1.0 Title Page

Statistical Analysis Plan

Study B19-227

Relative Bioavailability and Effect of Food on DSM265-TPGS 34% SDD Powder in Healthy Adult Subjects

Date: 13 August 2018

Version 1.0

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Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AUC_{168}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 168 hours post dose
AUC_{inf}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_t	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
β	Slope parameter associated with the power model used to evaluate dose proportionality
C_{168}	Plasma concentration at 168 hours post dose
C_{max}	Maximum measured concentration of the analyte in plasma
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
SAP	Statistical Analysis Plan
SOC	System Organ Class
$t_{1/2}$	Terminal half-life of the analyte in plasma
T_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed for the DSM265 (A-1400550) Study Protocol B19-227 Version 1.0. This SAP also provides details that describe analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 (SAS Institute Inc., Cary, NC 27513) or higher under the UNIX operating system.

4.0 Study Background

4.1 Objective

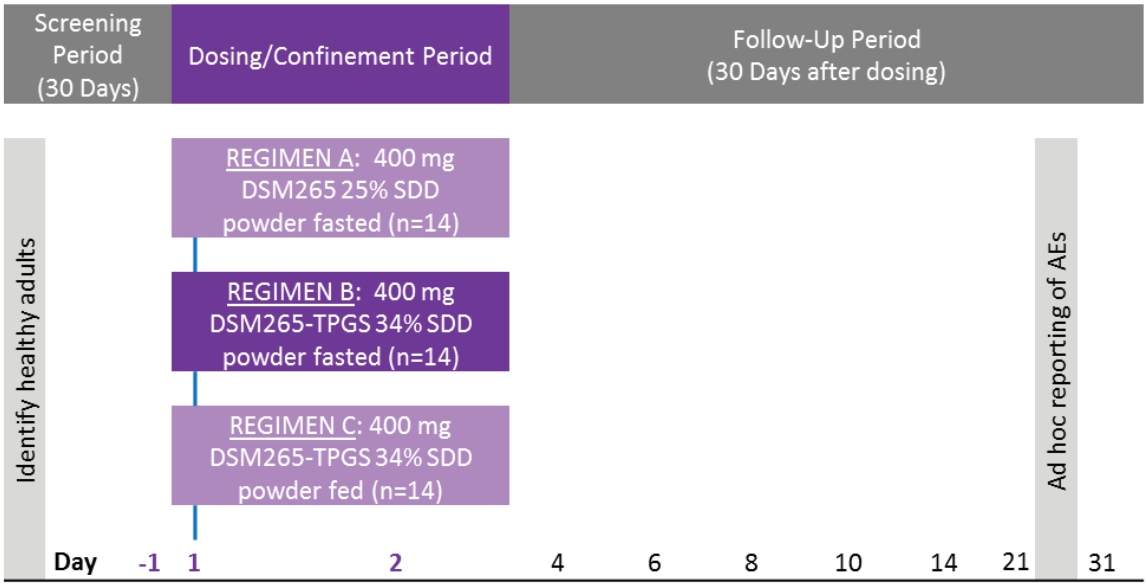
The objective of this study is to compare the relative bioavailability of the oral DSM265-TPGS 34% SDD powder with that of a reference DSM265 25% SDD powder for suspension formulation. Another objective of the study is to evaluate the effect of food on the bioavailability of DSM265-TPGS 34% SDD powder.

4.2 Study Design

This Phase 1, single-dose, open-label study will be conducted according to a randomized parallel group design in adult male and female (non-childbearing potential) subjects. Three groups of 14 subjects each will be confined for 3 days with outpatient assessments through 21 days. Blood samples will be collected for 480 hours after dosing.

A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic



Bold = Confinement; Line = Dosing Day

Parallel groups will be utilized as the half-life of DSM265 is relatively long. Each subject will be randomly assigned to one of the three regimens to avoid bias.

4.3 Endpoints

4.3.1 Safety Endpoints

Safety evaluations will include adverse event (AE) monitoring, physical examinations, vital signs measurements, electrocardiogram (ECG) variables and clinical laboratory testing.

Adverse events and potentially clinically significant laboratory abnormalities, vital signs and ECG measurements will be summarized by regimen.

4.3.2 Pharmacokinetic Endpoints

The values for the pharmacokinetic parameters of DSM265 and possible metabolite(s) including C_{max}, T_{max}, apparent terminal phase elimination rate constant (β), $t_{1/2}$, AUC from time 0 to the time of the last measurable concentration (AUC_t), AUC from time 0 to 168 hours (AUC_{168}) and from time 0 to infinity (AUC_{inf}) will be determined using non-compartmental methods. Plasma concentration at 168 hours (C_{168}) will also be measured. Additional parameters may be estimated if useful in the interpretation of the data. In addition, these blood samples may be used for other exploratory analysis.

4.4 Sample Size Justification

The sample size used in this study is not based on statistical power considerations. A sample size of 14 per regimen is considered sufficient for evaluation of the pharmacokinetics and safety of DSM265.

5.0 Analysis Populations

Available data from all subjects will be used in the pharmacokinetic analyses. All subjects who receive at least one dose of study drug will be included in the safety analyses.

6.0 Demographics, Baseline Characteristics, and Other Assessments

6.1 Demographic and Baseline Characteristics

Descriptive statistics will be provided for demographic variables by regimen.

7.0 Pharmacokinetic Analysis

7.1 Tabulations and Summary Statistics

Plasma concentrations and pharmacokinetic parameter values of DSM265 and possible metabolite(s) will be tabulated for each subject by regimen. Summary statistics will be

computed for concentrations at each sampling time and for each parameter by regimen. Significant pharmacokinetic sample time deviations will be identified and listed.

7.2 Model and Tests

An analysis of variance (ANOVA) will be performed for T_{max}, the terminal phase elimination rate constant β, and the natural logarithms of C_{max}, AUC_t, AUC_{168}, AUC_{inf}, and C_{168}. The model will include the effects for regimen. For the tests on regimen effects, the denominator sum of squares will be the residual sum of squares for error. Within the ANOVA modeling framework, the test regimen will be compared to the respective reference regimen by a test with a significance level of 0.05.

Two comparisons will be performed: DSM265-TPGS 34% powder fasted (Test 1, Regimen B) vs. DSM265 25% SDD powder fasted (Reference 1, Regimen A), and DSM265-TPGS 34% powder fed (Test 2, Regimen C) vs. DSM265-TPGS 34% powder fasted (Reference 2, Regimen B). The bioavailability of each test regimen relative to that of each reference regimen will be assessed via 90% confidence intervals obtained from the analyses of the natural logarithms of C_{max} and AUC. These confidence intervals will be obtained by taking the antilogarithm of the upper and lower limits of confidence intervals for the difference of the least squares means on the logarithmic scale within the framework of the ANOVA model. Bioequivalence between a test regimen and the respective reference regimen will be concluded if the 90% confidence intervals from the analyses of the natural logarithms of C_{max} and AUC are within the 0.80 to 1.25 range.

Additional analyses will be performed if useful and appropriate.

7.3 Missing Values and Model Violations

All available data will be included in the ANOVA analysis. Data exclusion, if any, will be documented and justification will be provided.

The possibility of bias from missing data of subjects who prematurely discontinue for reasons possibly related to study drug will be assessed and addressed. Normally values of

pharmacokinetic variables (C_{max}, AUC, etc.) will be determined without replacing missing individual concentration values, simply using the available data, and if necessary doing the analysis with some missing values for a pharmacokinetic variable. However, missing concentration values for isolated individual blood samples may be replaced (imputed) if such might affect study conclusions or meaningfully affect point estimates.

It is expected that the logarithmic transformation will be used for C_{max}, AUC and C_{168}. However, if the assumption of normal probability distributions is seriously violated for the logarithms of C_{max}, AUC and C_{168} or for any of the other variables to be analyzed, appropriate transformations will be sought.

8.0 Safety Analyses

Safety analyses will be conducted on adverse events, clinical laboratory data, vital signs, and ECG data. The analyses described below in Section 8.1 through Section 8.3 will be performed. Additional analyses will be performed if deemed useful and appropriate.

8.1 Analysis of Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects having treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug) will be tabulated by primary System Organ Class (SOC) and MedDRA preferred term with a breakdown by regimen.

The tabulation of the number of subjects with treatment-emergent adverse events also will be provided with further breakdowns by severity rating (according predefined criteria specified in study protocol Section 6.1) and relationship to study drug. Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe incident. Subjects reporting more than one type of event within a SOC will be counted only once for that SOC.

8.2 Analysis of Laboratory Data and Vital Signs

8.2.1 Clinical Laboratory Data

Abnormal laboratory test values that are Very High or Very Low, according to Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), will be identified. The baseline laboratory value will be defined as the last measurement prior to the initial dose of study drug.

8.2.2 Vital Signs Data

Vital signs measurements that are potentially clinically significant according to criteria listed below will be identified.

Systolic blood pressure: < 80 mmHg, > 150 mmHg, or > 20 mmHg change from baseline; Diastolic blood pressure: < 50 mmHg, > 100 mmHg, or > 20 mmHg change from baseline; Pulse: < 40 BPM, > 100 BPM, or > 30 BPM change from baseline; Temperature: < 35°C or > 37.8°C.

8.3 ECG Data

Abnormal ECG values will also be identified.

9.0 Summary of Changes

9.1 Summary of Changes Between the Previous Version and the Current Version

This is the original version of the SAP for this study.

Signature Page

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Medicines for Malaria Venture (MMV)

Protocol B19-227 (MMV_DSM265_18_01)

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