STATISTICAL ANALYSIS PLAN

SSDXA-14

A Double-Blind, Placebo-Controlled, Crossover Study of Sacrosidase for the Treatment of Subjects with Fructan Intolerance

PROTOCOL VERSION: 1.0

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Table 1: List of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
ANOVA	Analysis Of Variance
ATC	Anatomic Class
CRF	Case Report Form
DSQ	Daily Symptom Questionnaire
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary of Regulatory Activities
PP	Per-protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SQ	Symptom Questionnaire
TEAEs	Treatment-emergent AEs
TSS	Total Symptom Score

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the intended analyses and reporting for protocol SSDXA-14. The development of this SAP takes into account the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline titled "Guidance for Industry: Statistical Principles for Clinical Trials" and the latest ICH E3 Guideline titled "Guidance for Industry: Structure and Content of Clinical Study Reports."

This SAP provides a comprehensive description of the data that will be analyzed, including subject characteristics, efficacy measures, and safety assessments that will be evaluated. Additionally, it offers detailed information on the specific statistical methods to be employed. It is important to note that the statistical analysis methods outlined in this document will take precedence over those described in the clinical protocol.

Should there be a need for supplementary analyses to complement the planned analyses stated in this SAP, they may be conducted and will be duly identified in the final clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To determine if sacrosidase is effective in reducing the incidence and severity of GI symptoms in subjects with fructan intolerance.

2.2 Secondary Objectives

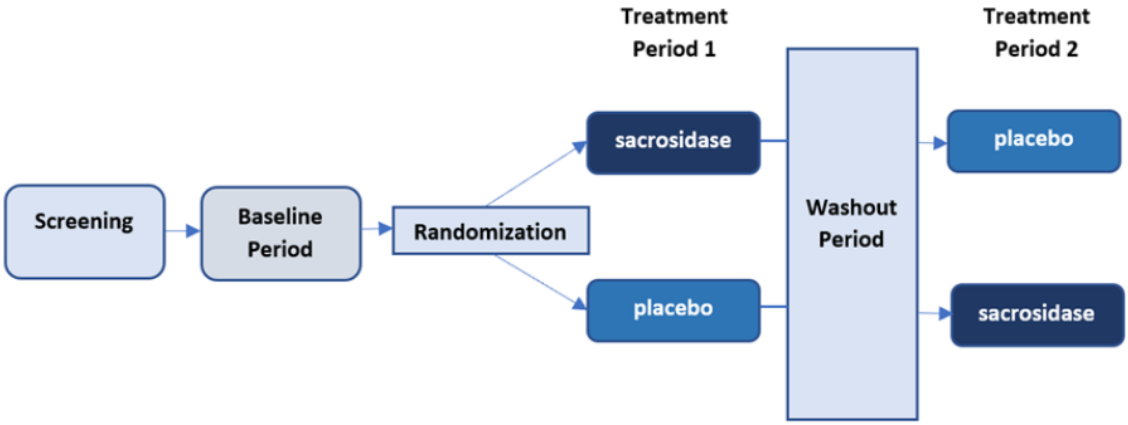
The secondary objective of this study is:

- To determine if sacrosidase is effective in reducing the incidence and severity of abdominal bloating, and to assess the safety and tolerability of sacrosidase compared to placebo in subjects with fructan intolerance.

3 OVERALL STUDY DESIGN AND PLAN

This is a feasibility/pilot double-blind, placebo-controlled, crossover study to evaluate the efficacy and safety of sacrosidase and placebo in 25 subjects with fructan intolerance. This study will consist of a Screening Visit, Baseline Period, Treatment Period 1, Washout Period, and Treatment Period 2. The study design is depicted graphically in Figure 1.

Figure 1: Crossover Study Design



The study timeline was illustrated in the following Figure 2.

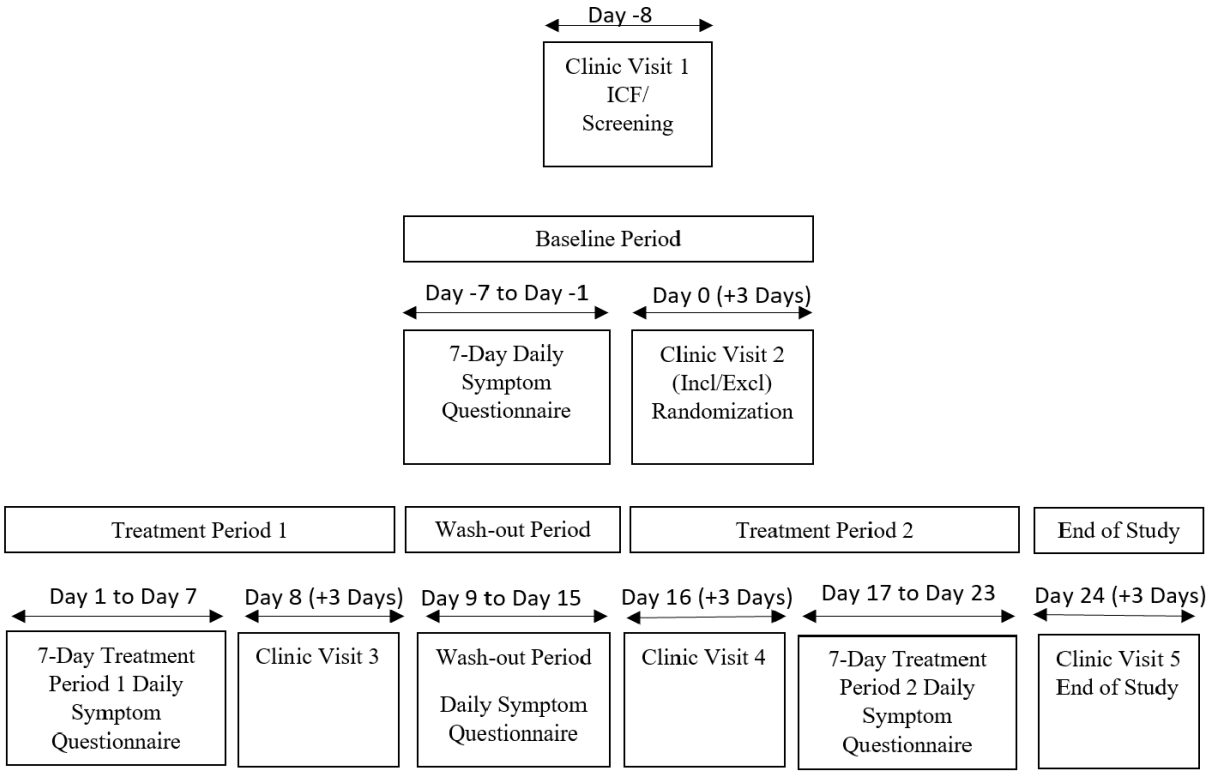


Figure 2: Study timelines for each period.

3.1 Study Population

Approximately 25 participants who meet the selection criteria and have fructan intolerance will be enrolled in this study. The complete list of inclusion and exclusion criteria can be found in the SSDXA-14 protocol.

3.2 Treatment Regimens

Subjects will take either sacrosidase or placebo, 2 mL (17,000 IU) with every meal or snack. The recommended dosage for subjects greater than 15 kg in body weight is 2 mL (17,000 IU) or 2 full measuring scoops (each full measuring scoop equals 1 mL); taken orally with each meal or snack diluted with 4 ounces (120 mL) of water or milk. The beverage should be served cold or at room temperature. The beverage should not be warmed or heated before or after addition of sacrosidase or placebo because heating is likely to decrease potency. Sacrosidase or placebo should not be reconstituted or consumed with fruit juice since its acidity may reduce the enzyme activity.

It is recommended that approximately half of the dosage be taken at the beginning of the meal or snack and the remainder be taken during the meal or snack.

The recommended dosage for this study is as follows:

- 2 mL (17,000 IU) (two full measuring scoops or 56 drops) per meal or snack for subjects over 15 kg in body weight.

3.3 Sample Size Considerations

Assuming approximately 15% of subjects will not be evaluable, a total of 25 subjects will be enrolled to provide 21 evaluable subjects. A total of 21 evaluable subjects will provide approximately 80% power to detect a mean difference of 2.0 between response to sacrosidase and placebo in the primary endpoint (mean change from baseline in the daily TSS), based on a two-sided t-test with a statistical significance of $P < 0.05$, assuming a standard deviation of 3.0 for paired differences.

4 GENERAL ANALYSIS AND REPORTING CONVENTIONS

The study variables will be listed, and selected variables will be summarized and analyzed, as appropriate. The analysis will be conducted using the SAS System version 9.3 or higher.

Categorical variables will be summarized using counts (n) and percentages (%), presented as "n (XX.X)". Percentages will be displayed with one decimal place (XX.X), except for 100%, which will be shown without additional decimal places. If a count is 0, no percentage will be displayed. Summaries for categorical and discrete variables will include all categories, even if no subjects had a response in a specific category, to ensure completeness.

Continuous variables will be summarized by the number of subjects, mean, median, standard deviation (SD), minimum, and maximum. The mean and median will be reported with one more decimal place than the precision of the data, while the SD will be reported with two more decimal

places. The minimum and maximum values will be reported with the same level of precision as the original observations. Calculated values, such as those resulting from unit conversion, will generally be rounded to the same number of decimal places as the original data. To round, consider the digit to the right of the last significant digit: if it is less than 5, round down; if it is greater than or equal to 5, round up.

For treated subjects, the last non-missing observation across all visits before the study drug begins will be considered the **baseline value**.

Data will be listed by treatment arm and subject when appropriate. Subject data listings will be provided for all subjects, unless otherwise specified.

When testing hypotheses of treatment arm differences, the associated p-value will be reported, where applicable. Unless necessary, p-values will be reported with three decimal places, displaying values less than 0.001 as "<0.001". All hypothesis testing will be conducted at a two-sided 5% significance level, unless otherwise specified.

5 ANALYSIS POPULATIONS

Subject inclusion into each population will be determined prior to the final analysis.

5.1 Intention-to-Treat (ITT) Population

The intent-to-treat (ITT) study population will include all enrolled subjects who underwent randomization, which will occur during Clinic Visit 2.

5.2 Modified Intention-to-Treat (mITT) Population

The modified intention-to-treat (mITT) study population will include all randomized subjects who took at least one dose of sacrosidase and provided completed questionnaires for at least one day of that treatment period (Treatment 1 for Group 1 and Treatment 2 for Group 2).

5.3 Safety Analysis Population

The safety analysis population will include all subjects who took at least one dose of sacrosidase during Treatment 1 for Group 1 and Treatment 2 for Group 2.

5.4 Per-Protocol (PP) Analysis Population

The per-protocol population will be the subset of the ITT population who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of treatment according to the underlying scientific rationale. This will be those subjects who used sacrosidase with at least one meal on every day of the treatment period.

6 STUDY SUBJECTS

6.1 Disposition of Subjects

Study completion and reasons for discontinuation among ITT Population will be summarized separately for each treatment arm. Discontinuations will be tabulated by reason, both for each treatment arm and overall.

6.2 Protocol Deviations

Strict adherence to the protocol is expected, and deviations should be avoided. In the event that deviations do occur, the investigator must review the implications of the deviation. Any deviation must be documented, including the reason, date, action taken, and the impact on the subject and/or the trial. If protocol deviations are captured in the CRF or database, a data listing of all such deviations will be provided. Subjects with significant protocol deviations may be excluded from the per-protocol (PP) analyses at the discretion of the sponsor.

7 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Demographic and Baseline Characteristics

Descriptive statistics for all demographic and baseline characteristics will be provided, based on ITT Population and mITT population. Demographic data will be summarized using descriptive statistics or frequency tables, both overall and categorized by treatment arms. Categorical variables will be presented with the number and percentages of subjects in each category. Continuous variables will be summarized with the number of subjects with available data, along with the mean, median, standard deviation (SD), minimum, and maximum values.

7.2 Medical History

Medical histories of Safety Analysis Population will be summarized based on treatment arms. The summaries will utilize the System Organ Class (SOC) and Preferred Term (PT) coding from the Medical Dictionary for Regulatory Activities (MedDRA), Version to be specified in TFL outputs. The listed conditions will include the investigator's verbatim description of the relevant medical condition, the corresponding coded terms (SOC, PT), start date, end date, and indication of whether the condition is ongoing.

7.3 Prior and Concomitant Medications

Medications or therapies administered prior to the first dose of study medication will be considered as prior medications. Medications or therapies administered on or after the first dose of study medication, but not starting after study discontinuation or end of study, if it comes last, will be considered as concomitant medications. Prior medication that were taken by the subject within 30 days of study enrollment will also be considered as concomitant medications. Throughout the study and at early discontinuation, concomitant medications (medications taken while on study medication) will be recorded. These medications will be coded using the WHO-Drug Dictionary

(version to be specified in TFL output). The number of subjects among Safety Analysis Population using prior or concomitant medications will be categorized by Anatomic Class (ATC) Level 3 and Preferred Term (PT) and presented for each treatment arm. It is important to note that within a specific category, such as a drug category, each subject will only be counted once.

8 EFFICACY

8.1 Outcome

8.1.1 Primary Outcome

The primary outcome measurement of the study is the total symptom score (TSS). The TSS is derived from the subject's responses to the daily symptom questionnaire (DSQ). The DSQ captures the frequency and severity of seven GI symptoms (abdominal bloating, abdominal pain, abdominal cramps, abdominal gas/flatulence, diarrhea, constipation, and nausea) using the following scoring system:

- Symptom frequency score: Subjects are asked to score the number of hours each GI symptom was experienced in the past 24 hours using a 6-point scale (0, 1, 2, 3, 4, and 5 or more) with "5 or more" being treated as a score of 5.
- Symptom severity score: Subjects are asked to score the worst severity of each GI symptom experienced in the past 24 hours using a 10-point scale (0 to 9).

The numeric value of the TSS is derived from the DSQ as follows:

1) The daily symptom score is calculated by summing the frequency and severity scores and has a maximum value of 14 for each symptom. A missing value will be treated as a score of 0. If a subject reports a "1"' or higher for severity and "0" for frequency, or vice versa, then this data should be flagged as an inconsistency. In cases where the severity score is 0 and the frequency score is greater than 0, the frequency score will be adjusted to 0. Conversely, if the severity score is greater than 0 and the frequency score is 0, the frequency score will be set equal to: $\frac{severity\ score}{9} \times 5$, which ensures it is within the range of 0 to 5, and rounded to the nearest integer.
2) The combined daily symptom score is calculated by summing the daily symptom score for all seven GI symptoms and has a maximum value of 98.
3) The TSS is calculated by averaging the combined daily symptoms scores for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period. The TSS has a maximum value of 98. Each subject who completes the study will have four TSS.

8.1.1.1 Daily Symptom Questionnaire Compliance

Subjects are instructed to complete their Daily Symptom Questionnaire at the end of each day throughout the Baseline Period, Treatment Period 1, Washout Period and Treatment Period 2, spanning a duration of 7 days each.

8.1.2 Secondary Outcome

The secondary efficacy outcome includes:

- Frequency of abdominal bloating experienced within the past 24 hours during a 7-day period calculated by averaging the daily scores for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period,

Missing data imputation and resolution of data inconsistencies outlined for the primary outcome in Section 8.1.1 will be applied to these secondary efficacy outcomes.

8.1.3 Exploratory Outcomes

The exploratory efficacy outcomes include:

- Total symptom severity score calculated by averaging the daily total severity scores for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period
- Total symptom frequency score calculated by averaging the daily total frequency scores for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period
- Worst TSS calculated by taking the maximum of the daily sum scores (sum of severity and frequency scores over all symptoms) across 7 days for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period
- Worst symptom severity score calculated by averaging the daily worst symptom severity scores for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period. A daily worst severity symptom is the symptom with the highest severity score for a given day
- Worst symptom frequency score calculated by averaging the daily worst symptom frequency scores for each of the four periods: Baseline Period, Treatment 1 Period, Washout Period and Treatment 2 Period. A daily worst frequency symptom is the symptom with the highest frequency score for a given day

Missing data imputation and resolution of data inconsistencies outlined for the primary outcome in Section 8.1.1 will be applied to these exploratory efficacy outcomes.

8.2 Analysis Methods

8.2.1 Primary Efficacy Analyses

A linear mixed-effects analysis of covariance (ANCOVA) model will be utilized to compare the change from baseline Total Symptom Score (TSS) between the sacrosidase and placebo groups after each treatment period. The model will incorporate fixed effects for the baseline score, treatment (sacrosidase or placebo), treatment periods (1 or 2), and sequence, while subjects will be considered as a random effect. The objective of this analysis is to evaluate the efficacy of sacrosidase in reducing the TSS relative to placebo. If the least squares means of the change demonstrate a significant difference ($p < 0.05$ for a two-sided test) between the sacrosidase and placebo groups, with a favorable outcome in favor of sacrosidase, the study findings will confirm the hypothesis that sacrosidase has the potential to improve GI symptoms in individuals who have received an objective diagnosis of fructan intolerance.

In order to validate the crossover design, additional analyses will be conducted to examine the presence of carryover effects. Under the condition that there is no carryover effect, the outcomes obtained during washout period should be similar to these obtained during baseline period. The change from the baseline to the washout period in outcomes will be tested using ANCOVA model, where the change from baseline to washout period in outcomes is the dependent variable, baseline score and treatment will be the independent variables. If a carryover effect is observed with 2-sided test at a significant level of 0.05, inferences regarding efficacy will be based on the data obtained during Treatment period 1 in the final analysis. The efficacy assessment of treatment period 2 may be conducted by using washout period outcomes as the baseline of treatment period 2.

The primary efficacy analyses will be based on the mITT population.

8.2.2 Sensitivity Analysis of the Primary Outcome

The primary analysis will also include the Per Protocol Population to assess treatment efficacy. Additionally, separate ANCOVA models will be utilized to compare the treatment effect in TSS during Period 1 and Period 2, respectively. In these period-specific analyses, the models will include baseline score and treatment as a fixed effect and no random effects will be included. This approach allows for a focused evaluation of the treatment's effect within each period of the study. These period-specific analyses will be conducted for the mITT population and for the Per Protocol Population, respectively.

8.2.3 Secondary Efficacy Analyses

The analysis model described in 8.2.1, except the carryover effect analysis, will also be used for the analysis of the secondary endpoint. The secondary analysis will also include the Per Protocol Population, as a sensitivity analysis.

8.2.4 Exploratory Efficacy Analyses

The analysis model described in 8.2.1, except the carryover effect analysis, will also be used for the analysis of the exploratory outcomes. The exploratory analysis will also include the Per Protocol Population, as a sensitivity analysis.

8.3 Supplemental Analyses

To evaluate the correlation between the primary outcome and GI symptoms, Spearman correlations will be estimated for each of the symptom sum score, frequency score and severity score to the TSS, by treatment arms at each Study Visit, based on the mITT population.

9 SAFETY EVALUATION

The safety of sacrosidase will be based on the nature, frequency, severity, and seriousness of AEs including any changes vital signs or other safety parameters.

All safety analysis will be performed for safety analysis population. All safety endpoints will be summarized by treatment arms, treatment periods and overall treatment when appropriate.

For the analyses of change from baseline, only subjects with a baseline and at least one post-baseline measure will be included in the analysis. Unless otherwise specified, baseline is defined as the latest non-missing observation across all the visits in the baseline period, before the first dose of study drug is administered.

The safety evaluation of sacrosidase will encompass an assessment of adverse events (AEs), considering their nature, frequency, severity, and seriousness. Additionally, changes in vital signs and other safety parameters will be considered. These safety analyses will be conducted on the safety analysis population and will be descriptive with no statistical hypothesis testing.

All safety endpoints will be summarized based on treatment arms and, when appropriate, treatment periods and overall treatment.

9.1 Study Drug Exposure

Sacrosidase dosing information will be listed. Total number of doses taken will be summarized by treatment arms and, when appropriate, treatment periods.

9.2 Adverse Events (AEs)

The definition of an adverse event (AE), its severity, and its relationship to study medication are presented in Protocol Section 11.4.

The onset date and time of an adverse event (AE) will be compared to the date and time of each treatment to determine if the AE is treatment emergent and if it is related to a specific treatment

(Sacrosidase vs Placebo). In cases where the AE onset date is missing or partial, efforts will be made to compare it with the date of the dose administered prior to the occurrence of the AE. AEs will be considered treatment emergent unless there is clear evidence, such as comparison of partial dates or assessment indicating that the AE started before a given dose of the study medication.

Treatment-emergent AEs (TEAEs) will be defined as any AE reported on or after the date of the first dose of the study drug. All TEAEs will be coded using the most recent version of the Medical Dictionary of Regulatory Activities (MedDRA) preferred terms and will be grouped according to system, organ, and class (SOC) designation.

The secondary safety outcomes include:

- Frequency and severity of TEAEs and TESAEs,
- Any premature study withdrawals related to adverse reactions.

The severity, frequency, and relationship of TEAEs to the investigational product will be presented based on the preferred term and SOC grouping. Each TEAE, based on preferred terminology, will be counted only once for each patient. If the same TEAE occurs multiple times, the highest severity and relationship to the investigational product will be assumed. Therefore, study patients will not be counted multiple times in the calculation of frequencies for a specific TEAE. The severity, frequency, and relationship of SAEs to the investigational product will be presented based on the preferred term and SOC grouping.

A summary of AEs will be provided, including the number and percentage of subjects who experienced at least one TEAE, categorized by treatment arms, treatment periods and overall treatment when appropriate. The following events will be included in the summary:

- TEAE
- Treatment-related TEAE
- TEAE leading to early study drug discontinuation
- TEAE leading to study drug interruption
- Treatment-emergent serious adverse event (SAE)
- Treatment-related treatment-emergent SAE
- TEAEs Leading to Study Discontinuation

Detailed listings of each individual AE will be provided, including the start date, stop date, severity, relationship to the study drug, outcome, and duration.

9.3 Vital Signs and Abbreviated Physical Exam

Vital signs, as listed in protocol Sections 11.1, will be summarized using descriptive statistics. Baseline, post-baseline, and change from baseline data will be summarized, as applicable, for each

treatment arm at each Study Visit. Vital signs and abbreviated physical examination will be presented in listings.

10 CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Not applicable.

11 OUTPUTS PLANNED FOR THE CLINICAL STUDY REPORT

Tables and Listings will be specified in the Data Presentation Specification document

11.1 Figures to be Included in the Clinical Study Report

No figures are planned for the CSR.

11.2 Tables and Listings be Included in the Clinical Study Report

1. TABLES TO BE INCLUDED IN STUDY REPORT

1.1 Summary of Subject Disposition

Table 14.1.1.1 Subject Disposition - ITT Population

1.2 Demographic and Other Baseline Characteristics

Table 14.1.2.1a Summary of Demographic and Other Baseline Characteristics by Treatment Sequences - ITT Population

Table 14.1.2.1b Summary of Demographic and Other Baseline Characteristics by Treatment Sequences - MITT Population

Table 14.1.2.2 Number and Percentage of Subjects with Medical History by Treatment Sequences, MedDRA System Organ Class, and Preferred Term - Safety Analysis Population

Table 14.1.2.3 Number and Percentage of Subjects with Prior Medications by Treatment Sequences, Anatomic Class Level 3 Name, and Preferred Term - Safety Analysis Population

Table 14.1.2.4 Number and Percentage of Subjects with Concomitant Medications by Treatment Sequences, Anatomic Class Level 3 Name, and Preferred Term - Safety Analysis Population

Table 14.1.2.5 Summary of Study Drug Exposure by Treatment Sequences and Treatment Periods - Safety Analysis Population

1.3 Clinical Efficacy Results

Table 14.2.1.1a Summary of Total Symptom Score at Each Study Visit - MITT Population

Table 14.2.1.1b Analysis of Treatment Effect on Change from Baseline to Both Periods in Total Symptom Score Using ANCOVA Model - MITT Population

Table 14.2.1.1c Analysis of Treatment Effect on Change from Baseline to Both Periods in Total Symptom Score Using ANCOVA Model - Per Protocol Population

Table 14.2.1.1d Analysis of Total Symptom Score at Baseline and during the Washout Period using ANCOVA Model (Carryover Effect) - MITT Population

Table 14.2.1.1e Analysis of Treatment Effect on Change from Baseline to Period 1 in Total Symptom Score Using ANCOVA Model - MITT Population

Table 14.2.1.1f Analysis of Treatment Effect on Change from Baseline to Period 1 in Total Symptom Score Using ANCOVA Model - Per Protocol Population

Table 14.2.1.1g Analysis of Treatment Effect on Change from Baseline to Period 2 in Total Symptom Score Using ANCOVA Model - MITT Population

Table 14.2.1.1h Analysis of Treatment Effect on Change from Baseline to Period 2 in Total Symptom Score Using ANCOVA Model - Per Protocol Population

Table 14.2.2.1a Summary of Frequency Score of Abdominal Bloating at Each Study Visit - MITT Population

Table 14.2.2.1b Analysis of Treatment Effect on Change from Baseline to Both Periods in Frequency Score of Abdominal Bloating Using ANCOVA Model - MITT Population

Table 14.2.2.1c Analysis of Treatment Effect on Change from Baseline to Both Periods in Frequency Score of Abdominal Bloating Using ANCOVA Model - Per Protocol Population

Table 14.2.3.1a Summary of Total Symptom Severity Score at Each Study Visit - MITT Population

Table 14.2.3.1b Analysis of Treatment Effect on Change from Baseline to Both Periods in Total Symptom Severity Score Using ANCOVA Model - MITT Population

Table 14.2.3.1c Analysis of Treatment Effect on Change from Baseline to Both Periods in Total Symptom Severity Score Using ANCOVA Model- Per Protocol Population

Table 14.2.3.2a Summary of Total Symptom Frequency Score at Each Study Visit - MITT Population

Table 14.2.3.2b Analysis of Treatment Effect on Change from Baseline to Both Periods in Total Symptom Frequency Score Using ANCOVA Model- MITT Population

Table 14.2.3.2c Analysis of Treatment Effect on Change from Baseline to Both Periods in Total Symptom Frequency Score Using ANCOVA Model - Per Protocol Population

Table 14.2.3.3a Summary of Worst Total Symptom Score at Each Study Visit - MITT Population

Table 14.2.3.3b Analysis of Treatment Effect on Change from Baseline to Both Periods in Worst Total Symptom Score Using ANCOVA Model - MITT Population

Table 14.2.3.3c Analysis of Treatment Effect on Change from Baseline to Both Periods in Worst Total Symptom Score Using ANCOVA Model - Per Protocol Population

Table 14.2.3.4a Summary of Worst Symptom Severity Score at Each Study Visit - MITT Population

Table 14.2.3.4b Analysis of Treatment Effect on Change from Baseline to Both Periods in Worst Symptom Severity Score Using ANCOVA Model - MITT Population

Table 14.2.3.4c Analysis of Treatment Effect on Change from Baseline to Both Periods in Worst Symptom Severity Score Using ANCOVA Model - Per Protocol Population

Table 14.2.3.5a Summary of Worst Symptom Frequency Score at Each Study Visit - MITT Population

Table 14.2.3.5b Analysis of Treatment Effect on Change from Baseline to Both Periods in Worst Symptom Frequency Score Using ANCOVA Model - MITT Population

Table 14.2.3.5c Analysis of Treatment Effect on Change from Baseline to Both Periods in Worst Symptom Frequency Score Using ANCOVA Model - Per Protocol Population

Table 14.2.3.6a Spearman Correlation between Each Symptom Sum Score and Total Symptom Score at Each Study Visit by Treatment Sequence - MITT Population

Table 14.2.3.6b Spearman Correlation between Each Symptom Frequency Score and Total Symptom Score at Each Study Visit by Treatment Sequence - MITT Population

Table 14.2.3.6c Spearman Correlation between Each Symptom Severity Score and Total Symptom Score at Each Study Visit by Treatment Sequence - MITT Population

Table 14.2.3.7a Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Sum Score of Abdominal Bloating Using ANCOVA Model - MITT Population

Table 14.2.3.7b Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Sum Score of Abdominal Pain Using ANCOVA Model - MITT Population

Table 14.2.3.7c Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Sum Score of Abdominal Cramps Using ANCOVA Model - MITT Population

Table 14.2.3.8a Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Frequency Score of Abdominal Pain Using ANCOVA Model - MITT Population

Table 14.2.3.8b Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Frequency Score of Abdominal Cramps Using ANCOVA Model - MITT Population

Table 14.2.3.8c Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Frequency Score of Abdominal Gas/Flatulence Using ANCOVA Model - MITT Population

Table 14.2.3.9a Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Severity Score of Abdominal Pain Using ANCOVA Model - MITT Population

Table 14.2.3.9b Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Severity Score of Abdominal Cramps Using ANCOVA Model - MITT Population

Table 14.2.3.9c Analysis of Treatment Effect on Change from Baseline to Both Periods in Symptom Severity Score of Abdominal Gas/Flatulence Using ANCOVA Model - MITT Population

1.4 Clinical Safety Results

Table 14.3.1.1 Overall Summary of Adverse Events - Safety Analysis Population

Table 14.3.1.2 Number and Percentage of Subjects with TEAEs by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.1.3a Number and Percentage of Subjects with TEAEs by Maximum Severity by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.1.3b Number and Percentage of Subjects with TESAEs by Maximum Severity by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.1.4a Number and Percentage of Subjects with TEAEs by Maximum Relationship by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.1.4b Number and Percentage of Subjects with TESAEs by Maximum Relationship by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.1.5 Number and Percentage of Subjects with Treatment-Related TEAEs by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.2.1 Number and Percentage of Subjects with Treatment-Related TESAEs by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.2.2 Number and Percentage of Subjects with TEAEs Leading to Treatment Discontinuation by Treatment Sequence and Treatment Period, and Treatment - Safety Analysis Population

Table 14.3.5.1 Summary of Vital Signs at Each Study Visit by Treatment Sequence - Safety Analysis Population

2. LISTINGS TO BE INCLUDED IN STUDY REPORT

2.1 Subject Disposition

Listing 16.2.1.1 Subject Disposition - ITT Population

Listing 16.2.1.2 Eligibility Criteria - Enrolled Population

Listing 16.2.2.1 Protocol Deviations – ITT Population

2.2 Demographics and Baseline Characters

Listing 16.2.4.1a Demographic and Baseline Characteristics - ITT Population

Listing 16.2.4.1b Demographic and Baseline Characteristics - MITT Population

Listing 16.2.4.2 Medical History - Safety Analysis Population

Listing 16.2.4.3 Prior and Concomitant Medications - Safety Analysis Population

2.3 Study Drug Accountability

Listing 16.2.5.1 Study Drug Accountability - Safety Analysis Population

2.4 Clinical Safety Data

Listing 16.2.7.1 Adverse Events - Safety Analysis Population

Listing 16.2.7.2 Serious Adverse Events - Safety Analysis Population

Listing 16.2.7.3 Treatment-Related Adverse Events - Safety Analysis Population

Listing 16.2.7.4 Adverse Events Leading to Treatment Discontinuation - Safety Analysis Population

Listing 16.2.7.5 Adverse Events Leading to Study Discontinuation - Safety Analysis Population

Listing 16.2.7.6 Adverse Events Leading to Death - Safety Analysis Population

Listing 16.2.8.1 Urine Pregnancy Tests - Safety Analysis Population

Listing 16.2.9.1 Vital Signs - Safety Analysis Population

12 APPENDIX

Example SAS Code for the Primary Analysis

The model incorporates fixed effects for treatment (sacrosidase or placebo), treatment periods (1 or 2), and sequence (1 or 2), while subjects will be considered as a random effect.

```
proc mixed data=dataset noclprint=2 covtest;
        class sequence(ref='1') visit(ref='Period1') group(ref='Placebo') id;
        model chg= baseline_score group sequence visit/s ddfm=kr2 noint;
        random int/sub=id;
        lsmeans group/cl diff;
run;
*chg: change from baseline in TSS
*ID: subject ID
*Group: sacrosidase or placebo
*Sequence: sequence 1: placebo first; sequence 2: Sacrosidase first
*Visit: Period 1 and Period 2

*---------Testing Carryover Effect------------------------------;
*Testing whether the change from baseline to the washout period is significantly different from 0 for each treatment arm.
proc mixed data=chg noclprint=2 covtest;
        where visit = 'Washout';
        class group(ref='Placebo');
        model chg=bl_score group/s ddfm=kr2 noint;
        lsmeans group/cl;
run;
```

APPROVAL FOR STATISTICAL ANALYSIS PLAN

Protocol Title:	**A Double-Blind, Placebo-Controlled, Crossover Study of Sacrosidase for the Treatment of Subjects with Fructan Intolerance**
Reference:	**SSDXA-14/SAP**
Version:	**1.0**
Date Effective:	
Author:	**Nan Chen, Biostatistics, Inventiv Matrix, Inc.**

Author's signature: Date:

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Reviewer/Approver:

Position/Title:

Signature for Sponsor: Date: