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Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

17 July 17

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MICROBIOME STATISTICAL ANALYSIS PLAN

SERES-101

A Multiple Dose Study to Evaluate the Safety, Tolerability and Microbiome Dynamics of SER-287 in Subjects with Mild-to-Moderate Ulcerative Colitis

Statistical Analysis Plan for Primary and Exploratory Microbiome Endpoints

Version: Final 1.0

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TABLE OF CONTENTS

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
CSP	Clinical Study Protocol
CSR	Clinical Study Report
NGS	Next Generation Sequencing
OTU	Operational Taxonomic Unit
SAP	Statistical Analysis Plan
RNA-seq	RNA sequencing
TLF/s	Tables, Lists, and Figures
WMS	Whole Metagenomic Sequencing

1. MICROBIOME STATISTICAL ANALYSIS PLAN

This Microbiome Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing primary and exploratory microbiome endpoint study data and outlines the analysis that will generate Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP). This SAP addresses planned analysis and presentation of microbiome, transcriptomic, and metabolomic alterations. The analysis of safety and clinical efficacy is described in the Clinical Statistical Analysis Plan, which is a separate document.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. Any deviations from the planned analyses will be described and justified in the final clinical study report (CSR).

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To evaluate the safety and tolerability of SER-287 vs. placebo in adult subjects ≥18 years of age with mild-to-moderate ulcerative colitis
- To compare the baseline composition of the intestinal microbiome to the post-baseline composition after initiation of SER-287 or placebo
- To determine the engraftment of SER-287 bacteria into the intestinal microbial community in each of the SER-287 arms compared to the placebo arm

2.2 Secondary Objectives

- To determine the proportion of subjects in each of the treatment arms who, at 8 weeks post initiation of treatment, achieve a clinical response, complete remission, and endoscopic improvement
- To assess changes in serum and fecal biomarkers from baseline throughout treatment

2.3 Exploratory Objectives

- To compare the changes in exploratory biomarkers from mucosal biopsies and stool samples in each of the treatment arms from baseline throughout treatment.
- To determine the complement of metabolic pathways from stool in each of the treatment arms from baseline throughout treatment.

3. STUDY DESIGN

This is a Phase 1b multicenter, randomized, double-blind, placebo-controlled multiple dose study designed to evaluate the safety and tolerability of SER-287 and to evaluate the microbiome alterations and pharmacokinetics and pharmacodynamics associated with two dosing regimens of SER-287 in adult subjects with mild-to-moderate ulcerative colitis (UC). Subjects will be randomized to one of 4 study arms:

A) Pre-treatment of placebo, followed by once weekly dosing of SER- 287 for 8 weeks;

B) Pre-treatment of placebo, followed by once daily dosing of placebo for 8 weeks;

C) Pre-treatment of vancomycin, followed by once daily dosing of SER-287 for 8 weeks;

D) Pre-treatment of vancomycin, followed by once weekly dosing of SER-287 for 8 weeks.

The doses, route, and schedule of study drug administration are shown below:

Group	Pre--treatment: Vanco or Pbo				Treatment Period: SER---287 or Pbo			
	Vanco or Pbo	Regimen	Admin	Duration	SER--287 or Pbo	Regimen	Admin	Duration
A	Pbo	Pbo	One capsule four times daily orally	6 days	SER-287 + Pbo	SER-287 Weekly ($1x10^8$ SporQs) +Pbo 6d/wk	Four capsules once daily orally	8 wks
B	Pbo	Pbo	One capsule four times daily orally	6 days	Pbo	Placebo Daily	Four capsules once daily orally	8 wks
C	Vanco	Vanco 125 mg qid	One capsule four times daily orally	6 days	SER-287	SER-287 Daily ($1x10^8$ SporQs)	Four capsules once daily orally	8 wks
D	Vanco	Vanco 125 mg qid	One capsule four times daily orally	6 days	SER-287 + Pbo	SER-287 Weekly ($1x10^8$ SporQs)+Pbo 6d/wk	Four capsules once daily orally	8 wks

The study has 5 study periods: Screening (Day-17 to Day-1), Pre-treatment, Treatment, a 4 Week Short Term Safety Follow-up and a Long Term Safety Follow-up. The Schedule of Events is presented in Table 3 of the CSP.

The Pre-Treatment Period (Day 1 to Day 7) includes administration of either oral vancomycin 125 mg four times a day for 6 days or matching placebo.

The Treatment Period (8 weeks, Day 8-63) includes administration of 4 capsules taken orally once a day of SER-287 or placebo according to the treatment group to which they have been

assigned: SER-287 once daily, SER-287 once weekly with matching placebo on other days, or placebo daily.

4. STUDY POPULATION

The study population will consist of adult subjects with active mild-to-moderate ulcerative colitis.

Detailed lists of inclusion and exclusion criteria are shown in Sections 4.1 and 4.2 of the CSP.

5. STATISTICAL BASIS FOR SAMPLE SIZE

No formal sample size calculation was performed. A sample size of approximately 55 subjects with 15 subjects randomized to each of the active arms (Treatment Groups A, C and D) and 10 subjects in the placebo arm (Treatment Group B) is considered sufficient to evaluate the primary microbiome endpoints and exploratory endpoints of the study.

6. SUBJECT IDENTIFICATION AND RANDOMIZATION

Subject identification, methods of assigning patients to study treatment, and randomization codes are described in Sections 6.1-6.3 of the Clinical SAP.

6.1 Breaking the Study Blind at the End of Study

The primary study period (Visit 1 through Visit 13) will be conducted as a double-blind study. The final database for the primary study period will remain blinded until all clinical data collected through Visit 13 has been entered, cleaned and declared complete and final. The CSR will be finalized after results from the primary study period are complete; all available data post-Visit 13 pertaining to mortality will be provided in the CSR. Because of the time lag involved in generating microbiome data, clinical results by treatment group, but not subject by subject unblinded data, will be available before microbiome analysis for Visit 12 and Visit 13 samples is complete. Below, we describe how we will maintain the study blind for analysis of microbiome data to ensure unbiased analysis of all populations.

Samples from Visit 12 and Visit 13 will be processed in a fashion to ensure unbiased analysis of all populations. Specifically, blinded genomic data will be generated for samples from Visit 12 and Visit 13 as samples become available. Data will be processed through a pre-defined computational pipeline prior to interim database lock to generate microbiome profiles. During this pre-processing step, the study blind will be maintained through the use of dummy randomization codes.

Final TLFs for all patients at Visit 12 will be generated using true treatment codes upon unblinding after interim database lock when all subjects complete their Visit 13, but before all subjects have completed the long-term safety follow-up (Day 246). Since the study is still ongoing, only a limited number of study team members will have access to the true treatment code at subject level. To ensure unbiased analysis of Visit 13 samples, we will process blinded Visit 13 samples through the pre-defined computational pipeline using dummy randomization codes to check data quality and integrity. Generation of final TLFs for the Visit 13 samples using unblinded clinical data will not occur until TLFs for Visit 12 are final.

The primary microbiome genomic sequence datasets will be generated by a team at our audited sequencing vendor. Data transfer from the vendor to Seres will occur via encrypted and password-protected hard drive and will be transferred to a secure, restricted-access location on a Seres server. All TLFs will be stored in a- secure network location, which only the unblinded genomic data team at Seres will be able to access. After interim lock at Visit 13, all clinical data,

sequence data, and TLFs will remain unchanged and locked until the study is completed and all patients complete the long-term safety follow-up. A change log will be maintained on the primary data files to ensure that they are not modified. If any samples need to be re-sequenced due to issues of poor quality, this will be noted in the final analysis.

7. STATISTICAL ANALYSIS CONVENTIONS

7.1 Analysis Variables

7.1.1 Primary Endpoints

The following primary endpoints are discussed in this SAP:

- Microbiome Alterations
- Engraftment

This SAP documents the presentation and analysis of genomic sequence results for assessment of microbiome alterations as measured by changes in the composition of the intestinal microbiome, and engraftment of SER-287 bacteria. For clarity, we present below the schedule of assessments (Table 7.1.1.1) filtered to show only samples collected for the primary and exploratory endpoints addressed in this document.

For the purposes of all analyses described in this document, the baseline sample will be defined as the closest evaluable sample collected prior to the start of dosing with vancomycin or placebo during the pre-treatment period (Days 1-7).

7.1.1.1 Schedule of Assessments for Primary and Exploratory Endpoints

Table 7.1.1.1: Schedule of Assessments for Primary and Exploratory Endpoints

Visit Number	Study Day	Sample Type	Study Phase	Microbiome	Metabolomics	Mucosal transcriptomics	Mucosal microbiome
1	Pre-Tx	Stool	Screening	Y	Y	N	N
2	Pre-Tx	Biopsy	Screening	N	N	Y	Y
3	1	Any	Randomization-Start of pre-treatment period	N	N	N	N
4	8 +/- 1d	Stool	Initiation of treatment period	Y	Y	N	N

4	11 +/- 1d	Stool	Treatment period	Y	Y	N	N
5	15 +/- 1d	Stool	Treatment period	Y	N	N	N
5	18 +/- 1d	Stool	Treatment period	Y	N	N	N
6	22 +/- 1d	Stool	Treatment period	Y	Y	N	N
7	29 +/- 1d	Any	Treatment period	N	N	N	N
8	36 +/- 1d	Any	Treatment period	N	N	N	N
9	43 +/- 1d	Any	Treatment period	N	N	N	N
10	50 +/- 1d	Any	Treatment period	N	N	N	N
11	57+/- 1d	Any	Treatment period	N	N	N	N
12	64 +/- 3d	Stool + Biopsy	End of treatment period	Y	Y	Y	Y
13	92 +/- 2d	Stool	Short term safety follow-up	Y	Y	N	N

7.1.1.2 Sample and Sequencing Variables

The record of stool samples collected at Visit 1, Visit 4, Visit 5, Visit 6, Visit 12 and Visit 13 or the Early Termination Visit (if applicable), and any Unscheduled Visit will include record of date and time produced, refrigerated (Yes/No) and status (frozen, ambient or cooled).

Sequencing quality variables will include the number of total sequencing reads, the number of reads mapping to human genome, and/or the number of reads mapping to a taxonomic marker database.

7.1.2 Exploratory Endpoints

The following exploratory endpoints are discussed in this SAP:

- Stool metabolic pathways

  Samples collected for stool metabolomic profiling are described in Section 7.1.1.1 and will be analyzed as described in Section 7.3.5.5.1.

- Mucosal microbiome profiling

  Mucosal microbiome profiling will be performed on biopsy samples collected at Visit 2 and Visit 12. Analysis of these results is described in Section 7.3.5.5.3.

- Mucosal transcriptomic profiling

  Mucosal transcriptome profiling will be performed on biopsy samples collected at Visit 2 and Visit 12. Analysis of these results is described in Section 7.3.5.5.2.

7.2 Analysis Populations

Populations for analysis are reported in Listings 16.2.1-16.2.5.

7.2.1 Microbiome Modified Intent-to-Treat (mcITT) Population

The Microbiome Modified Intent-to-Treat (mcITT) Population will consist of all randomized patients with an evaluable stool sample collected at baseline, and at least one evaluable stool sample collected on or between Visits 4 and 6, inclusive, who were exposed to any amount of study drug, and will be analyzed based on the treatment to which they were randomized. All primary endpoint analyses specified in this SAP will be carried out on the mcITT population or subsets thereof as defined below. The mcITT population is reported in Listing 16.2.1.

7.2.2 Sensitivity Analysis Population - 1

The Sensitivity Analysis Population – 1 (SAP – 1) will consist of all randomized subjects with an evaluable stool sample collected at baseline and one evaluable stool sample collected at Visit 12 or Early Termination (ET) visit collected within a 2 week window surrounding Visit 12. The SAP—1 population is reported in Listing 16.2.2.

7.2.3 Long-term Engraftment (LTE) Population

The LTE Population will be a subset of the SAP—1 population. It will consist of all patients meeting the criteria of the SAP—1 population with the additional requirement of an evaluable stool sample collected at Visit 13. If subjects terminated early from the treatment period but continued in the study and finished short-term safety follow-up, they will not be included in the LTE population. The LTE population is reported in Listing 16.2.3.

7.2.4 Mucosal biopsy analysis population (MBP)

The mucosal biopsy analysis population will consist of all randomized patients with evaluable biopsy samples collected at both Visit 2 and Visit 12, and will be analyzed based on the treatment to which they were randomized. If subjects terminated early from the treatment period with collection of an evaluable biopsy sample, then that subject will be included in the analysis. The MBP population is reported in Listing 16.2.5.

7.2.5 Metabolomic analysis population (MTP)

The metabolomic analysis population will consist of all randomized patients with an evaluable stool sample for metabolomics collected at baseline and at least one evaluable stool sample collected at Visit 12 or ET visit (provided that the ET visit occurred within a 2 week window surrounding Visit 12) and will be analyzed based on the treatment to which they were randomized. The MTP population is reported in Listing 16.2.5.

7.3 Statistical Analysis Methods

7.3.1 Statistical Analysis and Significance Level

Statistical analyses will be separately defined for each endpoint. There will be no adjustment of p-values for multiplicity unless specifically noted. P-values generated for this study are not intended to be conclusive, but provided for guidance only. Any calculated p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as ‘p<0.001’ and p-values greater than 0.999 will be presented as ‘p>0.999’.

7.3.2 Planned Comparisons for All Endpoints

In general, inferential analysis will be based on the following pairwise comparisons:

- Treatment groups A, C and D separately compared to placebo (B). Compares individual pre-treatment and dosing regimens to placebo.
- A and D pooled together compared to placebo (B). Compares arms with weekly administration of SER-287 regardless of vancomycin pre-treatment with placebo.
- A, C and D pooled together compared to placebo (B). Compares all arms with SER-287 treatment to placebo.
- The A vs D comparison examines the impact of vancomycin pre-treatment outcomes for subjects who received weekly doses of SER-287.
- The C vs D comparison examines the impact of daily versus weekly dosing for subjects who received vancomycin pre-treatment.

7.3.3 Sample and Sequencing Acceptability Criteria

Samples are collected according to the time period described in the Schedule of Events. The samples collected out of visit window will be mapped to the closest appropriate visit. A sensitivity analysis may be conducted after excluding those samples collected out of visit window which are considered as major protocol deviations. Failure to meet sequencing quality thresholds defined prior to unblinding will result in removal of a sample from analysis. Deviations in sample handling may result in removal of a sample from analysis. If removal of a sample causes a subject to no longer meet the criteria defined for analysis populations as defined in Section 7.2, the subject will be removed from the analysis population prior to unblinded analysis.

Specifically, sequencing quality thresholds will be assessed as follows. To ensure comparability between different drug product lots and between subject samples, each sample will be subsampled after read mapping to a taxonomic marker database to equalize the number of mapped reads before subsequent analyses. Subsampling will be performed to a read level which maximizes the number of included samples, but which is above a predefined base level of mapped reads to ensure sample quality. Any subject sample with a number of mapped reads below this base level will be discarded from further analysis, with the exception that drug product lots with mapped reads below the base level will be resequenced as appropriate until the base level of mapped reads is achieved. These criteria will be defined and pre-coded in the computational pipeline prior to the interim Visit 13 clinical database lock.

The number of samples from all subjects which pass quality criteria at each timepoint will be reported for the mcITT population in Table 14.4.1, the Sensitivity Analysis Population—1 in Table 14.4.2, the LTE population in Table 14.43, the MTP population in Table 14.4.4, and the MBP population in Table 14.4.5.

7.3.4 Missing and Spurious Data

For the purposes of primary and exploratory endpoint analyses, an ET visit will be considered to be equivalent to a Visit 12 visit if the ET visit occurred within a two week window surrounding Visit 12. In this subset of cases, the ET sample will be pooled with Visit 12 samples for analysis.

Missing data will not be imputed. Any apparently spurious data will be verified. No verified data will be excluded from summaries or analyses.

7.3.5 Endpoints for Analysis

7.3.5.1 Microbiome Primary Endpoints - Overview

Here we describe methods for analysis of genomic sequence results of the stool samples and assessment of microbiome alterations, composition of the intestinal microbiome and engraftment of SER-287 bacteria. Engraftment refers to the germination and outgrowth of the bacterial spores in the drug product. The analysis populations for the microbiome endpoints are the mcITT, Sensitivity Analysis Population-1, and LTE populations.

Microbiome alteration and engraftment of SER-287 bacteria will be assessed between Study Day 11 and Visit 12 or Early Termination, inclusive, as defined above. For the LTE population analysis, microbiome alteration and engraftment will be assessed additionally at Visit 13. If subjects have evaluable Study Day 8 samples (defined as the end of the pre-treatment period) we will also characterize the subject microbiome immediately prior to the initiation of SER-287 dosing.

All comparisons and statistics will be reported as described below for the mcITT, Sensitivity Analysis Population –1, and LTE populations. P-values generated for this study are not intended to be conclusive, but are provided for guidance only.

The composition of the microbiome will be measured in terms of both the number of unique types of spore-forming bacteria (i.e., α-diversity) and the microbial composition, including both spore-forming and non-spore-forming bacteria (i.e., β-diversity). Differences between changes in the microbiome across treatment arms, as specified in Section 7.3.2, will be evaluated using both non-parametric tests for α-diversity and multivariate analysis of variances of dissimilarity

matrices for β-diversity. Engraftment of SER-287 bacteria will be measured in terms of the prevalence and richness of specific spore-forming bacteria found in SER-287 drug product in stool from subjects.

We will perform sensitivity analyses comparing whether any use of antibiotics after initiation of treatment with SER-287 or placebo (Study Day 8) affected subject microbiome profiles for the mcITT and LTE populations, if applicable. The sensitivity population will be defined to exclude subjects who used any antibiotic during the treatment period (Visit 4 through Visit 12).

7.3.5.2 Microbiome Primary Endpoints- Methods

SER-287 is an ecology of bacterial spores enriched from human stool. We will assess the taxonomic composition of SER-287 drug product lots used in the SERES-101 trial and subject stool samples using whole metagenomic sequencing (WMS). WMS is a widely used method for profiling microbiomes which involves shotgun genomic sequencing of bulk DNA obtained from samples of interest. WMS data can be used to identify specific species in samples of interest (Franzosa et al., 2015), subject to limitations due to assay sensitivity and the availability of complete bacterial genomes required for constructing reference databases.

Taxonomic profiling of WMS reads for both SER-287 drug product lots and subject samples will be performed using the MetaPhlAn2 software (Segata et al., 2012; Truong et al., 2015), a widely used and extensively evaluated method (Sczyrba et al., 2017) that was foundational to the Human Microbiome Project (The Human Microbiome Project Consortium 2012). The MetaPhlAn2 method involves mapping filtered sequencing reads to a set of ~1 million species-specific genomic markers covering 7500 species, followed by estimation of the relative abundance of each species based on the distribution of mapped reads (Truong et al., 2015). Raw WMS sequence reads will be pre-processed to remove human sequences following methods used in the HMP (The Human Microbiome Project Consortium 2012) and to filter out technical artifacts before mapping.

To ensure comparability between different drug product lots and between subject samples, each sample will be subsampled after read mapping to a taxonomic marker database to equalize the number of mapped reads before subsequent analyses. Subsampling will be performed to a read level which maximizes the number of included samples, but which is above a predefined base level of mapped reads to ensure sample quality. Any subject sample with a number of mapped reads below this base level will be discarded from further analysis, with the exception that drug product lots with mapped reads below the base level will be resequenced as appropriate until the base level of mapped reads is achieved. These criteria will be defined and pre-coded in the

computational pipeline prior to the interim Visit 13 clinical database lock. Outputs from this pre-defined computational pipeline will be referred to as the "microbiome profile" of a sample.

For analyses of the diversity of spore forming bacteria, the set of species identified by MetaPhlAn2 will be filtered against a proprietary, curated database of species experimentally demonstrated to form spores or identified in the literature as spore-forming species. For analyses of engraftment, the set of spore-forming species found in patients will be filtered against the set of spore-forming species identified in SER-287 drug product lots.

7.3.5.3 Microbiome Alteration Primary Endpoint

Richness of spore-forming bacteria (Alpha-diversity)

We will explore whether treatment with SER-287 impacts bacterial richness (S_{obs}) in subject stool samples as compared with placebo. The strength of the S_{obs} index is that it accounts for the total number of species present in a sample, despite potential experimental bias in evaluating relative abundance, as is characteristic of microbial data sets (Chao, 1984; Colwell and Coddington, 1994; Hughes et al., 2001). Here, we will examine the change in bacterial richness from baseline for the visits specified below (ΔS_{obs}). ΔS_{obs} is a quantitative measure of the change in the number of microbes in a subject relative to baseline. ΔS_{obs} will be calculated using WMS data subsampled as described above. To assess changes in α-diversity we will use the nonparametric two-sided Mann-Whitney U test to determine if there is a change in the ΔS_{obs} diversity metric in subjects receiving SER-287 relative to subjects receiving placebo. We will also report on the change in richness of spore-forming species only (ΔS_{obs_spore}) and the change in richness of non-spore forming species ($\Delta S_{obs\_nonspore}$).

We will test the following hypotheses at Visits 4, 5, 6, 12, and 13 for the mcITT, SAP—1, and LTE populations (Section 7.2):

- H_0: The distribution of ΔS_{obs} values does not differ between subjects treated with SER-287 and placebo subjects.
- H_A: The distribution of ΔS_{obs} values differs between subjects treated with SER-287 and placebo subjects.

Two-sided non-parametric Mann-Whitney U tests will be applied to each comparison detailed in Section 7.3.2 and p-values will be reported. Summary statistics for changes in spore-former and non-spore former richness will also be reported for each analysis population. Results for the mcITT population are reported in Tables 14.5.1.1-14.5.1.2 and Figures 14.3.1.1 and 14.3.1.2.

Results for the Sensitivity Analysis Population – 1 are reported in Tables 14.5.1.3-14.5.1.4 and Figures 14.3.1.1 and 14.3.1.2. Results for the LTE population are reported in Tables 14.5.1.4-14.5.1.5 and Figure 14.3.2.1.

Microbiome change (Beta-diversity)

We will explore whether treatment with SER-287 leads to an overall shift in the microbiome profile in subjects after the initiation of dosing (Visit 4) relative to the microbiome profile in subjects receiving placebo. Specifically, we will apply two complementary and widely used beta-diversity metrics (Binary Jaccard and Bray-Curtis) to microbiome profiles generated from subsampled WMS data. The Binary Jaccard distance ranges between 0 and 1, with 0 indicating samples sharing the exact same set of species, and 1 indicating samples that have no species in common. The abundance of species is not considered in calculations of the metric. The Bray-Curtis metric uses the abundance of species in the calculation of distance between samples. These methods are widely used in the study of microbial communities and represents a balanced approach, with minimal bias to the presence of low- and high-abundance bacteria (Binary Jaccard) and sensitivity to changes in abundance (Bray-Curtis) (Parks and Beiko, 2013).

We will calculate the Binary Jaccard and Bray-Curtis distances between baseline and each available post-treatment timepoint for each subject. A Mann-Whitney test will be used to assess whether the distributions of these baseline to post-treatment distances differ significantly between treatment arms for all the pairwise comparisons detailed in Section 7.3.2. The Mann-Whitney test will be applied separately to each timepoint.

Specifically, we will test the following hypotheses at each of Visits 4, 5, 6, 12, and 13 as defined for the mcITT, SAP—1, and LTE populations in Section 7.2:

- H_0: The microbiome profile of subjects receiving SER-287 does not differ from the microbiome profile of subjects receiving placebo.
- H_A: The microbiome profile of subjects receiving SER-287 differs from the microbiome profile of subjects receiving placebo.

2-sided p-values and summary statistics for the mcITT population are reported in Table 14.5.2.1 and Figure 14.3.2.1, results for the Sensitivity Analysis Population – 1 are reported in Table 14.5.2.2 and Figure 14.3.2.2, and results for the LTE population are reported in Table 14.5.2.3 and Figure 14.3.2.3.

7.3.5.4 Microbiome Engraftment Primary Endpoint

The set of spore-forming bacteria present in clinical drug product lots of SER-287 will be defined by WMS sequencing followed by taxonomic profiling and filtering against a curated reference spore former species database as described in Section 7.3.5. Determinations of engraftment will be made on the basis of assessing the presence or absence of spore forming bacterial species present in SER-287 drug product lots in subject stool after the initiation of treatment. The abundance of spore-forming bacteria in SER-287 drug product lots will not be considered. Specifically, we will determine which spore-forming bacterial species in SER-287 drug product lots are absent in subjects at baseline, and are present after the start of treatment with SER-287 or placebo. The prevalence and richness of these new SER-287 spore-forming species in subject stool will be assessed at each timepoint on or after Study Day 11, which is the day the first sample is collected after the initiation of dosing of SER-287 or placebo on Study Day 8. Engraftment will be assessed in all pairwise comparisons defined in Section 7.3.2.

Prevalence of spore-forming species found in drug product lots

Specifically, we will test the following hypotheses at each of Visits 4, 5, 6, 12, and 13 as defined for the mcITT, SAP—1, and LTE populations in Section 7.2:

- H_0: The prevalence of spore-forming species found in drug product lots absent at baseline and present after the start of treatment does not differ between subjects treated with SER-287 versus placebo.
- H_A: The prevalence of spore-forming species found in drug product lots absent at baseline and present after the start of treatment differs between subjects treated with SER-287 versus placebo.

To test these hypotheses, we will perform separate tests of significance for the distribution of each spore-forming species found in drug product lots across arms. For an overall test of engraftment across species, we will aggregate the resulting p-values using Fisher's combined test (Fisher, 1932) to generate a single p-value for the pairwise comparison of each time point by subject and by cohort.

The specific statistical methods used for each pairwise comparison are detailed below:

- Identify the set of spore-forming species present in SER-287 drug product lots using microbiome profiles as described above.

- Generate 2x2 contingency tables for each spore-forming species found in drug product lots based on the presence or absence of that species in subjects' stool across treatment groups. The contingency table will have two categories: SER-287 spore-forming species present after treatment, but absent at baseline, and SER-287 spore-forming species present at baseline.
- Calculate the 2-sided p-value for Fisher's exact test on each table.
- Combine the p-values by Fisher's combined test and calculate the overall p-value for the comparison. We assume that prevalence of individual species are independent of each other.

Summary results for all pairwise comparisons for the mcITT population will be presented in Table 14.6.1. 2-sided p-values for individual species for all pairwise comparisons for the mcITT population will be reported in Table 14.6.2. Summary results for all pairwise comparisons for the Sensitivity Analysis Population – 1 will be presented in Table 14.6.3. 2-sided p-values for individual species for all pairwise comparisons for the Sensitivity Analysis Population – 1 will be reported in Table 14.6.4. Summary results for all pairwise comparisons for the LTE population will be presented in Table 14.6.5. 2-sided p-values for individual species for all pairwise comparisons for the LTE population will be reported in Table 14.6.6.

Appearance of new spore-forming species found in drug product lots

We will also assess engraftment of spore-forming bacteria in SER-287 by examining the richness of spore-forming species found in drug product lots which appear newly in subject stool on or after Study Day 11 ($\Delta S_{obs\_spore\_dose}$). To assess changes in α-diversity of SER-287 species from baseline to each individual timepoint, we will use the nonparametric one-sided Mann-Whitney U test to determine if there is a greater change in $\Delta S_{obs\_spore\_dose}$ in subjects receiving SER-287 relative to subjects receiving placebo.

Specifically, we will test the following hypotheses at each of Visits 4, 5, 6, 12, and 13 as defined for the mcITT, SAP—1, and LTE populations in Section 7.2:

- H_0: The change in richness of spore-forming species ($\Delta S_{obs\_spore\_dose}$) found in drug product lots absent at baseline and present after the start of treatment in subjects treated with SER-287 is smaller or equal to that found in placebo.
- H_A: The change in richness of spore-forming species ($\Delta S_{obs\_spore\_dose}$) found in drug product lots absent at baseline and present after the start of treatment is higher in subjects treated with SER-287 versus placebo.

Results for the mcITT population are reported in Table 14.6.7 and Figure 14.4.1. Results for the Sensitivity Analysis Population – 1 are reported in Table 14.6.8 and Figure 14.4.2. Results for the LTE population are reported in Table 14.6.9 and Figure 14.4.3.

7.3.5.5 Exploratory Endpoints

Results of the following exploratory endpoints collected at baseline and post-baseline visits will be listed and presented in descriptive summary tables.

7.3.5.5.1 Stool Metabolomic Profiling

Described here are the statistical methodologies that will be used to analyze stool metabolomic datasets from subjects enrolled in SERES-101. The analysis population for the stool metabolomic profiling endpoint is the MTP population as defined in Section 7.2.5. Statistics will be reported for comparisons outlined in Section 7.3.2.

Gastrointestinal (GI) microbes produce metabolites that can impact the metabolic state of the human host; some of these microbial metabolites can be measured in the host feces. The metabolites that are produced and consumed by microbes change the environment of the GI tract and in turn affect the health and immune status of the host (Brestoff and Artis, 2013). Literature using metabolomic platforms including gas chromatography, LC-MS, and NMR spectroscopy support an association of altered microbial metabolite profiles between UC patients and healthy volunteers. In particular, in UC patients the fecal bile acid profiles have reduced levels of microbial-derived secondary bile acids and are differentially conjugated relative to healthy controls (Kruis et al, 1986; Jacobs et al 2016). Additionally, there are reported shifts in fecal tryptophan metabolites (e.g. serotonin, indoles, kynurenines), short chain fatty acids, branched-chain amino acids, and polyamines in UC patients compared to healthy controls (Jacobs et al 2016, Marchesi et al 2007, Le Gall et al 2011; Bjerrum et al 2015).

The fecal metabolome of patients in the MTP population will be characterized by LC-MS and/or LC-MS/MS through global profiling. We may also perform targeted metabolomic profiling. In targeted metabolomic profiling the concentrations of a specific set of metabolites (e.g., short chain fatty acids, bile acids, tryptophan metabolites) is determined with well-defined limits of quantification. In global profiling, hundreds of metabolites across diverse classes are identified and quantitated in an unbiased manner, but the quantitative concentrations are not determined.

We will compare the change in the fecal metabolome of subjects between Visit 12 and baseline to determine whether treatment with SER-287 alters the fecal metabolome compared with placebo. We will additionally assess whether administration of vancomycin prior to treatment

with SER-287 alters the fecal metabolome compared with placebo, via comparison of the change in the fecal metabolome between Visit 12 and Study Day 8 for treatment and placebo arms. We may additionally assess the fecal metabolome on Study Day 11, Study Day 22, and/or Study Day 92.

Specifically, we will test the following hypotheses:

- H_0: The change in the fecal metabolomic profile from baseline and Day 8 to Day 64 does not differ between subjects treated with SER-287 versus placebo.
- H_A: The change in the fecal metabolomic profile from baseline and Day 8 to Day 64 differs between subjects treated with SER-287 versus placebo.

We will perform sensitivity analyses comparing whether any use of antibiotics after initiation of treatment with SER-287 or placebo (Study Day 8) affected subject metabolome profiles for the MTP population, if applicable. The sensitivity population will be defined to exclude subjects who used any antibiotic during the treatment period (Visit 4 through Visit 12).

The change in metabolome profiles (i.e., delta) from baseline to Visit 12 and from Study Day 8 to Visit 12 for all pairwise comparisons will be assessed. The specific methods used for each comparison are detailed below:

- Calculate the delta in metabolite abundance between timepoints (e.g., baseline to Visit 12, Study Day 8 to Visit 12) within each subject.
- The significance of difference between the sets of delta values for the comparison arms will be assessed using a two-sided Mann-Whitney test.
- Metabolites will be grouped according to pathways based on a proprietary functional database curated by the audited metabolomic vendor for the SERES-101 trial. This is referred to as the "pathway profile" of a sample.
- A Fisher's combined test will be used to assess whether there are overall differences between each pathway profile across arms, aggregating across metabolites within a profile.

The p-values for the 25 most significantly different pathways for delta between baseline and Visit 12 will be reported in Table 14.7.1, and p-values for the 25 most significantly different pathways for delta between Study Day 8 and Visit 12 will be reported in Table 14.7.2. We will additionally report Fisher's combined p-value aggregated across all metabolites to assess overall metabolomic change in Tables 14.7.3 (baseline to Visit 12) and 14.7.4 (Study Day 8 to Visit 12).

We may conduct additional exploratory analysis including correlation of metabolomic profiles with microbiome profiles and/or clinical biomarkers and outcomes.

7.3.5.5.2 Biopsy Transcriptome Profiling

Described here are the statistical methodologies that will be used to analyze human mucosal transcriptomic datasets from subjects enrolled in SERES-101. The analysis population for the mucosal transcriptomic profiling endpoint is the MBP population as defined in Section 7.2.4. Statistics will be reported for all the comparisons outlined in Section 7.3.2.

The transcriptome of patients in the MBP population will be characterized with whole transcriptome sequencing using next-generation sequencing technology (NGS). RNA-Seq analysis on the NGS data from the mucosal biopsy samples from each subject will generate data on gene expression in host biopsy tissue, subject to the limit of detection of the RNA-Seq assay. Total RNA will be extracted from biopsies and reverse transcribed to generate cDNA libraries that are suitable for sequencing using Illumina's high-throughput short read technology. Sequence data will be processed for quality with well-established sequencing criteria and reads will be aligned to a current reference human genome. Following alignment to the human reference genome, mapped gene counts will be computed.

We will compare the difference (delta) in transcriptome profiles of treatment subjects at Visit 12 to paired baseline profiles, to the delta in transcriptome profiles of placebo subjects at Visit 12 to paired baseline profiles. This comparison of deltas will be made for each predefined comparison listed in Section 7.3.2 to determine whether treatment with SER-287 alters the host transcriptome profile in subjects compared with placebo.

Specifically, we will test the following hypotheses:

- H_0: The change in the human transcriptomic profile from baseline to Visit 12 does not differ between subjects treated with SER-287 versus placebo.
- H_A: The change in the human transcriptomic profile from baseline to Visit 12 differs between subjects treated with SER-287 versus placebo.

We will use DESeq2 (Love *et al.* 2014) to assess differential expression for all such comparisons to determine whether treatment with SER-287 alters the host transcriptome profile in subjects compared with placebo. We will report the top 100 protein-coding human genes differentially expressed for each pairwise comparison of deltas between Visit 12 and baseline in Table 14.8.1.

We may conduct additional exploratory analysis including correlation of specific differentially expressed genes with microbiome profiles and/or clinical biomarkers and outcomes.

7.3.5.5.3 Mucosal Microbiome Profiling

Described here are the statistical methodologies that will be used to analyze mucosal microbiome datasets from subjects enrolled in SERES-101. The analysis population for the mucosal microbiome profiling endpoint is the MBP population as defined in Section 7.2.4. Statistics will be reported for all the comparisons outlined in Section 7.3.2.

The mucosal microbiome of subjects in the MBP population will be characterized by using 16S V4 genomic data sets generated from biopsies collected at the time points defined in Section 7.1.1.1 (baseline and Visit 12). Genomic data sets will define the microbial composition of the mucosal microbiome of a subject at a given time point. We will analyze genomic sequence read data sets to assign a taxonomic identity at the resolution of species, the Operational Taxonomic Unit (OTU) and phylogenetic clade (clade) and, further, to define the relative proportion of each OTU and clade to all other OTUs and clades in a given sample. The resulting data are referred to below as the "mucosal microbiome profile."

For reference, an OTU is a genetically distinct bacterium as defined by nucleic acid sequence. OTUs that share at least 97% of average nucleotide identity across the 16S V4 variable region of the 16S are typically considered the same species (Achtman and Wagner, 2008; Konstantinidis et al., 2006) Generally, OTU taxonomic assignments derived by using 16S V4 cannot definitively resolve bacterial species because of insufficient information content in the 16S V4 region. To address this limitation in specificity of such data and to obtain robust taxonomic identities for cross-sample comparisons, 16S V4 sequence reads are additionally assigned to phylogenetic clades. A clade is a group of distinct bacteria that are phylogenetically more related to one another than bacteria in another clade. Clades are defined based on maximum-likelihood evolutionary analysis of a curated reference data set of 16S full-length sequences and mapping for 16S V4 sequences to this phylogeny. A clade is formally defined as a group of OTUs that cluster and are downstream of a statistically valid branch point (Wróbel, 2008) in a phylogenetic tree. Clades typically provide a taxonomic resolution that is greater than genus assignment but less than species; the resolution depends on the ability of different regions of the reference phylogenetic tree to distinguish OTUs at different taxonomic levels. Importantly, clades define the group of bacterial species that are not reliably distinguished from one another by using the 16S V4 sequencing assay but can be distinguished from other bacterial species in other clades.

For statistical comparisons, we will compare the mucosal microbiome profile of subjects at the clade level.

We will explore whether treatment with SER-287 leads to an overall shift in the mucosal microbiome of treated subjects at the end of the treatment period (Visit 12) relative to baseline, in comparison with the corresponding change in the mucosal microbiome profile of subjects receiving placebo.

Specifically, we will test the following hypotheses:

- H_0: The change in the mucosal microbiome profile of subjects receiving SER-287 does not differ from the change in the microbiome profile of subjects receiving placebo between baseline and Visit 12.
- H_A: The change in the mucosal microbiome profile of subjects receiving SER-287 differs from the change in the microbiome profile of subjects receiving placebo between baseline and Visit 12.

We will calculate the Binary Jaccard and Bray-Curtis distances between baseline and each available post-treatment timepoint for each subject. A Mann-Whitney test will be used to assess whether the distributions of these baseline to post-treatment distances differ significantly between treatment arms for all the pairwise comparisons detailed in Section 7.3.2. The Mann-Whitney test will be applied separately to each timepoint.

2-sided p-values and summary statistics will be reported for each comparison and beta diversity metric. Results will be reported in Table 14.9.1.

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9. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Sample and Sequencing Acceptability

Table 14.4.1 Sample Acceptability Criteria for All Timepoints (mcITT population)

Table 14.4.2 Sample Acceptability Criteria for All Timepoints (Sensitivity Analysis Population –1)

Table 14.4.3 Sample Acceptability Criteria for All Timepoints (LTE population)

Table 14.4.4 Sample Acceptability Criteria for All Timepoints (MTP population)

Table 14.4.5 Sample Acceptability Criteria for All Timepoints (MBP population)

Microbiome Alteration Primary Endpoint

Table 14.5.1.1 P-values for Spore-Forming Species Richness Between All Planned Comparisons (mcITT population)

Table 14.5.1.2 Summary Statistics for Spore-Forming Species Richness Between All Planned Comparisons (mcITT population)

Table 14.5.1.3 P-values for Spore-Forming Species Richness Between All Planned Comparisons (Sensitivity Analysis Population—1)

Table 14.5.1.4 Summary Statistics for Spore-Forming Species Richness Between All Planned Comparisons (Sensitivity Analysis Population—1)

Table 14.5.1.5 P-values for Spore-Forming Species Richness Between All Planned Comparisons (LTE population)

Table 14.5.1.6 Summary Statistics for Spore-Forming Species Richness Between All Planned Comparisons (LTE population)

Table 14.5.2.1 Summary Statistics for Beta-Diversity Between All Planned Comparisons (mcITT population)

Table 14.5.2.2 Summary Statistics for Beta-Diversity Between All Planned Comparisons (Sensitivity Analysis Population—1)

Table 14.5.2.3 Summary Statistics for Beta-Diversity Between All Planned Comparisons (LTE population)

Microbiome Engraftment Primary Endpoint

Table 14.6.1 P-Values for Overall Engraftment of SER-287 Drug Product Lot Species – mcITT population

Table 14.6.2 P-Values for Engraftment of Individual SER-287 Drug Product Lot Species – mcITT population

Table 14.6.3 P-Values for Overall Engraftment of SER-287 Drug Product Lot Species – Sensitivity Analysis Population –1

Table 14.6.4 P-Values for Engraftment of Individual SER-287 Drug Product Lot Species – Sensitivity Analysis Population –1

Table 14.6.5 P-Values for Overall Engraftment of SER-287 Drug Product Lot Species – LTE Population

Table 14.6.6 P-Values for Engraftment of Individual SER-287 Drug Product Lot Species – LTE Population

Table 14.6.7 P-values for Richness of Spore-Forming Species found in Drug Product Lots in mcITT population

Table 14.6.8 P-values for Richness of Spore-Forming Species found in Drug Product Lots in Sensitivity Analysis Population –1

Table 14.6.9 P-values for Richness of Spore-Forming Species found in Drug Product Lots in LTE Population

Metabolome Exploratory Endpoint

Table 14.7.1 25 Most Differentially Abundant Metabolites Between Baseline to Visit 12 For All Pairwise Comparisons

Table 14.7.2 25 Most Differentially Abundant Metabolites Between Study Day 8 to Visit 12 For All Pairwise Comparisons

Table 14.7.3 Fisher's Combined P-Value Statistic for Pathway Profile Changes in All Pairwise Comparisons - Baseline to Visit 12

Table 14.7.4 Fisher's Combined P-Value Statistic for Pathway Profile Changes in All Pairwise Comparisons - Study Day 8 to Visit 12

Transcriptome Exploratory Endpoint

Table 14.8.1 Top 100 Genes Differentially Expressed Between Arms Between Baseline And Visit 12 For All Comparisons

Mucosal Microbiome Exploratory Endpoint

Table 14.9.1 Summary Statistics for Mucosal Microbiome Beta Diversity

10. FIGURES TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Microbiome Alteration Primary Endpoint

Figure 14.3.1.1 Spore-Former Species Richness By Timepoint for the mcITT Population For All Pre-Specified Comparisons

Figure 14.3.1.2 Spore-Former Species Richness By Timepoint for the Sensitivity Analysis Population – 1 For All Pre-Specified Comparisons

Figure 14.3.1.3 Spore-Former Species Richness By Timepoint for the LTE Population For All Pre-Specified Comparisons

Figure 14.3.2.1 Beta-Diversity Metrics for the mcITT Population

Figure 14.3.2.2 Beta-Diversity Metrics for the Sensitivity Analysis Population – 1

Figure 14.3.2.3 Beta-Diversity Metrics for the LTE Population

Microbiome Engraftment Primary Endpoint

Figure 14.4.1 Drug Product Lot-Specific Spore-Former Species Richness By Timepoint for the mcITT Population For All Pre-Specified Comparisons

Figure 14.4.2 Drug Product Lot-Specific Spore-Former Species Richness By Timepoint for the Sensitivity Analysis Population – 1 For All Pre-Specified Comparisons

Figure 14.4.3 Drug Product Lot-Specific Spore-Former Species Richness By Timepoint for the LTE Population For All Pre-Specified Comparisons

11. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

Analysis Populations

Listing 16.2.1 Assignment to Analysis Populations (mcITT)

Listing 16.2.2 Assignment to Analysis Populations (Sensitivity Analysis Population – 1)

Listing 16.2.3 Assignment to Analysis Populations (LTE)

Listing 16.2.4 Assignment to Analysis Populations (MBP)

Listing 16.2.5 Assignment to Analysis Populations (MTP)