTOCOL VIOLATIONS LEADING TO DATA EXCLUSION ONLY				
PROTOCOL VIOLATION 1	XX	(XX.X)	XX	(XX.X)
PROTOCOL VIOLATION 2	XX	(XX.X)	XX	(XX.X)

Corega Tabs Dental Weiss für Raucher - CCI (1 tablet/day) – German Marketed Product
Corega Tabs Dental Weiss für Raucher - CCI (1 tablet at day 7) – German Marketed Product

PPD

Protocol: 205202 Program Run Date:ddmonyyyy

Table 9.2.1.1
Demographics
Safety Population

Study Population: Safety Population (N=XX)

Demographic variables	Overall (N=XX)
SEX n (%)	
MALE	xx (xx.x)
FEMALE	xx (xx.x)
RACE n (%)	
AMERICAN INDIAN OR ALASKA NATIVE	xx (xx.x)
AGE (YEARS)	
N	XX
MEAN	XX.X
SD	XX.XX
MEDIAN	XX.X
MINIMUM	XX
MAXIMUM	XX

7)

Page x of y

PPD

PPD

Programming Note: The categories for all the races should be displayed.

Protocol: 205202 Program Run Date:ddmonyyyy

Table 9.3.1.1.1
Summary of aerobic bacteria microbial count (CFU/disc) - by visit for Denture Disc Sample
Intent to treat Population

Study Population: Intent to Treat Population (N=XX)

Day	Statistics	Daily Use Tablet (N=XX)		Weekly Use Tablet (N=XX)	
		Untransformed Count	Log10(Count+1)	Untransformed	Log10(Count+1)
DAY -1 PRE-PROPHYLAXIS	N	XX	XX	XX	XX
	MISSING	X	X	X	X
	MEAN	XX.XX	XX.XX	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	MEDIAN	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	GEOMETRIC MEAN		XX.XXX		XX.XXX
	MINIMUM	XX.XX	XX.XX	XX.XX	XX.XX
	MAXIMUM	X.XX	X.XX	X.XX	X.XX
DAY -1 POST PROPHYLAXIS	N	XX	XX	XX	XX
	MISSING	X	X	X	X
	MEAN	XX.XX	XX.XX	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	MEDIAN	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	GEOMETRIC MEAN		XX.XXX		XX.XXX
	MINIMUM	XX.XX	XX.XX	XX.XX	XX.XX
	MAXIMUM	X.XX	X.XX	X.XX	X.XX
DAY 0 PRE-TRT (BASELINE)	N	XX	XX	XX	XX
	MISSING	X	X	X	X
	MEAN	XX.XX	XX.XX	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	MEDIAN	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	GEOMETRIC MEAN		XX.XXX		XX.XXX
	MINIMUM	XX.XX	XX.XX	XX.XX	XX.XX
	MAXIMUM	X.XX	X.XX	X.XX	X.XX
DAY 0 POST-(BASELINE)	N	XX	XX	XX	XX
	MISSING	X	X	X	X
	MEAN	XX.XX	XX.XX	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	MEDIAN	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	GEOMETRIC MEAN		XX.XXX		XX.XXX
	MINIMUM	X.XX	XX.XX	XX.XX	XX.XX
	MAXIMUM	X.XX	X.XX	X.XX	X.XX

Corega Tabs Dental Weiss für Raucher - CCI (1 tablet/day) – German Marketed Product
Corega Tabs Dental Weiss für Raucher - CCI (1 tablet at day 7) – German Marketed Product

PPD

Programming Note:

Display Day 3 and 7 pre and post treatment in the same table.

Control the pagination in the table such a way that each treatment's pre and post assessment falls in the same page.

For molecular microbial count data present all species.

Use the table template for other microbial (anaerobic bacteria and Candida) counts as well as listed in the Appendix of list of tables.

Protocol: 205202 Program Run Date:ddmonyyyy

Table 9.3.1.2.1

Statistical Analysis of Change from Baseline in aerobic bacteria microbial count (CFU/disc) on Day 3 (post treatment) and Day 7 (post treatment)- Denture Disc Sample

Intent to treat Population

Study Population: Intent to Treat Population (N=XX)

Day	Statistics	Daily Use Tablet (N=XX)		Weekly Use Tablet (N=XX)	
		Untransformed Change from baseline	Log10{(Count+1) /(Baseline+1)}	Untransformed Change from baseline	Log10{(Count+1)/(Baseline+1)}
DAY 7	N	XX	XX	XX	XX
	MISSING	X	X	X	X
	MEAN	XX.XX	XX.XX	XX.XX	XX.XX
	STANDARD DEVIATION	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	MEDIAN	XX.XXX	XX.XXX	XX.XXX	XX.XXX
	MINIMUM	XX.XX	XX.XX	XX.XX	XX.XX
	GEOMETRIC MEAN[6]		XX.XX		XX.XX
	MAXIMUM	X.XX	X.XX	X.XX	X.XX
	ADJUSTED MEAN[1,2]		XX.XX		XX.XX
	STANDARD ERROR[2]		X.XXX		X.XXX

COMPARISON BETWEEN TREATMENTS	DIFFERENCE [1, 3]	95% CI [1]	P VALUE [1]	RATIO [1,4]	95% CI for RATIO[4]
Daily Use Tablet vs. Weekly use Tablet	X.XX	(XX.XXX,XX.XXX)	X.XXXX	X.X	(XX.XXX,XX.XXX)

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[1] Analyses was performed using ANCOVA Model with Log10 Change from Baseline in Aerobic bacteria Microbial Count as response variable, Treatment and Period as fixed effect, subject level and Period level pre-treatment microbial count as covariates and Subject as random effect.
[2] Within-subject standard errors for Adjusted Means are on the log scale.
[3] Difference is first named treatment minus second named treatment in log10{(count+1)/(baseline+1)} such that a positive difference favors the second named treatment.
[4] Ratio of geometric means obtained by taking the antilog of the treatment difference obtained from the ANCOVA model.
[5] Geometric mean is the geometric mean of the values as 10^ log10(count+1)
[6] Geometric mean is the geometric mean of the ratio of post treatment count to baseline as 10^(Mean log10(count+1)-log10(baseline+1))

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Programming Note: Display the results for Day 3 in the same table. Use footnote 5 against geometric mean at Day 0 Baseline. Use this template for other tables for other microbial (anaerobic bacteria and Candida) counts as well as per Appendix list of outputs.

Protocol: 205202 Program Run Date:ddmonyyyy

Table 9.3.2.1.1
Summary of Plaque Scores in tissue fitting surfaces on by visit
Intent to treat Population

Study Population: Intent to Treat Population (N=XX)

Day	Statistics	Daily Use Tablet (N=XX)	Weekly Use Tablet (N=XX)
DAY -1(PRE-PROPHYLAXIS)	N	X	X
	MISSING	XX.XX	XX.XX
	MEAN	XX.XXX	XX.XXX
	SD	XX.XXX	XX.XXX
	MEDIAN	XX.XX	XX.XX
	MINIMUM	X.XX	X.XX
	MAXIMUM	X.XX	X.XX
DAY -1(POST-PROPHYLAXIS)	N	X	X
	MISSING	XX.XX	XX.XX
	MEAN	XX.XXX	XX.XXX
	SD	XX.XXX	XX.XXX
	MEDIAN	XX.XX	XX.XX
	MINIMUM	X.XX	X.XX
	MAXIMUM	X.XX	X.XX
DAY 0(Baseline)	N	X	X
	MISSING	XX.XX	XX.XX
	MEAN	XX.XXX	XX.XXX
	SD	XX.XXX	XX.XXX
	MEDIAN	XX.XX	XX.XX
	MINIMUM	X.XX	X.XX
	MAXIMUM	X.XX	X.XX
DAY 3	.....	.....	.....
DAY 7 PRE-TRT	N	X	X
	MISSING	XX.XX	XX.XX
	MEAN	XX.XXX	XX.XXX
	SD	XX.XXX	XX.XXX
	MEDIAN	XX.XX	XX.XX
	MINIMUM	X.XX	X.XX
	MAXIMUM	X.XX	X.XX
DAY 7 POST-TRT	N	X	X
	MISSING	XX.XX	XX.XX
	MEAN	XX.XX	XX.XX
	SD	XX.XXX	XX.XXX
	MEDIAN	XX.XX	XX.XX
	MINIMUM	X.XX	X.XX
	MAXIMUM	X.XX	X.XX

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Programming note:

Add the following visits in the table.
Day -1 Pre-Prophylaxis, Day -1 Post-Prophylaxis, Day 0 Baseline (Pre- Treatment) Day 0 Baseline (Post Treatment), Day 3 (Pre Treatment), Day 3 (Post Treatment), Day 7 (Pre Treatment), Day 7 (Post Treatment)

Use this table template to include maxillary dentures polished surfaces and teeth data tables as per the appendix of TLFs.

Protocol: 205202 Program Run Date: ddmonyyyy

Table 9.3.2.3.1
Repeatability Analysis of Plaque Level Scores in maxillary dentures tissue fitting surfaces
Repeatability Population

Study Population: Repeatability (N = xxx)

	Second Assessment				
	Missing	0	1	2	3
First assessment [1]					
MISSING	xx	xx	xx	xx	xx
0	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
1	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3	xx	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

WEIGHTED KAPPA = 0.xxx
95% C.I. = x.xxx, x.xxx

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Note: Percentages are based on total of all non-missing combinations
[1] The first assessment is the one used in the efficacy analysis.
Stain Area:
0 = No visible plaque; no matter adherent to flat plastic instrument on light scraping;
1 = No visible plaque; matter adherent to flat plastic instrument on light scraping;
2 = Deposits of plaque just visible on careful examination without need to confirm by scraping;
3 = Deposits of plaque clearly visible;
4 = Gross plaque deposits (“velvet appearance”)

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Programming note: Please present table for maxillary dentures polished surfaces and teeth.

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Table 9.3.4.2
Summary of OTU's from the microbiome data
Intent to treat population

Study Population: Intent to Treat Population (N=XX)

Treatment	Sample Number	Number of OTU's
Corega Daily Use	401	51
	403	XX
	408	XX
Corega Weekly Use	401	51
	403	XX
	408	XX

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Programming note:
Please use external data spreadsheet "GSK_otu_table.from_biom". The number of OTU's is defined by a value greater than 0 so for example if sample number 401 has 45 non-zero values as OTU's, please present 45 as the number in the third column above.

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Table 9.3.5.1
Summary of Subject Assessment Questionnaire (SAQ) Data on Day 7
Intent to treat Population

Study Population: Intent to Treat Population (N=XX)

Day	Question	Daily Use Tablet (N=XX)	Weekly Use Tablet (N=XX)
Day -1(Pre prophylaxis)	How clean does your denture look (Outside of mouth)?		
	Clean	Xx(xx.x%)	Xx(xx.x%)
	Fairly Clean	Xx(xx.x%)	Xx(xx.x%)
	Not Very Clean	Xx(xx.x%)	Xx(xx.x%)
	Not at all clean	Xx(xx.x%)	Xx(xx.x%)
	Don't Know	Xx(xx.x%)	Xx(xx.x%)
	Missing response	Xx(xx.x%)	Xx(xx.x%)
	Comparison (Pre vs. Post treatment)	P-value	P-value
		0.xxx	0.xxx
	How fresh does your denture look (After placing in mouth)?		
	Clean	Xx(xx.x%)	Xx(xx.x%)
	Fairly Clean	Xx(xx.x%)	Xx(xx.x%)
	Not Very Clean	Xx(xx.x%)	Xx(xx.x%)
	Not at all clean	Xx(xx.x%)	Xx(xx.x%)
	Don't Know	Xx(xx.x%)	Xx(xx.x%)
	Missing response	Xx(xx.x%)	Xx(xx.x%)
	How fresh does your breath feel (After placing in mouth)?		
	Clean	Xx(xx.x%)	Xx(xx.x%)
	Fairly Clean	Xx(xx.x%)	Xx(xx.x%)
	Not Very Clean	Xx(xx.x%)	Xx(xx.x%)
	Not at all clean	Xx(xx.x%)	Xx(xx.x%)
	Don't Know	Xx(xx.x%)	Xx(xx.x%)
	Missing response	Xx(xx.x%)	Xx(xx.x%)
	How clean does your denture feel (running the tongue)?		
	Clean	Xx(xx.x%)	Xx(xx.x%)
	Fairly Clean	Xx(xx.x%)	Xx(xx.x%)
	Not Very Clean	Xx(xx.x%)	Xx(xx.x%)
	Not at all clean	Xx(xx.x%)	Xx(xx.x%)
	Don't Know	Xx(xx.x%)	Xx(xx.x%)
	Missing response	Xx(xx.x%)	Xx(xx.x%)
DAY 7 (Prior to Denture Cleaning)	.....		

Day	Question	Daily Use Tablet (N=XX)	Weekly Use Tablet (N=XX)
DAY 7 (Post Denture Cleaning)	.....		

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Percentages will be calculated using number of subjects available in ITT population in that treatment

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Programming note: Control the pagination for pre and post treatment in a single page. After each question pre and post display test statistic value, ~~CI~~ and p-value.

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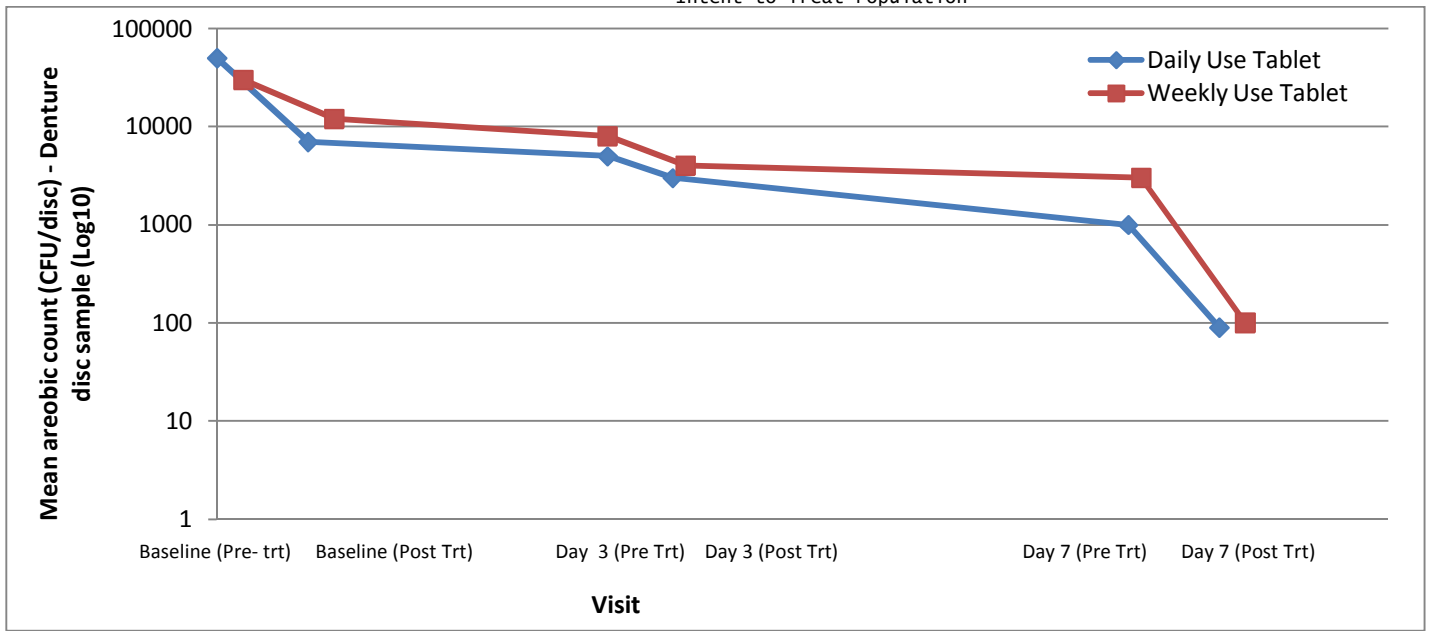
Figure 9.1.1
Plot of Log 10 Raw Means ± SE of Aerobic bacteria microbial count (CFU/disc) for the Denture Disc Sample by Visit and Treatment
Intent to Treat Population



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Programming note:

For the aerobic count figure use the Y-axis in logarithm (base 10) scale. Add the Error Bars.

Please also present the data for anaerobic and candida counts under the same figure number on following pages.

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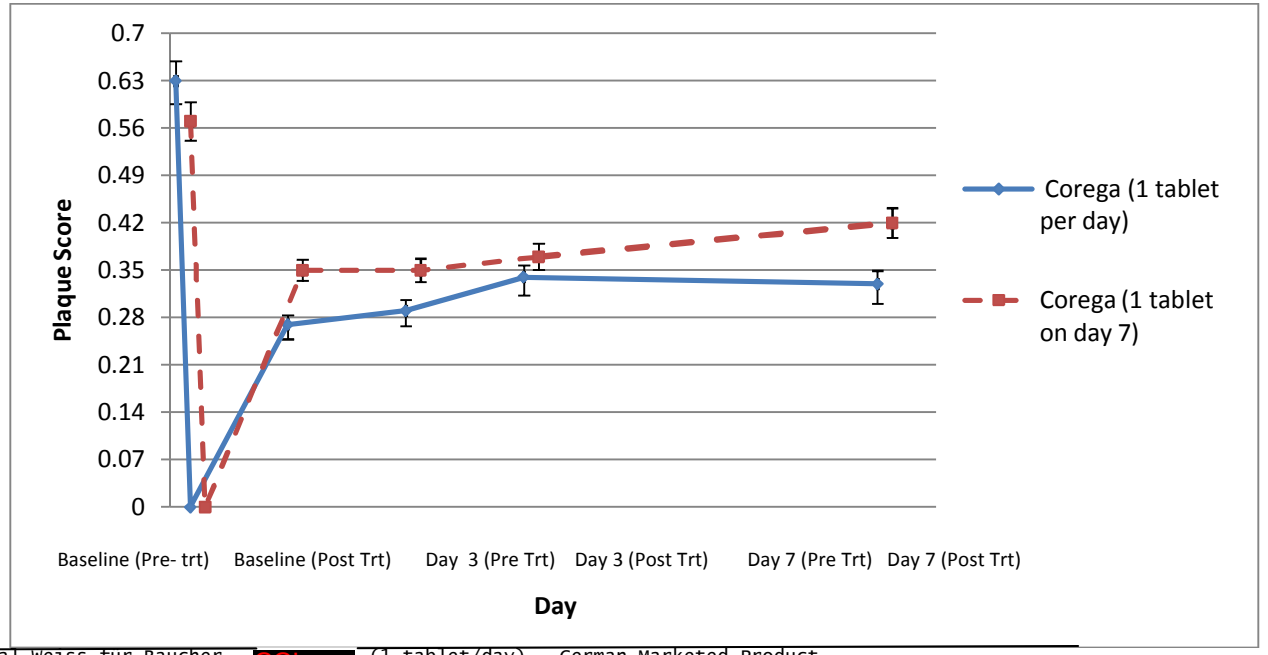
Figure 9.3.1
Raw mean plaque score in tissue fitting surfaces for Day 0 (pre-treatment) Day 3 and Day 7 by Visit and treatment
ITT population



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*Dentures can accumulate plaque and stain over time. The plaque on the denture will be measured by assessing the surfaces of the denture including the teeth using the modification of the Clinical Categorization of Denture Cleanliness Index (Blair et al., 1995).

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Programming note:

Use the actual visits for the, plaque level score for tissue fitting surfaces. For stain outputs use the following footnote:

*Dentures can accumulate plaque and stain over time. Stain on the surfaces of the denture including the teeth will be assessed by modification of the Denture Cleanser Index (Mylonas et al., 2014) before and after use of the denture cleanser treatment regimens.

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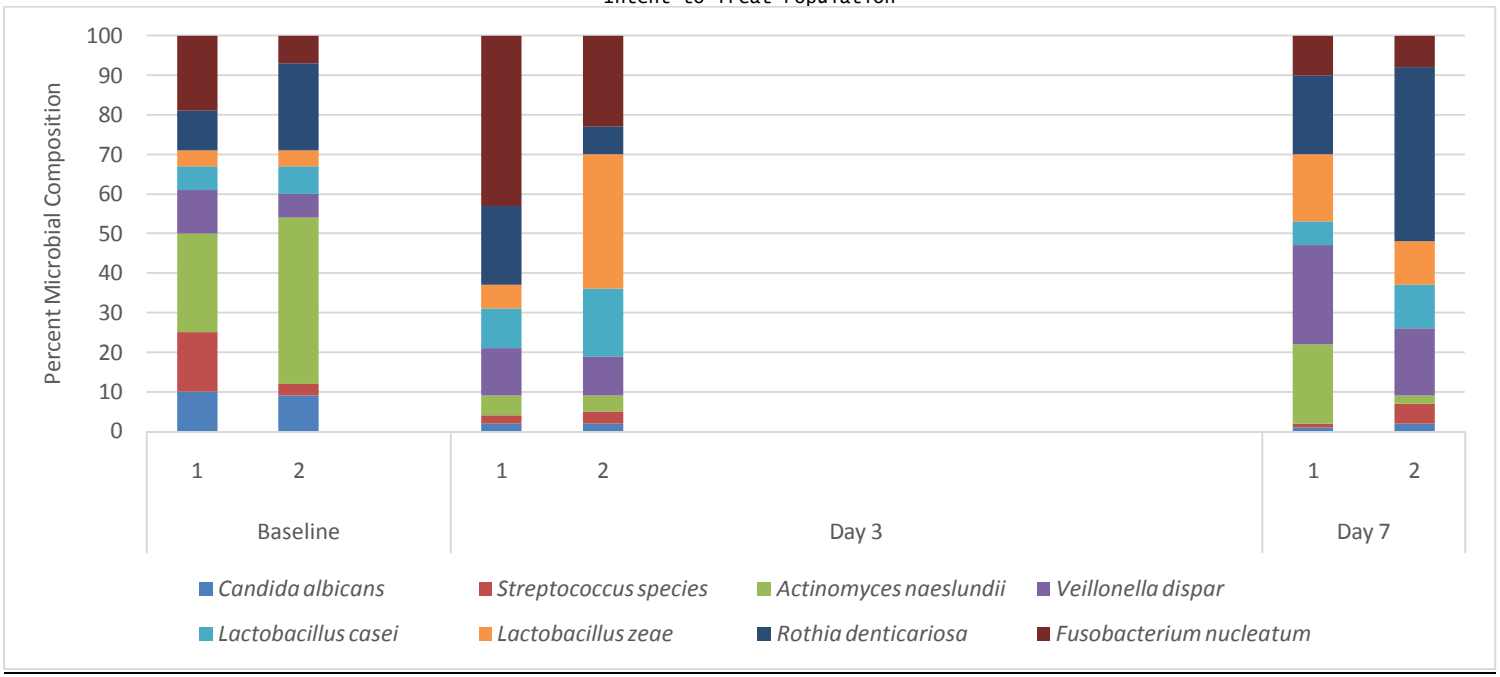
Figure 9.4.1
Stacked Bar Chart of all Microbial species by Treatment for Day 0 (pre-treatment) Day 3 and Day 7 for the Denture Disc Sample
Intent to Treat Population



TRT1: Corega Tabs Dental Weiss für Raucher - CCI (1 tablet/day) – German Marketed Product
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FOOTNOTE FOR REFERENCE: 1:TRT1 & 2:TRT2; This data is from QPCR.

Protocol: 205202

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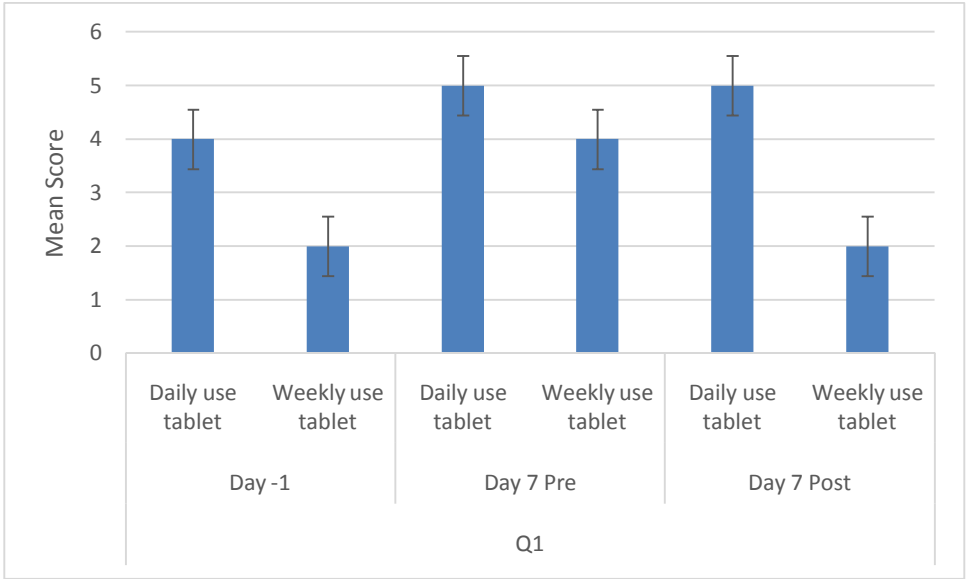
Figure 9.6
Bar Chart for Subject Questionnaire Data
Intent to Treat Population



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Q1: How clean does your denture look?;
Q2: How fresh does your denture feel?;
Q3: How does your breath feel?
Q4: How clean does your denture feel?

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Programming note: Prepare a chart for each question

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SAP Amendment Oct 2017 Final.docx

Date	Signed By
16-Nov-2017 11:20:37	PPD
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16-Nov-2017 11:23:23	PPD
Justification	Biostatistics Approval

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	

Date	Signed By
Justification	