STATISTICAL REPORTING AND ANALYSIS PLAN

Impact of a Nutritional supplement on Bone turnover markers in Indian healthy premenopausal women (25-45 yrs; inclusive) after 6 months of intervention: A randomised double blind controlled trial

Protocol Number: 207192

Phase: N/A

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	13-February-2018	Not applicable (N/A)
Final Statistical Reporting and Analysis Plan Amendment Version 1.0	13-April-2018	1. Section 1.4 is updated for the typo. 2. Seven day dietary intake assessment information is collected at baseline and at Month 6 (visit 6) as per Protocol and eCRF. However, this information was missed while developing the RAP. Therefore, Section 4.6 has been updated to include this information as well as one summary table and one listing. 3. Section 4.4.1.2 is updated with 97.5 % CI. This is because 95% CI was as per protocol just to correct the same RAP section is updated along with tables 14.2.2.2, 14.2.3.2 and 14.2.2.2a, 14.2.3.2a. 4. Section 5, updated to document the changes from the protocol and RAP. 5. The analysis population on template for Table 14.2.2.2a was planned as safety however, there was a typo and it is now updated from ITT to Safety population. 6. The title and the format of the laboratory shift tables (Table 14.3.5.3 till 14.3.12) updated since it will be helpful for the programmers and reviewers... 7. Section 4.7.2 is updated since vendor laboratory confirmed that for the following tests, normal ranges will not be available: Serum Cross-Linked C-Telopeptide of Type 1 Collagen, Ratio of Carboxylated to Under-Carboxylated Osteocalcin, Urinary C-Telopeptide of Type 1 Collagen, Serum Vitamin D (using 25-OH D3), Urinary Calcium/Creatinine Ratio and Serum Folate. The shift tables related to these parameters are deleted and programming note is added for the listings. 8. Added Table 14.2.20.1, for the summary of dietary assessment 9. Deleted two rows from the Table 14.3.1.3 “Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity since those are not required in this table. 10. From listing 16.2.9.3 three columns (Blood collection date and time, kit number and cold chain start time,) have been deleted since these are

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
		same for all blood related parameters and not specific for the HB assessment. Also a footnote is added to explain the meaning of assessment performed (yes/no). 11. Updated the title of all the tables related to the statistical analysis to reflect that the analysis is performed on the change from baseline response variable. 12. Fourth column name in the Listing 16.2.5.1 updated to adjust the space and programming note added.
Final Statistical Reporting and Analysis Plan Addendum Version 1.0	01-June-2018	1. Added Section 4.3.1.1 which details a study product compliance summary by categories 0-3 months and 3-6 months. This is added to check if the difference in compliance could be linked to the difference in the primary parameter results between Month 3 and Month 6. 2. Added statistical model for the sensitivity analysis for log-transformed s-CTX1 in Section 4.4.1.2 3. Added Section 4.4.1.4 which details a subgroup ANCOVA analysis on s-CTX1 change from baseline by age strata at Month 3 and Month 6. This analysis is added to check if age has an impact on the treatment effect. 4. Added statistical model for the sensitivity analysis for log-transformed data for the secondary endpoints in Section 4.4.2. 5. Added Section 4.6.1 which details an ANCOVA analysis on the change from baseline of each dietary intake parameter assessment. This is added to assess if significant changes in dietary intake can be linked to change in primary endpoints at Month 6. 6. Details added to Section 5 summarizing the above ad-hoc analyses with justification and timing.
Final Statistical Reporting and Analysis Plan Addendum Version 2.0	23-July-2018	1. Added section 4.6.2 which details further post hoc analysis for a new lab parameter urine CTX-1 over creatinine ratio (CTX1CR). This variable was not previously specified in the protocol or previous versions of the analysis plan.

Amendments incorporate all revisions to date.

Table of contents

Abbreviation

Abbreviation	Term
AE	Adverse Event
ALP	Alkaline Phosphatase
BDRM	Blinded Data Review Meeting
BSAP	Bone Specific Alkaline Phosphatase
Ca	Calcium
CI	Confidence Interval
c-OC	Carboxylated osteocalcin
c-OC/uc-OC	Ratio of carboxylated osteocalcin to under carboxylated osteocalcin
GSK CH	GlaxoSmithKline Consumer Healthcare
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
P	Phosphorous
PP	Per-Protocol
PT	Preferred Term
s-CTX-1	Serum C-terminal cross-linking telopeptide of type I collagen
s-NTX-1	Serum N-terminal cross-linking telopeptide of type I collagen
s-P1NP	Serum N-terminal propeptide of type I procollagen
SD	Standard Deviation
SE	Standard Error
Se	Selenium
SI	International System of units
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
25 OH D3	25 Hydroxycalciferol
uc-OC	Under carboxylated osteocalcin
u - CTX-1	Urinary C-terminal telopeptide of type I collagen
Zn	Zinc

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 CCI 207192.

1 Summary of Key Protocol Information

Change in life style, dietary habits and environment is known to have significant effect on women's physiology and bones are not spared from the impact. In post-menopausal women, the prevalence of low bone mineral density (BMD), its association to fracture risk and efficacy of pharmacologic therapy to reduce the risk of fractures are well established. The World health Organization (WHO) criteria for diagnosing Osteopenia and Osteoporosis are also based on epidemiological data obtained in post-menopausal women and the treatment guidelines are also targeted for post-menopausal women.

GSK India consumer healthcare has developed a customized nutritional supplement product designed to improve bone health in Indian women. The purpose of this study is to assess efficacy of the supplement on bone health. Two reference bone turnover markers serum C-telopeptide of type I collagen (s-CTX-1) and N-terminal propeptide of type I procollagen (PINP) recommended by International Osteoporosis foundation will be utilized to assess the impact of Women's Horlicks in Indian health pre-menopausal women aged group 25-45 years (inclusive), following six months supplementation.

1.1 Study Design

This is a double blind, single-centre, two-arm, parallel group, randomized-controlled, in 25-45 year old menopausal women. This subject will be stratified by age bands with an aim to recruit a target ratio of 50% in the ≥25-<35 years age band and 50% in the ≥35-≤45 years age band with a minimum of 40% of either age band.

The trial will have two groups.

Test product (Group 1): Protein rich beverage powder fortified with MMN

Reference product (Group 2): Low protein non-fortified iso-caloric beverage powder

1.2 Study Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To compare the changes in Bone Resorption marker: serum C-telopeptide of type 1 collagen (s-CTX-1) at end line 6 months from baseline in test and control groups	• Change from baseline in s-CTX-1 at 6 months
• To compare the changes in the ratio of carboxylated (c-OC) to under-carboxylated	• Change from baseline in the ratio of c-OC to uc-OC at 6 months

Objectives	Endpoints
Osteocalcin (uc-OC) at end line 6 months from baseline in test and control groups	
Secondary Objectives	**Secondary Endpoints**
Efficacy	
• To compare the changes in Bone Resorption marker: serum C-telopeptide of type 1 collagen (s-CTX-1) at mid line 3 months from baseline in test and control groups	• Change from baseline in s-CTX-1 at 3 months
• To compare the changes in the ratio of carboxylated (c-OC) to under-carboxylated Osteocalcin (uc-OC) at mid line 3 months from baseline in test and control groups	• Change from baseline in the ratio of c-OC to uc-OC at 3 months
• To compare the changes in Bone Resorption marker: urinary CTX -1 at mid line 3 months and end line 6 months from baseline in test and control groups	• Change from baseline in urinary CTX-1 at 3 months and at 6 months
• To compare the changes in Bone Resorption marker: serum N-terminal telopeptide of type 1 collagen (s-NTX-1) at mid line 3 months and at end line 6 months from baseline in test and control groups	• Change from baseline in s-NTX-1 at 3 months and at 6 months
• To compare in bone formation marker serum procollagen type 1 N-terminal propeptide (s-P1NP), bone specific alkaline phosphatase (BSAP) at baseline, at mid line 3 months and at end line 6 months in test and control groups	• Change from baseline in s-P1NP and BSAP at 3 months and at 6 months
• To compare calcium status using s-PTH and urinary calcium, serum Ca, P and total alkaline phosphatase (ALP) at mid line 3 months and end line 6 months to see change in level from baseline in both the groups	• Change from baseline in s-PTH and urinary calcium, serum Ca, P and total alkaline phosphatase (ALP) at 3 months and at 6 months
• To compare the changes in Vitamin D status using serum 25-hydroxycholecalciferol (25 OH D3) at mid line 3 months and end line 6 months from baseline in test and control groups	• Change from baseline in 25-hydroxycholecalciferol (25 OH D3) at 3 months and 6 months
• To compare the changes in micronutrient profile status sing serum Se, Folic acid, B12 and plasma Zn and B6 at mid line 3 months and end line 6 months from baseline in test and control groups	• Change from baseline in Se, Folic acid, B12 and plasma Zn and B6 status at 3 months and 6 months
Exploratory Objectives	**Exploratory Endpoints**

Objectives	Endpoints
• To compare the changes in growth markers IGF-1 at mid line 3 months and end line 6 months from baseline in test and control groups	• Change from baseline in IGF-1 at 3 months and 6 months

1.3 Treatments

The study products are as follows:

	Test Product 1	Reference Product 1
Product Name	Cereal based fortified Beverage (Proprietary food)	Low protein non fortified isocaloric beverage
Product Formulation Code (MFC)	CCI [redacted]	CCI [redacted]
Dose	60 grams daily in two divided doses	60 grams daily in two divided doses
Route of Administration	Oral	Oral
Dosing Instructions	30 grams powder made up in 200 mL water, administered twice daily	30 grams powder made up in 200 mL water, administered twice daily

1.4 Sample Size Calculation

The first primary objective for this study is changes in s-CTX-1 levels. Naylor et al. (2015) used bone turnover markers to identify women who responded to bisphosphonate treatment for osteoporosis. The change in CTX with risedronate (above the effect of the calcium and vitamin D supplement) was 30%. Thus, we can say that a 30% reduction has been shown to be associated with a reduction in fractures. Hence, a reduction of 20% in test product as compared to placebo could be considered as a clinically significant difference.

Estimates of mean s-CTX-1 and variability from Kruger et al, 2006 were as follows:

Estimates of s-CTX-1 and variability from Kruger et al, 2006 (Mean ± Standard Deviation [SD]1)

Endpoint		Test Product	Control Product
CTX-1	Baseline	0.45 ± 0.166	0.44 ± 0.032
	Post-Baseline (Week 16)	0.30 ± 0.094	0.46 ± 0.092
	Change from baseline	-0.15 ± 0.144	0.02 ± 0.142

1: Standard Error (SE) values were reported in the paper. SD was calculated as SE*SQRT (N).

SD values for change from baseline were not reported in the paper. These were calculated using following formula considering correlation coefficient between baseline and post-baseline values as 0.5:

$$SD_{E,change} = \sqrt{SD^2_{E,baseline} + SD^2_{E,final} - (2 \times Corr \times SD_{E,baseline} \times SD_{E,final})}$$

SDE,change = SD for change from baseline

SDE,baseline = SD for baseline

SDE,final = SD for post-baseline

Corr = correlation coefficient between baseline and final values

Considering similar baseline values and 20% clinically relevant decrease in test product (lower values are better) from baseline, -0.09 will be used as change from baseline value in test product. This gives a treatment difference of -0.11.

Based on the above estimates of treatment difference and taking the larger estimate for variability (SD = 0.144), to be able to achieve 90% power, 44 participants per treatment arm (Total = 88) will be required to complete the study. This assumes 2.5% level of significance (two tailed t-test).

To allow for 20% drop-out rate, a total of 54 participants (Total = 108) will be randomized per treatment arm.

The co-primary objective for this study is changes in (c-OC/uc-OC) levels. From Binkley et al. the following data related to the end point was received.

From the estimates of %uc-OC, and Total OC from Binkley et al (Mean), the estimates of c-OC have been calculated. From the available data the following table has been tabulated.

Endpoint		Test Product	Control Product
c-OC/uc-OC	Baseline	11.7206	11.96
	Post-Baseline (Week 2)	31.806	18.60
	Change from baseline	20.14	7.53

Considering the delta value as 12.5 and the SD as 13 using Taylor series expansion the sample size to be able to achieve 90% power, 30 participants per treatment arm (Total = 60) will be required to complete the study. This assumes 2.5%% level of significance (two tailed t-test).

To allow for 20% drop-out rate, a total of 36 participants (Total = 72) will be randomized per treatment arm.

However, the sample size for the first primary end point is larger so the sample size will be required for this study is 108 in total.

The sample size is based on the primary endpoint. No sample size considerations have been taken into account for secondary objectives.

Approximately 135 participants will be screened to randomize approximately 108 participants in order to obtain 88 participants completing the study.

Following assumptions have been taken for sample size estimation:

Estimates of s-CTX-1 will be similar in Indian Women as compared to New Zealand Population (Kruger et al, 2006). Product used in Kruger et al, 2006 and in the proposed study will provide similar estimates of s-CTX-1.

Values at 6 months in the proposed study will be similar to values at 4 months from Kruger et al, 2006.

Women 25-35 years old will have similar estimates of s-CTX-1 as 36-45 years old from Kruger et al.

Vitamin K supplementation reduces serum concentrations of under carboxylated osteocalcin in healthy young and elderly adults from Binkley et al.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

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

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

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value. Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

3.2 Subgroups/Stratifications

In this study subjects will be stratified by their age groups defined as follows:

- Stratum 1: Age ≥ 25 years; age < 35 years
- Stratum 2: Age ≥ 35 years; age ≤ 45 years

For details on subgroup analyses please refer to section 4.1.4.

3.3 Centers Pools

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

3.4 Time points and Visit Windows

The time points and visits for this study are defined in the section "Schedule of Events" of the protocol. Any deviation from the study schedule will be reviewed case-by-case basis to determine whether the data should be excluded from the Per-Protocol (PP) population. A time window non-compliance listing will be produced for the Blinded Data Review Meeting (BDRM) only.

4 Data Analysis

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

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

Unless otherwise described below, all listings will be produced for All Randomized Subjects.

4.1 Populations for Analysis

4.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A summary of the number of subjects screened and the number of screen failures with reasons why subjects were not randomized will be presented (Table 14.1.1). For the summary of screen failure subjects the percentages will be based on total number of screened subjects.

Subject disposition will also be summarized by treatment group and overall as the number and percentage of subjects who complete the study, with the number who discontinue broken down by reason for discontinuation (Table 14.1.1). The table will also summarize the number and percent of subjects assigned to each analysis population (refer to Section 4.1.3). The percentage will be based on total number of subjects randomized in each product and overall.

Subject disposition including the subject status (completer, Yes/No), demographic data (age and race), screening date, study product start date and time, the duration in the study or trial [(date/time of completion/withdrawal minus date of first dose administration)+1] and the specific reason for discontinuation, will be listed for randomized subjects (Listing 16.2.1.1.1) by product group.

Subject disposition information for non-randomized subjects will include subject number, demographic information (age and race), screening date, reason for screen failure and details if any regarding the reason for screen failure (Listing 16.2.1.1.2).

4.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to un-blinding and closure of the database to ensure all important deviations are captured and categorized. Subjects with major protocol deviations (defined below) will be excluded from the PP population.

Major deviations of the protocol procedures identified as liable to influence the efficacy outcomes of the study may include, but will not be necessarily limited to the following:

- Violation of inclusion or exclusion criteria
- Significant non-compliance with assigned treatment
- Efficacy assessments outside the specified time windows
- Use of prohibited treatment or medication before or during the study
- Any other reason identified which may affect the efficacy assessments

The number and percentage of subjects with any major protocol deviations will be presented by product group and overall (Table 14.1.2) and listed in Listing 16.2.2.1. Any minor protocol deviations will be listed similarly (Listing 16.2.2.2).

4.1.3 Analysis Populations

In this study the following analysis populations are defined:

Population	Definition / Criteria	Analyses Evaluated
Randomized Population	• All subjects who are randomized and may or may not have received the study product	Disposition
Safety Population	• All subjects who are randomized and have received at least one dose of study product. • The safety population will be analysed as per product received.	Safety
Intent-to-treat (ITT) Population	• All subjects in the safety population who have at least one post product co-primary efficacy assessment (either s-CTX-1 or ratio of carboxylated (c-OC) to under-carboxylated Osteocalcin (uc-OC).	Efficacy
PP Population	• A subset of the ITT population excluding subjects with major protocol deviations. Depending on the nature of the major protocol deviation and impact on the efficacy variable(s), subjects will be either wholly excluded from the PP population or only partially excluded from the PP analyses. This will be determined on a case-by-case basis.	Efficacy

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

Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1, with the reason for exclusion.

The primary population for assessment of efficacy will be the ITT population. A PP analysis will be performed for the co-primary endpoints only if 10% or more ITT subjects are excluded from the PP population.

4.2 Subject Demographics and Other Baseline Characteristics

4.2.1 Demographic Characteristics

Descriptive statistics (number of subjects [n], mean, median, standard deviation [SD], minimum and maximum) for the continuous variables and frequency (n) and percentages (%) for categorical variables will be provided for demographic variables. The demographic and baseline data will include age (years), sex, race, weight (kg), height (cm) and body mass index (kg/m^2). The number and percentage of subjects in each stratum will also be presented.

All demographic information will be tabulated by product group and overall in Table 14.1.4.1 for the Safety population, Table 14.1.4.2 for the ITT population, Table 14.1.4.3 for the PP population and listed in Listing 16.2.4.1.

4.2.2 General Medical History

Medical history and current medical conditions will be listed in Listing 16.2.4.2, with start date and end date or ongoing.

4.2.3 Characteristics of Disease

Not Applicable.

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

4.3.1 Study Product Compliance and Exposure

The descriptive summary of total number of dispensed, consumed and returned sachets will be presented by product group and overall for all subjects in ITT population (Table 14.2.1.1). The data used for these summaries will be taken directly from the eCRF recorded data. These are the following things which will be re-calculated due to some data discrepancies observed in data capturing –

Percentage compliance with study product will be computed for each subject at each visit as:

(Actual number of sachets consumed / expected number of sachets consumed) X 100

where:

actual total number of sachets consumed = (number of sachets dispensed –number of sachets unconsumed returned)

expected number of sachets consumed = (2 sachets X number days between visits).

For the by visit compliance calculation the number of days between visits will be between two consecutive visits. For the overall compliance calculation the number of days between visits will be between visit 2 and visit 6.

Percentage overall study product compliance across the entire study duration will be computed as:

(Total number of actual sachets consumed/total number of expected sachets consumed) X 100.

The "actual number of sachets consumed" will not use the number of returned empty sachets reported on the eCRF, as some sachets may be consumed but not returned by subjects.

Summary statistics of overall study product compliance will be presented by product group (Table 14.2.1.1). Subject will be considered non-compliant if the compliance calculation is less than 80% of the total amount of recommended dose. The number of compliant and non-compliant subjects will be summarized by frequency count and percentage (Table 14.2.1.1). The date/time of product administration, exposure and study product compliance will also be listed in Listing 16.2.5.1.

Exposure to the study product in days will be calculated as date of last study product administration minus date of first study product administration +1. Exposure to the study product will be summarized descriptively by product group and overall for all subjects in ITT population in the same table mentioned above and will be listed in Listing 16.2.5.1.

Study product compliance will be reviewed during then BDRM and a listing will be produced for evaluation of protocol deviations. Study product non-compliance regarded to influence the primary efficacy endpoints will be excluded from PP analysis. Any subject and/or time point excluded from PP analysis will be clearly documented in population definition document.

4.3.1.1 Study Product Compliance Post hoc Analyses

Summary statistics of the overall study product compliance between 0-3 months and 3-6 months will be presented by product group (Table 14.2.1.1a). The categories will be defined in the following ways –

Category 1: 0 - 3 months: This category will assess the compliance between Visit 2 to Visit 4, where the compliance assessment will be calculated using Visit 3 and Visit 4.

Category 2: 3 - 6 months: This category will assess the compliance between Visit 4to Visit 6 where the compliance assessment will be calculated using Visit 5 and Visit 6.

For the overall compliance calculation the number of days between visits will be between visit 2 and visit 4 for category 1 and between visit 4 and visit 6 for category 2 respectively.

4.3.2 Prior and Concomitant Medication

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

Prior medications are defined as the medications which started and stopped before first administration of study product. If the stop date is unknown or incomplete and medication cannot be considered as stopped prior to first administration of study product then the medication will be considered as a concomitant medication.

Concomitant medications are defined as medications which started before the first administration of study product and continued during the study or medication taken between the date of first dose and last dose of study product.

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

Prior and concomitant medications/non-drug therapies will be listed by subject, with drug name, GSK drug synonym, indication, route, dose, frequency, start date, end date or ongoing and start day of medication (relative to first dose of study product) (Listing 16.2.5.2 and Listing 16.2.5.3).

4.4 Analysis of Efficacy

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variables of the study are:

- Change from baseline in bone resorption marker s-CTX-1 after 6 months.
- Change from baseline in the ratio of c-OC to uc-OC (c-OC/uc-OC) after 6 months.

4.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary success criteria is to observe a statistically significantly greater reduction in s-CTX-1 for the test product than the reference product or to observe a statistically significantly greater increase in c-OC/uc-OC for the test product than the reference product, after 6 months of treatment

The hypotheses for the co-primary endpoints are :

- s-CTX-1:
  H_{0P}: There is no difference in mean change from baseline in bone resorption marker s-CTX-1 between reference product and test product after 6 months of treatment
  H_{0P1}: There is a difference in mean change of baseline in bone Resorption marker s-CTX-1 between reference product and test product after 6 months of treatment

- c-OC/uc-OC:
  H_{0CP}: There is no difference in mean change from baseline in the c-OC/uc-OC between reference product and test product after 6 months of treatment
  H_{0CP1}: There is a difference in mean change from baseline in the c-OC/uc-OC between reference product and test product after 6 months of treatment

Summary statistics (n, mean, SD, SE, median, minimum and maximum) by product group and visit of the observed and change from baseline values will be provided for both s-CTX-1 and c-OC/uc-OC (Table 14.2.2.1 and 14.2.3.1, Listing 16.2.6.1 and 16.2.6.2).

The co-primary efficacy variables will be analysed using the analysis of covariance (ANCOVA). The ANCOVA will have product group, age strata as fixed effects and the corresponding baseline value (baseline value of s-CTX-1 and/or c-OC/uc-OC as appropriate) as covariate. Adjusted means, 95% confidence intervals (CIs), within product p-values for each product group, product group difference, SE, 97.5% confidence interval of the difference and the between-product p-values based on the statistical model described above will also be presented (Table 14.2.2.2, 14.2.3.2). Statistical tests to compare treatments will be two-sided and will employ a level of significance of $\alpha = 0.025$.

The setting of the significance level of 0.025 for these 2 co-primary endpoints will ensure that the overall significance level for the primary endpoint is less than or equal to 0.05.

Assumptions of normality and homogeneity of variances in the ANCOVA model will be evaluated after study un-blinding. If violations are observed then the following will be performed as a post-hoc sensitivity analysis and results will be compared with primary analysis results:

1. Suitable data transformations will be tried to achieve the assumptions.

2. If suitable transformations cannot be found, then the non-parametric Van Elteren tests will be performed adjusting for age strata for each endpoint.

To visually inspect the treatment effect of s-CTX-1 and c-OC/uc-OC, plots across time (Baseline, Month 3 and Month 6) will be displayed with LSmeans and ± SE bars which will be obtained from the ANCOVA analysis. The plot will display a different symbol line for each treatment group (Figure 14.2.2.1 and 14.2.3.1).

As post-hoc sensitivity analysis s-CTX-1 will be log-transformed (natural logarithm) and the log-transformed data will be analysed using ANCOVA model with product group, age strata as fixed effects and the corresponding log-transformed baseline value as a covariate. The interpretation of the data will be based on the geometric mean ratio and 95% confidence interval and p-value (Table 14.2.2.2c).

4.4.1.3 Supportive Analyses

A supportive analysis will be performed on the co-primary variables of s-CTX-1 and c-OC/uc-OC using the statistical methodology described in Section 4.4.1.2 on all subjects in PP population, if more than 10% of the subjects in the ITT population are excluded from the PP population (Table 14.2.2.3, 14.2.3.3).

A sensitivity analysis using multiple imputations to handle missing data will be performed for each of the primary efficacy endpoints on the safety population (see Section 4.4.3).

4.4.1.4 Post hoc Analyses

Summary statistics (n, mean, SD, SE, median, minimum and maximum) by product group, age strata and visit of the observed and change from baseline values will be provided for s-CTX-1 (Table 14.2.2.1a).

A post hoc subgroup ANCOVA analysis will be performed on one of the co-primary variables s-CTX-1 by age strata (as defined in section 3.2) using ITT population. The ANCOVA model will have product group, strata and (product * strata) interaction as fixed effects and the corresponding baseline value (baseline value of s-CTX-1) as covariate. Adjusted means, 95% confidence intervals (CIs), within product p-values for each product group, product group difference, SE, 95% confidence interval of the difference and the between-product p-values based on the statistical model described above will also be presented (Table 14.2.2.2b). Statistical tests to compare treatments will be two-sided and will employ a level of significance of $\alpha = 0.05$.

4.4.2 Secondary Efficacy Variables

The secondary efficacy variables are:

- Change from baseline in Serum C-telopeptide of type I collagen (s-CTX-1) after 3 months of treatment
- Change from baseline in Ratio of Carboxylated Osteocalcin to Under Carboxylated Osteocalcin (c-OC/uc-OC) after 3 months of treatment
- Change from baseline in Urinary C-telopeptide of type I collagen (u- CTX-1) after 3 and 6 months of treatment
- Change from baseline in Serum N-terminal telopeptide of type –I collagen (s-NTX-1) after 3 and 6 months of treatment
- Change from baseline in Serum procollagen type I N-terminal propeptide (s-P1NP) after 3 and 6 months of treatment
- Change from baseline in Bone Specific Alkaline Phosphatase (BSAP) after 3 and 6 months of treatment
- Change from baseline in Serum Parathyroid Hormone (s-PTH) after 3 and 6 months of treatment
- Change from baseline in Urinary Calcium/Creatinine ratio (USING CREATININE IN SPOT TEST TO NORMALISE) after 3 and 6 months of treatment
- Change from baseline in Serum Calcium (Ca) after 3 and 6 months of treatment
- Change from baseline in Serum Phosphorus (P) after 3 and 6 months of treatment
- Change from baseline in Serum Alkaline phosphatase (ALP)after 3 and 6 months of treatment
- Change from baseline in 25 Hydroxycalciferol (25 OH D3) after 3 and 6 months of treatment
- Change from baseline in Serum Selenium (Se) after 3 and 6 months of treatment
- Change from baseline in Plasma Zinc (Zn) after 3 and 6 months of treatment
- Change from baseline in Serum Folic acid after 3 and 6 months of treatment
- Change from baseline in Plasma B6 after 3 and 6 months of treatment
- Change from baseline in Serum B12 after 3 and 6 months of treatment

Summary statistics (n, mean, SD, SE, median, minimum and maximum) by product group and visit of the observed and change from baseline values will be provided for all secondary efficacy variables in Section 4.2.2.

Each of these secondary efficacy variables will be analyzed using the ANCOVA. The ANCOVA will have product group, age strata as fixed effects and the corresponding baseline value as covariate. Adjusted means, 95% confidence intervals, within product p-values for each product group, product group difference, SE, 95% confidence interval of the difference and the between-product p-values based on the statistical model described above will also be presented (Table 14.2.4.2, Table 14.2.5.2, 14.2.6.2,14.2.7.2,14.2.8.2, 14.2.9.2, 14.2.10.2, 14.2.11.2,14.2.12.2, 14.2.13.2, 14,2.14.2,14.2.15.2, 14.2.16.2, 14.2.17.2, 14.2.18.2). Statistical tests to compare treatments will be two-sided and will employ a level of significance of $\alpha = 0.05$.

Assumptions of normality and homogeneity of variances in the ANCOVA model will be evaluated after study un-blinding. If violations are observed then the following will be performed as a post-hoc sensitivity analysis and results will be compared with primary analysis results:

1. Suitable data transformations will be tried to achieve the assumptions.
2. If suitable transformations cannot be found, then the non-parametric Van Elteren tests will be performed adjusting for age strata for each endpoint.

To visually inspect the treatment effect of s-CTX-1 and c-OC/uc-OC, plots across time (Baseline, Month 3 and Month 6) will be displayed with LSmeans and ± SE bars which will be obtained from the ANCOVA analysis. The plot will display a different symbol line for each treatment group (Figure 14.2.4.1, 14.2.5.1, 14.2.6.1, 14.2.7.1, 14.2.8.1, 14.2.9.1, 14.2.10.1, 14.2.11.1, 14.2.12.1, 14.2.13.1, 14.2.14.1, 14.2.15.1, 14.2.16.1, 14.2.17.1, 14.2.18.1).

As post-hoc sensitivity analysis Urinary Calcium/Creatinine ratio will be log-transformed (natural logarithm) and the log-transformed data will be analysed using ANCOVA model with product group, age strata as fixed effects and the corresponding log-transformed baseline value as a covariate. The interpretation of the data will be based on the geometric mean ratio and 95% confidence interval and p-value (Table 14.2.9.2a).

4.4.3 Handling of Missing Values/Censoring/Discontinuations

Missing data will not be replaced or imputed. Subjects who withdraw from the study prematurely will be included in the statistical analyses up to the point of discontinuation.

As a part of sensitivity analysis a multiple imputation technique for imputing missing data will be conducted on ANCOVA analysis for each of the primary efficacy endpoints on the safety population. This will help to assess the impact of missing data on the primary analysis.

The SAS procedure MI will be used and the details of MI procedure will be stated in the dataset specification and TFL annotation document. If the data is monotone missing, a regression model will be used for imputation. Otherwise, the MCMC method will be used. All variables included

in the analysis model and values at month 3 for the corresponding endpoint will be included in the imputation model (Table 14.2.2.2a, Table 14.2.3.2a).

4.5 Analysis of Secondary Objectives

4.5.1 Efficacy (Secondary)

Refer Section 4.4.2 for the analysis of secondary objectives.

4.6 Exploratory Analysis

The exploratory efficacy variable is:

- Change from baseline in Insulin –like growth Factor-1 (IGF-1) at 3 and 6 months.

Summary statistics (n, mean, SD, SE, median, minimum and maximum) by product group and visit of the observed and change from baseline values will be provided (Table 14.2.19.1).

The change in baseline IGF-1 variable will be analyzed using the ANCOVA. The ANCOVA will have product group, age strata as fixed effects and the corresponding baseline value as covariate. Adjusted means, 95% confidence intervals, within product p-values for each product group difference, SE, 95% confidence interval of the difference and the between-product p-values based on the statistical model described above will be presented (Table 14.2.19.2). Statistical tests to compare treatments will be two-sided and will employ a level of significance of $\alpha = 0.05$.

Assumptions of normality and homogeneity of variances in the ANCOVA model will be evaluated after study un-blinding. If violations are observed then the following will be performed as a post-hoc sensitivity analysis and results will be compared with primary analysis results:

1. Suitable data transformations will be tried to achieve the assumptions.
2. If suitable transformations cannot be found, then the non-parametric Van Elteren tests will be performed adjusting for age strata for each endpoint.

To visually inspect the treatment effect on each of the secondary endpoints, plots across time (Baseline, Month 3 and Month 6) will be displayed with LSmeans and ± SE bars which will be obtained from the ANCOVA analysis.. The plot will display a different symbol line for each treatment group (Figure 14.2.19.1).

Missing data will be handled as described in Section 4.4.3.

Seven day dietary intake assessment is conducted at baseline and at month 6.

Observed values at each visit (baseline and month 6) and change from baseline at month 6 will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum) by product group (Table 14.2.20.1).

Seven day dietary intake assessments will be listed in Listing 16.2.6.21.

4.6.1 Dietary Intake Assessment Post hoc Analyses

A post hoc ANCOVA analysis will be performed at Month 6 for each dietary intake parameter. The ANCOVA model will include the change in baseline dietary intake parameter as response variable and will have product group as fixed effects and the corresponding baseline values for each parameter as covariate. Adjusted means, 95% confidence intervals (CIs), within product p-values for each product group, product group difference, SE, 95% confidence interval of the difference and the between-product p-values based on the statistical model described above will also be presented (Table 14.2.20.2). Statistical tests to compare treatments will be two-sided and will employ a level of significance of $\alpha = 0.05$.

4.6.2 Further Post hoc Analysis

This post hoc analysis will be performed on urine CTX-1 over creatinine ratio (CTX1CR).

The efficacy variable is as follows:

- Change from baseline in CTX1CR after 3 and 6 months of treatment.

Summary statistics (n, mean, SD, SE, median, minimum and maximum) by product group and visit of the observed and change from baseline values will be provided for CTX1CR (Table 14.2.21.1).

The CTX1CR data will be provided in Listing 16.2.6.22.

The change from baseline in CTX1CR will be analysed using ANCOVA. The ANCOVA model will have product group, age strata as fixed effects and the corresponding baseline value as a covariate. Adjusted means, 95% confidence intervals, within product p-values for each product group, product group difference, SE, 95% confidence interval of the difference and the between-product p-values based on the statistical model described above will also be presented (Table 14.2.21.2). Statistical tests to compare treatments will be two-sided and will employ a level of significance of $\alpha = 0.05$.

Assumptions of normality and homogeneity of variances in the ANCOVA model will be evaluated. If violations are observed then the following will be performed as a post-hoc sensitivity analysis:

1. Suitable data transformations will be tried to achieve the assumptions.
2. If suitable transformations cannot be found, then the non-parametric Van Elteren tests will be performed adjusting for age strata for each endpoint.

4.7 Analysis of Safety

4.7.1 Adverse Events and Serious Adverse Events

Adverse events (AE) recorded during the study will be mapped to a system organ class (SOC) and preferred term (PT) using the current medical dictionary for regulatory activities (MedDRA).

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the date/time of the first administration of study product.

The following summary tables and listings will be presented by product group for safety population:

- Table of TEAEs by System Organ Class and Preferred Term (Table 14.3.1.1)
- Table of TEAEs related to study product by System Organ Class and Preferred Term (Table 14.3.1.2)
- Table of TEAEs by System Organ Class, Preferred Term and Severity (Table 14.3.1.3)
- Listing of all AEs (including all subjects: Listing 16.2.7.1.1 for all randomized subjects; Listing 16.2.7.1.2 for non-randomized subjects)
- Listing of death occurring during treatment (if any) will be listed by treatment, including the date and study day of death, and the principal cause of death (Listing 14.3.2.1)
- Listing of non-fatal serious adverse events (Listing 14.3.2.2)
- Listing of TEAEs leading to withdrawal (Listing 14.3.2.3)

4.7.2 Laboratory Tests

Laboratory and biomarker results at screening, baseline, and each follow-up visit until end of the study visit will be presented in shift tables (Tables 14.3.5.3 – 14.3.5.12).

* The tests are named according to the protocol. This naming convention of the parameters will be used for generating the outputs also.

Laboratory parameters for which reference ranges will be available will then be categorised with respect to reference ranges as: High, Low, Normal and Missing. The shift will be calculated with respect to reference ranges from baseline for the subsequent visits.

The reference ranges will not be available for the following laboratory tests –

Serum Cross-Linked C-Telopeptide of Type 1 Collagen, Ratio of Carboxylated to Under-Carboxylated Osteocalcin, Urinary C-Telopeptide of Type 1 Collagen, Serum Vitamin D (using 25-OH D3), Urinary Calcium/Creatinine Ratio and Serum Folate.

Laboratory normal ranges will be listed in Listing 16.2.6.20 and all laboratory test results will be listed in Listings 16.2.6.1 – 16.2.6.19.

4.7.3 Vital Signs

Vital signs (systolic and diastolic blood pressure (mmHg), heart rate (beats/min), and oral body temperature (ºF)) will be collected at screening, baseline, and each follow-up visit until end of the study visit.

Observed values at each visit and change from baseline at each post-baseline visit will be summarized on the safety population descriptively (n, mean, standard deviation, median, minimum, and maximum) by product group (Table 14.3.5.1).

All vital signs will listed in Listing 16.2.9.1.

4.7.4 Findings on Physical Examination

The findings on the physical examination performed at screening, baseline, and each follow-up visit until end of the study visit will be listed (Listing 16.2.9.2).

4.7.5 Other Safety Variables

Hemoglobin (g/dL) collected at screening, baseline, and each follow-up visit until end of the study visit will be summarized descriptively for all subjects in safety population.

Observed values at each visit and change from baseline at each post-baseline visit will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum) by product group (Table 14.3.5.2). Baseline will be defined as the last measurement before the first dose of study product; change will be defined as the post-baseline value minus the baseline value.

Hemoglobin measurements will be listed in Listing 16.2.9.3.

4.8 Analysis of Other Variables

Not applicable.

4.8.1 Quality of Life

Not applicable.

4.8.2 Patch Adhesion Performance

Not applicable.

5 Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol (Dated: 31/JUL/2017) are outlined in Table .

Table 2 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 9.2.1	• Section 4.1.3	• PP population definition is clarified and elaborated. Partial (in case of non-compliance in any particular visits) and full exclusion are defined.
• Section 9.3.2 • Section 9.3.3	• Section 4.4.1.2 • Section 4.5.1 • Section 4.6	• ANCOVA model for the primary, secondary and exploratory analysis has been updated. Age strata have been added as a fixed effect in the model to account for the baseline stratification. . • Also, 95% CI is being updated with 97.5% CI since the significance level for the primary analysis is 0.025.
• **RAP Addendum 1**		
This RAP addendum v1.0 provides details of the additional analyses requested from the analyses described in the Statistical Reporting and Analysis Plan Amendment 1.The additional post-hoc analyses were identified at the non-topline TFL review stage, and hence was after un-blinding but prior to development of the CSR. The additional post-hoc analyses will be discussed in the CSR. Sections 4.3.1.1, 4.4.1, 4.4.1.4, 4.4.2, and 4.6.1 were added in the RAP addendum describing the additional post-hoc analyses. The sections below provide a summary of this with the justification for the request.		
Protocol	**Reporting & Analysis Plan**	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 5.5	• Section 4.3.1	• Added Section 4.3.1.1 which details a study product compliance summary by categories 0-3 months and 3-6 months. • This is to assess if the difference in compliance between the time points could be linked to the difference in primary parameter results between Month 3 and Month 6.
• Section 9.3.2	• Section 4.4.1	• Added a statistical model for the log-transformed data of s-CTX1 to support sensitivity analysis.
• Section 9.3.2	• Section 4.4.1.2	• Added Section 4.4.1.4 which details a subgroup ANCOVA analysis on s-CTX1 change from baseline by age strata at Month 3 and Month 6. This is to asses if age has an impact on the treatment effect. •
•	•	•
• Section 6.10	• Section 4.6	• Added Section 4.6.1 which details an ANCOVA analysis on the change from baseline of each dietary intake parameter assessment. This is to assess if significant changes in dietary intake can be linked to the change in primary endpoint at Month 6.
• **RAP Addendum 2**		
This RAP addendum v2.0 provides details of the further post hoc analyses requested from the analysis described in the Statistical Reporting and Analysis Plan Addendum 1. This further post hoc analyses were identified after submission of all final TFLs, and hence after un-blinding. The further post-hoc analysis will be discussed in the CSR. The section below provides a summary of the further post hoc analysis with the justification for the request.		

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
Not Applicable	• Section 4.6.2	• Added Section 4.6.2 which details ANCOVA analysis of new variable urine CTX-1 over creatinine ratio. The rationale of this new analysis is to account for the impact of dilution and kidney function on urinary values, and to explore further the difference between urine and serum CTX-1 results.

Attachment 1: List of Data Displays

GSKCH_207192_Stat
istical Reporting and A

6 Template for Tables, Figures and Listings

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

The product labels for the column headings will be as follow:

- Test Product
- Reference Product

The product comparison will be:

- Test Product vs Reference Product

The below footnotes will be displayed on each output

- Test Product: Cereal based fortified beverage (Proprietary food)
- Reference Product: Low protein non fortified isocaloric beverage

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.1.1
Subject Disposition
All Screened Subjects

Study Population: All Screened Subjects (N=xxx)

	Test Product n (%)	Reference Product n (%)	Overall n (%)
TOTAL SUBJECTS SCREENED			xxx
SUBJECTS NOT RANDOMIZED			xxx (xx.x)
DID NOT MEET STUDY CRITERIA			xxx (xx.x)
ADVERSE EVENT			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 EVENT	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)

Percentages for not randomized category are based on number of screened subjects; percentages for randomized category are based on number of randomized subjects.

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMYYYY

Table 14.1.2
Incidence of Major Protocol Deviations
Randomized Population

Study Population: Randomized (N=xxx)

	Test Product n (%)	Reference Product n (%)	Overall n (%)
SUBJECTS WITH AT LEAST ONE MAJOR PROTOCOL DEVIATION	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
MAJOR PROTOCOL DEVIATIONS NOT LEADING TO EXCLUSION FROM PP	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
MAJOR PROTOCOL DEVIATIONS LEADING TO EXCLUSION FROM PP	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
All VISITS			
DEVIATION REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
VISIT Y	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
DEVIATION REASON 1	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Programming Note: *This table will list all major protocol deviations as defined in the population definition document.*

Protocol: 207192 Program Run Date: DDMMMYYYY

Table 14.1.4.1
Demographic and Baseline Characteristics
Safety Population

Study Population: Safety Population (N=XXX)

	Test Product (N = xxx)	Reference Product (N = xxx)	Overall (N = xxx)
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)

AGE (YEARS)			
n	xx	xx	xx
MEAN	xx.x	xx.x	xx.x

AGE GROUP n (%)			
≥ 25 - < 35 YEARS	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
≥ 35 - ≤ 45 YEARS	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
SEX n (%)			
FEMALE	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
HEIGHT (cm)			
n	xx	xx	xx
MEAN	xxx.xx	xxx.xx	xxx.xx

WEIGHT (kg)			
n	xx	xx	xx
MEAN	xxx.xx	xxx.xx	xxx.xx

BODY MASS INDEX (kg/m^2)			
n	xx	xx	xx
MEAN	xxx.xx	xxx.xx	xxx.xx

Percentages are based on number of subjects in each product group and overall.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *For continuous variables the summary statistics: n, Mean, SD, Median, Minimum and Maximum will be displayed. Similar table will be displayed for ITT population.*

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.1.1
Study Product Compliance
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

	Statistics	Test Product (N = xxx)	Reference Product (N = xxx)
TOTAL NUMBER OF SACHETS DISPENSED			
	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx
TOTAL NUMBER OF SACHETS CONSUMED	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx
TOTAL NUMBER OF SACHETS RETURNED	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx
COMPLIANCE	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx

	Statistics	Test Product (N = xxx)	Reference Product (N = xxx)
NUMBER OF SUBJECTS COMPLIANT	n (%)	xxx (xx.x)	xxx (xx.x)
NUMBER OF SUBJECTS NON-COMPLIANT	n (%)	xxx (xx.x)	xxx (xx.x)

Percentage is based on number of subjects in each product group.
Subject would be considered non-compliant if the subject consumes less than 80% of the total amount of recommended dose.
Compliance = (actual total number of sachets consumed/expected total number of sachets consumed)*100 where,
actual number of sachets consumed = (number of sachets dispensed – number of sachets unconsumed returned)

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.1.1a
Study Product Compliance by Time Categories
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Time Category: 0-3 Months

	Statistics	Test Product (N = xxx)	Reference Product (N = xxx)
TOTAL NUMBER OF SACHETS DISPENSED			
	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx
TOTAL NUMBER OF SACHETS CONSUMED	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx
TOTAL NUMBER OF SACHETS RETURNED	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx
	MAXIMUM	x.xx	x.xx
COMPLIANCE	n	xx	xx
	MEAN	x.xxx	x.xxx
	SD	x.xxxx	x.xxxx
	MEDIAN	x.xxx	x.xxx
	MINIMUM	x.xx	x.xx

	Statistics	Test Product (N = xxx)	Reference Product (N = xxx)
	MAXIMUM	x.xx	x.xx
NUMBER OF SUBJECTS COMPLIANT	n (%)	xxx (xx.x)	xxx (xx.x)
NUMBER OF SUBJECTS NON-COMPLIANT	n (%)	xxx (xx.x)	xxx (xx.x)

Percentage is based on number of subjects in each product group.
Subject would be considered non-compliant if the subject consumes less than 80% of the total amount of recommended dose.
Compliance = (actual total number of sachets consumed/expected total number of sachets consumed)*100 where,
actual number of sachets consumed = (number of sachets dispensed – number of sachets unconsumed returned)

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.2.1
Summary of Serum Cross Linking C-Telopeptide of Type 1 Collagen (Unit)
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Visit	Statistics	Test Product (N = xxx)		Reference Product (N = xxx)		Overall (N = xxx)	
		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
BASELINE	n	xxx		xxx		xxx	
	MEAN	xx.xx		xx.xx		xx.xx	
	SD	xx.xxx		xx.xxx		xx.xxx	
	SE	x.xx		x.xx		x.xx	
	MEDIAN	x.xx		x.xx		x.xx	
	MINIMUM	xx.x		xx.x		xx.x	
	MAXIMUM	xx.x		xx.x		xx.x	
MONTH 3	n	xxx	xxx	xxx	xxx		
	MEAN	xx.xx	xx.xx	xx.xx	xx.xx		
	SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx		
	SE	x.xx	x.xx	x.xx	x.xx		
	MEDIAN	x.xx	x.xx	x.xx	x.xx		
	MINIMUM	xx.x	xx.x	xx.x	xx.x		
	MAXIMUM	xx.x	xx.x	xx.x	xx.x		
MONTH 6	n	xxx	xxx	xxx	xxx		
	MEAN	xx.xx	xx.xx	xx.xx	xx.xx		
	SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx		
	SE	x.xx	x.xx	x.xx	x.xx		
	MEDIAN	x.xx	x.xx	x.xx	x.xx		
	MINIMUM	xx.x	xx.x	xx.x	xx.x		
	MAXIMUM	xx.x	xx.x	xx.x	xx.x		

Programming Note: *Similar table will be generated for all other primary, secondary and exploratory variables. Overall column will be displayed only for the Baseline visits.*

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.2.1a
Summary of Serum Cross Linking C-Telopeptide of Type 1 Collagen (Unit) by Age Strata
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Strata 1 : 25 -<35 years

Visit	Statistics	Test Product (N = xxx)		Reference Product (N = xxx)		Overall (N = xxx)	
		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
BASELINE	n	xxx		xxx		xxx	
	MEAN	xx.xx		xx.xx		xx.xx	
	SD	xx.xxx		xx.xxx		xx.xxx	
	SE	x.xx		x.xx		x.xx	
	MEDIAN	x.xx		x.xx		x.xx	
	MINIMUM	xx.x		xx.x		xx.x	
	MAXIMUM	xx.x		xx.x		xx.x	
MONTH 3	n	xxx	xxx	xxx	xxx		
	MEAN	xx.xx	xx.xx	xx.xx	xx.xx		
	SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx		
	SE	x.xx	x.xx	x.xx	x.xx		
	MEDIAN	x.xx	x.xx	x.xx	x.xx		
	MINIMUM	xx.x	xx.x	xx.x	xx.x		
	MAXIMUM	xx.x	xx.x	xx.x	xx.x		
MONTH 6	n	xxx	xxx	xxx	xxx		
	MEAN	xx.xx	xx.xx	xx.xx	xx.xx		
	SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx		
	SE	x.xx	x.xx	x.xx	x.xx		
	MEDIAN	x.xx	x.xx	x.xx	x.xx		
	MINIMUM	xx.x	xx.x	xx.x	xx.x		
	MAXIMUM	xx.x	xx.x	xx.x	xx.x		

Visit	Statistics	Test Product (N = xxx)	Reference Product (N = xxx)	Overall (N = xxx)

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.2.2
Statistical Analysis of Serum Cross Linking C-Telopeptide of Type 1 Collagen (Unit) Change from Baseline
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Visit	Product Group	N	Adjusted Mean	SE	95% CI	P-Value	Comparison with Reference Product		
							Difference (SE)	97.5% CI	P-Value
MONTH 3	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			
MONTH 6*	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

* one of the co-primary efficacy endpoints.

Analysis was performed using ANCOVA model with product group, age strata as fixed effects and the corresponding baseline value as covariate. Difference is test product minus reference product such that a negative difference favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Similar table will be generated for all primary endpoints. Direction of the difference should be with respect to the parameter which will be analyzed and should be checked with Clinical Research and Statistician for finalization.*
For month 3, alpha value will be used 0.05 and the confidence intervals for within and between comparisons will be of 95%. For month 6, alpha will be used 0.05 for the within and for between product group comparisons alpha will be 0.025 and the confidence interval will be 97.5%.
Show month 3 values in page 1 and month 6 values in page 2.

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.2.2a
Statistical Analysis of Serum Cross Linking C-Telopeptide of Type 1 Collagen (Unit) Change from Baseline using Imputed Missing Data
Safety Population

Study Population: Intent-to-Treat Population (N = xxx)

Visit	Product Group	N	Adjusted Mean	SE	95% CI	P-Value	Comparison with Reference Product		
							Difference (SE)	97.5% CI	P-Value
MONTH 6*	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

*one of the co-primary efficacy endpoints.
To impute the monotone missing pattern data a regression model method will be applied with following effects; product group, age strata and the corresponding baseline and Month 3 data will be used.
Analysis was performed using ANCOVA model with product group, age strata as fixed effects and the corresponding baseline value as covariate. Difference is test product minus reference product such that a negative difference favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Similar table will be generated for all primary endpoints using imputed missing data. Direction of the difference should be with respect to the parameter which will be analyzed and should be checked with Clinical Research and Statistician for finalization.*
For month 3, alpha value will be used 0.05 and the confidence intervals for within and comparisons will be of 95%. For month 6, alpha will be used 0.05 for the within and for between product group comparisons alpha will be 0.025 and the confidence interval will be 97.5%.
Show month 3 values in page 1 and month 6 values in page 2.

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.2.2b
Statistical Analysis of Serum Cross Linking C-Telopeptide of Type 1 Collagen (Unit) Change from Baseline by Age Strata
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Age Strata: 25-<35 years

Visit	Product Group	N	Adjusted Mean	SE	95% CI	P-Value	Comparison with Reference Product		
							Difference (SE)	97.5% CI	P-Value
MONTH 3	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			
MONTH 6*	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

* one of the co-primary efficacy endpoints.

Analysis was performed using ANCOVA model with product group, strata and product*strata interaction as fixed effects and the corresponding baseline value as covariate. Difference is test product minus reference product such that a negative difference favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Similar table will be generated for all primary endpoints. Direction of the difference should be with respect to the parameter which will be analyzed and should be checked with Clinical Research and Statistician for finalization.*
For month 3 and month 6, alpha value will be used 0.05 and the confidence intervals for within and between comparisons will be of 95%.

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.2.2c
Statistical Analysis of Serum Cross Linking C-Telopeptide of Type 1 Collagen (Unit) using Log Transformed Data
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Visit	Product Group	N	Geometric Mean	Geometric CV	95% CI	P-Value	Comparison with Reference Product		
							Geometric Mean Ratio (CV)	95% CI	P-Value
MONTH 3	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

Analysis was performed for log transformed data using ANCOVA model with product group, age strata as fixed effects and the corresponding log(baseline) value as covariate. Geometric mean ratio less than one favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note:
For Month 6 create a new page and use alpha as 0.025 and 97.5% CI.
Geometric mean = exp (LSmean); Geometric CV = sqrt(exp(variance)-1); Geometric mean ratio =exp(difference); Lower CI = exp(LCL) and Upper CI = exp(UCL)

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.4.2
Statistical Analysis of Urinary C-Telopeptide of Type 1 Collagen (Unit) Change from Baseline
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Visit	Product Group	N	Adjusted Mean	SE	95% CI	P-Value	Comparison with Reference Product		
							Difference (SE)	95% CI	P-Value
MONTH 3	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			
MONTH 6	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

Analysis was performed using ANCOVA model with product group, age strata as fixed effects and the corresponding baseline value as covariate. Difference is test product minus reference product such that a negative difference favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Similar table will be generated for all secondary and exploratory endpoints. Direction of the difference should be with respect to the parameter which will be analyzed and should be checked with Clinical Research and Statistician for finalization.*

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.9.2a
Statistical Analysis of Calcium/Creatinine Ratio (unit) using Log Transformed Data
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Visit	Product Group	N	Geometric Mean	Geometric CV	95% CI	P-Value	Comparison with Reference Product		
							Geometric Mean Ratio (CV)	95% CI	P-Value
MONTH 3	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			
MONTH 6	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

Analysis was performed for log transformed data using ANCOVA model with product group, age strata as fixed effects and the corresponding log(baseline) value as covariate. Geometric mean ratio less than one favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note:
Geometric mean = exp (LSmean); Geometric CV = sqrt(exp(variance)-1); Geometric mean ratio =exp(difference); Lower CI = exp(LCL) and Upper CI = exp(UCL)

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.20.1
Summary of Seven Day Dietary Intake Assessment
ITT Population

Study Population: ITT Population (N = xxx)

Parameter (Unit)	Visit	Statistics	Test Product (N = xxx)		Reference Product (N = xxx)		Overall (N = xxx)
			Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value
TOTAL ENERGY INTAKE (KCAL)	BASELINE	n	xxx		xxx		xxx
		MEAN	xxx.x		xxx.x		xxx.x
		SD	xxx.xx		xxx.xx		xxx.xx
		MEDIAN	xxx.x		xxx.x		xxx.x
		MINIMUM	xxx		xxx		xxx
		MAXIMUM	Xxx		Xxx		Xxx
	MONTH 6 (VISIT 6)	n	xxx	xxx	xxx	xxx	
		MEAN	xxx.x	xxx.x	xxx.x	xxx.x	
		SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	
		MEDIAN	xxx.x	xxx.x	xxx.x	xxx.x	
		MINIMUM	xxx	xxx	xxx	xxx	
		MAXIMUM	Xxx	Xxx	Xxx	Xxx	

Programming Note: *This table will continue for all parameters for dietary intake assessment [Total Energy intake (Kcal), Total Carbohydrate intake (gm), Total Fat intake (gm), Avergare Calcium intake (mg), Average protein intake (g), Average Vitamin D intake (mcg), Average Vitamin B6 intake (mg), Average Vitamin B12 intake (mg), Average Phosphorous intake (mg), Average Folic Acid intake (mcg), Average Zinc intake (mg), and Average Selenium intake (mcg)]. . Display overall only for the baseline visit.*

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.2.20.2
Statistical Analysis of Dietary Intake) Change from Baseline by Parameter
Intent-to-Treat Population

Study Population: Intent-to-Treat Population (N = xxx)

Parameter: Total Energy (Kcal)

Visit	Product Group	N	Adjusted Mean	SE	95% CI	P-Value	Comparison with Reference Product		
							Difference (SE)	95% CI	P-Value
MONTH 6	TEST PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx	xx.xx (xx.xxx)	xx.xx, xx.xx	0.xxxx
	REFERENCE PRODUCT	xxx	xx.xx	xx.xxx	xx.xx, xx.xx	0.xxxx			

Analysis was performed using ANCOVA model with product group, age strata as fixed effects and the corresponding baseline value as covariate. Difference is test product minus reference product such that a positive difference favors the test product.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *This table will continue for all parameters for dietary intake assessment [Total Energy intake (Kcal), Total Carbohydrate intake (gm), Total Fat intake (gm), Avergare Calcium intake (mg), Average protein intake (g), Average Vitamin D intake (mcg), Average Vitamin B6 intake (mg), Average Vitamin B12 intake (mg), Average Phosphorous intake (mg), Average Folic Acid intake (mcg), Average Zinc intake (mg), and Average Selenium intake (mcg)].*

Protocol 207192 Program Run Date: DDMMYYYY

Table 14.3.1.1
Treatment Emergent Adverse Event by System Organ Class and Preferred Term
Safety Population

Study Population: Safety Population (N=xxx)

System Organ Class Preferred Term	Test Product (N = xxx)		Reference Product (N = xxx)		Overall (N = xxx)	
	n (%)	nAE	n (%)	nAE	n (%)	nAE
NUMBER OF SUBJECTS WITH AT LEAST ONE AE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
NUMBER OF SUBJECTS WITH NO AE	xx (xx.x)		xx (xx.x)		xx (xx.x)	
SOC 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PT 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PT 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

SOC 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PT 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PT 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

---						

n (%) = Number (percent) of subjects; nAE = Number of adverse events.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Similar table will be generated for treatment related adverse events.*

Protocol 207192 Program Run Date: DDMMYYYY

Table 14.3.1.3
Treatment Emergent Adverse Event by System Organ Class, Preferred Term and Severity
Safety Population

Study Population: Safety Population (N=xxx)

System Organ Class Preferred Term	Test Product (N = xxx)						Reference Product (N = xxx)						Overall (N = xxx)					
	Mild		Moderate		Severe		Mild		Moderate		Severe		Mild		Moderate		Severe	
	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE	n (%)	nAE
SOC 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PT 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PT 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
---																		
.....																		

n (%) = Number (percent) of subjects; nAE = Number of adverse events.

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.3.5.1
Summary of Vital Signs
Safety Population

Study Population: Safety Population (N = xxx)
Vital Sign: <Parameter Name (Unit)>

Visit	Statistics	Test Product (N = xxx)		Reference Product (N = xxx)		Overall (N = xxx)
		Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value
SCREENING	n	xxx		xxx		xxx
	MEAN	xxx.x		xxx.x		xxx.x
	SD	xxx.xx		xxx.xx		xxx.xx
	MEDIAN	xxx.x		xxx.x		xxx.x
	MINIMUM	xxx		xxx		xxx
	MAXIMUM	Xxx		Xxx		Xxx
BASELINE	n	xxx		xxx		xxx
	MEAN	xxx.x		xxx.x		xxx.x
	SD	xxx.xx		xxx.xx		xxx.xx
	MEDIAN	xxx.x		xxx.x		xxx.x
	MINIMUM	xxx		xxx		xxx
	MAXIMUM	Xxx		Xxx		Xxx
VISIT 3	n	xxx	xxx	xxx	xxx	
	MEAN	xxx.x	xxx.x	xxx.x	xxx.x	
	SD	xxx.xx	xxx.xx	xxx.xx	xxx.xx	
	MEDIAN	xxx.x	xxx.x	xxx.x	xxx.x	
	MINIMUM	xxx	xxx	xxx	xxx	
	MAXIMUM	Xxx	Xxx	Xxx	Xxx	

Programming Note: *This table will continue for all other scheduled visits and for all vital signs [Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Heat rate (beats/min) and Oral body temperature (°F)] . Display overall only for the baseline visit.*

Protocol 207192 Program Run Date: DDMMMYYYY

Table 14.3.5.3
Shift Table for Serum N-Terminal Telopeptide of Type 1 Collagen (unit)
Safety Population

Study Population: Safety Population (N = xxx)
Reference range: <*xx-xx*>,

Visit	Result	Test Product Baseline Low n (%)	Test Product Baseline Normal n (%)	Test Product Baseline High n (%)	Test Product Baseline Missing n (%)	Test Product Baseline Total n (%)	Reference Product Baseline Low n (%)	Reference Product Baseline Normal n (%)	Reference Product Baseline High n (%)	Reference Product Baseline Missing n (%)	Reference Product Baseline Total n (%)
Month 3	Low	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Normal										
	High										
	Missing										
	Total										
Month 6	Low	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
	Normal										
	High										
	Missing										
	Total										

Low, normal, and high categories defined by reference ranges.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *This table will continue for all other scheduled visits and laboratory parameters*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.1.7
Randomization Information
All Randomized Subjects

Subject Number	Age/Race [1]	Strata	Randomization Number	Product Group	Date of Randomization
XXXXXX	XX/A1	Stratum 1: Age ≥ 25 - 35 years	XXXXXX		DDMMMYYYY

---

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = Multiple.
The block size of X was used for this randomization.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Block size information will be added after un-blinding of the treatment code.*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.1.1.1
Subject Disposition
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: XXXXXX

Subject Number	Age/Race [1]	Screening Date	Study Product Start Date and Time	Last Study Product Administration Date and Time	Date of Completion or Withdrawal	Duration in the Study (days) [2]	Completed the Study	Primary Reason for Withdrawal	Further Details [3]
XXXXXX	XX/A1	DDMMMYYYY	DDMMMYYYY:HH:MM	DDMMMYYYY:HH:MM	DDMMMYYYY	XXX	Yes		
XXXXXX	XX/A6	DDMMMYYYY	DDMMMYYYY:HH:MM	DDMMMYYYY:HH:MM	DDMMMYYYY	XXX	No	Other	XXXXXX
XXXXXX	XX/A4	DDMMMYYYY	DDMMMYYYY:HH:MM	DDMMMYYYY:HH:MM	DDMMMYYYY				

---

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = Multiple.
[2] Duration in the study = (completion/withdrawal date and time - study product start date/time) + 1.
[3] Further details of reasons for withdrawal.

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.1.1.2
Subject Disposition
All Non-Randomized Subjects

Subject Number	Age/Race [1]	Screening Date	Reason for Screen Failure	Further Details [2]
XXXXXX	XX/A1	DDMMMYYYY	XXXXXX	XXXXXX
---				

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = Multiple.
[2] Further details of reasons for screen failure.

Page x of y

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.2.1
Major Protocol Deviations
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: XXXXXX

Subject	Age/Race [1]	Visit(s)Excluded from PP Population	Deviation Reason
10001	25/I	All	Did not meet Inclusion criteria Did not meet Inclusion criteria
		From Visit 3	Inclusion criteria
		Visit 4 only	Treatment non-compliance
		XX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
		XX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = Multiple

Page x of y
Program: XXXXXXXXX.sas Source: Filename

Programming Note: *This listing is based on details in the population definition document.*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.2.2
Minor Protocol Deviations
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age/Race [1]	Deviation Sequence	Start Date/Time of Deviation	End Date/Time of Deviation	Deviation Description
XXXXXX	XX/A1	1	DDMMMYYYY:HH:MM	DDMMMYYYY:HH:MM	XXXXXX
---					

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = Multiple

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.3.1
Exclusion from Analysis Populations
All Randomized Subjects

Study Population: All Randomized Subjects (N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Safety Population	ITT Population	PP population
XXXXXX	XX/A1	YES	YES	YES

Programming Note: *This listing is based on population definition document.*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.4.1
Demographic and Baseline Characteristics
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age (years)	Sex	Race	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	Stratification
XXXXXX	XX	Female	African American/African Heritage	xxx.x	xxx.x	xx.x	≥ 25 - < 35 YEARS
XXXXXX	XX	Female	African American/African Heritage	xxx.x	xxx.x	xx.x	≥ 35 - ≤ 45 YEARS

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.4.2
Medical History
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Any Medical History	Medical Condition	Start Date	End Date or Ongoing
XXXXXX	XX/A1	Yes	XXXXXX	DDMMMYYYY	DDMMMYYYY
XXXXXX	XX/A6	Yes	XXXXXX	DDMMMYYYY	Ongoing

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = multiple

Page x of y

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.5.1
Study Product Administration and Compliance
All Randomized Subjects

Study Population: All Randomized Subjects (N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Visit	Date Study Product Dispensed	Date/Time of Product Administered	Exposure (in days)[2]	Number of Sachets Dispensed	Number of Empty Sachets Returned [3]	Number of Uncomsumed Sachets Returned	Actual Number of Sachets Consumed [4]	Expected number of Sachets consumed[5]	Compliance (%)[6]	Comments
XXXXXX	XX/A1	Baseline	DDMMM YYYY	DDMMMYYYY:HH:MM		xxx						
		Visit 3	DDMMM YYYY	DDMMMYYYY:HH:MM	x	xxx	xx	xx	x	x	97	
		Visit 4	DDMMM YYYY	DDMMMYYYY:HH:MM	x	xxx	xx	xx	x	x	97	
		Visit 5	DDMMM YYYY	DDMMMYYYY:HH:MM	x	xxx	xx	xx	x	x	98	
		Visit 6	DDMMM YYYY	DDMMMYYYY:HH:MM	x	xxx	xx	xx	x	x	98	
		Overall				xxx	xx	xx	x	x	98	

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native, A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT = multiple.
[2] Exposure = (Date/Time of Last Product Administered - Date/Time of First Product Administered)+1.
[3] As reported in eCRF.[4] actual number of sachets consumed = (number of sachets dispensed – number of sachets unconsumed returned)
[5] Expected number of sachets consumed = 2 sachets*Number of days between the visits.
[6] By Visit Compliance = (Actual number of sachets consumed / expected number of sachets consumed) * 100 ; Overall compliance = (actual total number of sachets consumed /expected total number of sachets consumed)*100

* Subjects with compliance > 120% or less than 80%.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *Overall compliance will not be calculated for the subjects who discontinued before completing visit 6*

Highlight compliance values with '' if the compliance is more than 120% or less than 80%.*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.5.2
Prior Medications
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Sequence Number	Drug Name [GSK Drug Synonym]	Reason for Medication	Route of Admin.	Dose per Admin. (unit)	Frequency	Start Date (Study Day [2])	End Date/ Ongoing
XXXXXX	XX/A6	1	XXXXXX [XXXXXX]	XXXXXX	XXXXXX	XXXXXX (xx)	XXXXXX	DDMMMYYYY (XX)	Ongoing
XXXXXX	XX/A6	1	XXXXXX [XXXXXX]	XXXXXX	XXXXXX	XXXXXX (xx)	XXXXXX	DDMMMYYYY (XX)	DDMMMYYYY

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT=Multiple.
[2] Study day relative to the date of first dose of treatment.

Program: xxxxxx.sas Source: Filename

Programming Note: *Similar listing will be generated for Concomitant Medications and Non-Drug Therapies.*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.6.1
Serum Type I Collagen CrossLinking C-Telopeptide
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product
Normal Range (xx.x – xx.x)

Subject Number	Age/Race [1]	Visit	Date of Visit	Was Assessment Performed?	Date of Sample Collection/Time of Sample Collection	Sample Assessment Date	Result (unit)	Change from Baseline	Comment
XXXXXX	XX/N	Screening	DDMMMYYYY	Yes	DDMMMYYYY/hh:mm	DDMMMYYYY	xx.x		xxx
		Baseline	DDMMMYYYY				xx.x		xxxx
		Visit 5	DDMMMYYYY	Yes	DDMMMYYYY/hh:mm	DDMMMYYYY	xx.x	xx.x	xxxxx
		Visit 6	DDMMMYYYY					xx.x	
---									

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native, A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT=Multiple.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note:

- *Repeat the same layout for listing 16.2.6.2-16.2.6.19 and 16.2.6.22*
- *For the following laboratory tests normal ranges will not be displayed Serum Cross-Linked C-Telopeptide of Type 1 Collagen, Ratio of Carboxylated to Under-Carboxylated Osteocalcin, Urinary C-Telopeptide of Type 1 Collagen, Serum Vitamin D (using 25-OH D3), Urinary Calcium/Creatinine Ratio and Serum Folate*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.6.20
Listing of Normal Range for Blood and Urine Parameters

Parameter (Unit)	Biological Matrix	Gender	Age Range (in years)	Normal Range	
				Lower Limit	Upper Limit
Serum Type I Collagen Cross-linked C-telopeptide (unit)	Blood	Male	xx-xx		
		Female	xx-xx		

Page x of y

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.6.21
Seven Day Dietary Intake Assessment
All Randomized Subjects

Study Population: All Randomized Subjects (N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Visit	Date of Visit	Total Energy (Kcal)						Average Selenium intake (mcg)	
				Observed value	Change from Baseline	Observed value	Change from Baseline	Observed value	Change from Baseline	Observed value	Change from Baseline
		Screening	DDMMMYYYY								

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native, A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT=Multiple.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: *This listing will include all parameters for dietary intake assessment [Total Energy intake (Kcal), Total Carbohydrate intake (gm), Total Fat intake (gm), Average Calcium intake (mg), Average protein intake (g), Average Vitamin D intake (mcg), Average Vitamin B6 intake (mg), Average Vitamin B12 intake (mg), Average Phosphorous intake (mg), Average Folic Acid intake (mcg), Average Zinc intake (mg), and Average Selenium intake (mcg)].*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.7.1.1
All Adverse Events
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Adverse Event (Preferred Term) [System Organ Class]	Start Date/Time/ Study Day[2]	End Date/ Time	Frequency/ Intensity	Related to Study Product?	Action Taken with Study Product	Outcome	Serious?	Subject Withdrawn
XXXXXX	XX/N	HEADACHE (NERVOUS SYSTEM DISORDER) [xxxxxxx]	31MAR2017/ HH:MM:SS/ 3	DDMMMYYYY/ HH:MM:SS	SINGLE EPISODE/ MILD	No	NOT APPLICABLE	RECOVERED/ RESOLVED	NO	NO

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native,A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage.
[2] Study day is the day relative to start of treatment.

Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note for Listing 16.2.7.1.2:

- *Repeat the same layout for listing 16.2.7.1.2*
- *Population should be used 'Non randomized Subjects'*
- *The fourth column should be only 'Start Date/Time (take out Study Day)'*

- *Delete the footnote related to study day and adjust the numbers accordingly.*

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.9.1
Vital Signs
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Visit	Date of Visit	Date of Assessment	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Heart Rate (beats/min)		Oral Temperature (F)	
					Observed value	Change from Baseline	Observed value	Change from Baseline	Observed value	Change from Baseline	Observed value	Change from Baseline
		Screening	DDMMMYYYY	DDMMMYYYY								

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native, A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT=Multiple.

Page x of y

Program: xxxxxx.sas Source: Filename

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.9.2
Physical Examination
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

Subject Number	Age/Race[1]	Visit	Date of Visit	Body System	Finding	Description of Abnormality, CS or Not Examined
XXXXXX	XX/N	Screening	DDMMMYYYY	CNS	Normal	
				Eyes	Normal	
				ENT	Abnormal, CS	xxxxxx
				Respiratory	Normal	

---						

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native, A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT=Multiple.

Programming Note for Listing 16.2.9.2: If subjects has abnormality description and CS description, please concatenate both separating with ‘,’.

Protocol 207192 Program Run Date: DDMMYYYY

Listing 16.2.9.3
Hemoglobin Assessment
All Randomized Subjects

Study Population: All Randomized Subjects(N=xx)
Product Group: Test Product

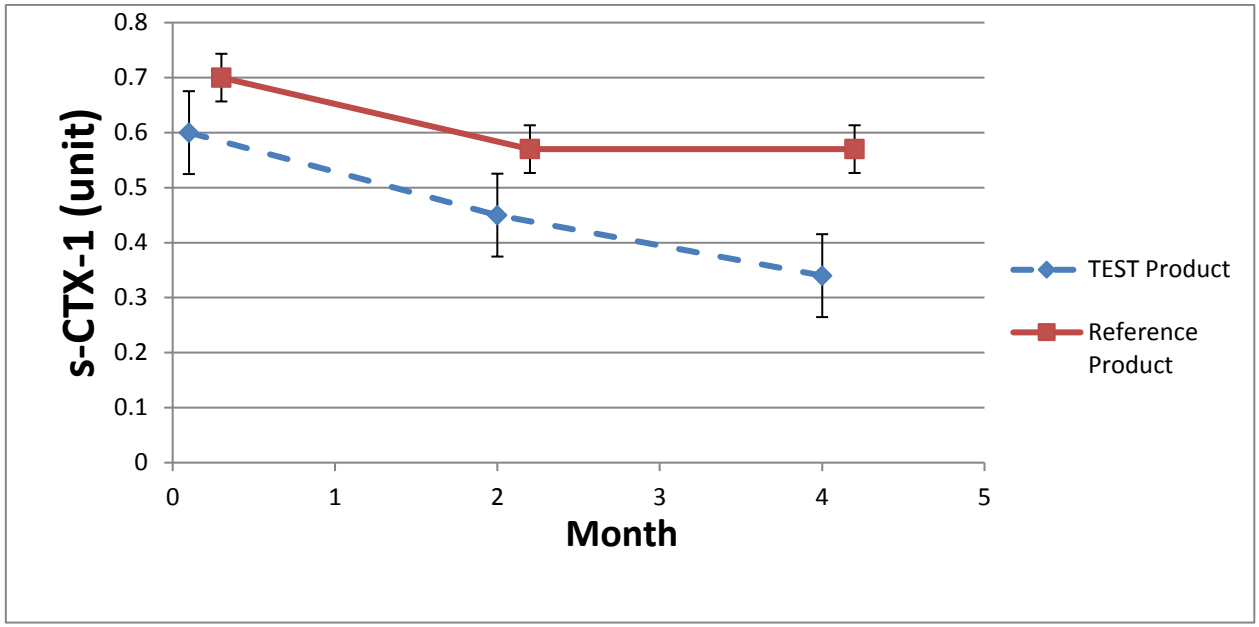
Subject Number	Age/Race [1]	Visit	Date of Visit	Was Hb Assessment Performed?[2]	Hb Assessment Results (g/dL)	
					Observed value	Change from Baseline
XXXXXX	XX/N	Screening	DDMMMYYYY	Yes		
		Baseline	DDMMMYYYY		xx.x	xx.x
					xx.x	xx.x
		Visit 5	DDMMMYYYY	Yes		
		Visit 6	DDMMMYYYY			xx.x
						xx.x

[1] Age in years; Race: A1 = African American/African Heritage, A2 = American Indian Or Alaskan Native, A3 = Asian-Central/South Asian Heritage, A4 = Asian-East Asian Heritage, A5 = Asian-Japanese Heritage, A6 = Asian-South East Asian Heritage, N = Native Hawaiian Or Other Pacific Islander, W1 = White-Arabic/North African Heritage, W2 = White - White/Caucasian/European Heritage, MT=Multiple.
[2] Yes = Assessment performed; No = Assessment not done.

Page x of y

Program: xxxxxx.sas Source: Filename

Figure 14.2.2.1
Serum Cross Linked C-Telopeptide of Type 1 Collagen Least Square Mean(+/-SE) by Time and Treatment
ITT Population



Page x of y

Program: xxxxxx.sas Source: Filename

Programming Note: All other figures will follow the same format. Use one solid line and one dotted line for each treatment. LSMEANS and SE will be obtained from Table 14.2.2.2. Baseline will obtained from the raw values. X-axis will be labeled for baseline, 3 Month and 6 Month.