

Protocol for Study B19-227 (MMV_DSM265_18_01)

Malaria: Relative Bioavailability and Food Effect of DSM265

VERSION:	1.0	DATE:	13 August 2018
SPONSOR:	Medicines for Malaria Venture (MMV)	NUMBER OF SITES:	1
INVESTIGATIONAL PRODUCT:	DSM265, A-1400550		

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

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TABLE OF CONTENTS

1	SYNOPSIS	4
2	INTRODUCTION	5
2.1	BACKGROUND AND RATIONALE	5
2.2	BENEFITS AND RISKS TO SUBJECTS	5
3	STUDY OBJECTIVES AND ENDPOINTS	5
3.1	OBJECTIVES	5
3.2	SAFETY ENDPOINTS	6
3.3	PHARMACOKINETIC ENDPOINTS	6
4	INVESTIGATIONAL PLAN	6
4.1	OVERALL STUDY DESIGN AND PLAN	6
4.2	DISCUSSION OF STUDY DESIGN	7
5	STUDY ACTIVITIES	8
5.1	ELIGIBILITY CRITERIA	8
5.2	PRIOR AND CONCOMITANT THERAPY	10
5.3	WITHDRAWAL OF SUBJECTS AND DISCONTINUATION OF STUDY	11
5.4	FOLLOW-UP FOR SUBJECT WITHDRAWAL FROM STUDY	11
5.5	STUDY DRUG	11
5.6	RANDOMIZATION/DRUG ASSIGNMENT	12
5.7	PROTOCOL DEVIATIONS	12
6	SAFETY CONSIDERATIONS	12
6.1	COMPLAINTS AND ADVERSE EVENTS	12
6.2	PRODUCT COMPLAINT	16
7	STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE	16
7.1	STATISTICAL AND ANALYTICAL PLANS	16
7.2	STATISTICAL ANALYSES FOR PHARMACOKINETICS	16
7.3	STATISTICAL ANALYSES FOR SAFETY	16

8	ETHICS	16
8.1	INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD (IEC/IRB)	16
8.2	ETHICAL CONDUCT OF THE STUDY	17
8.3	SUBJECT CONFIDENTIALITY	17
9	SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION	17
10	DATA QUALITY ASSURANCE	17
11	COMPLETION OF THE STUDY	17
12	REFERENCES	17

LIST OF TABLES

TABLE 1.	IDENTITY OF INVESTIGATIONAL PRODUCTS	12
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LIST OF FIGURES

FIGURE 1.	SINGLE-DOSE, OPEN-LABEL, RANDOMIZED PARALLEL GROUP DESIGN IN HEALTHY VOLUNTEERS	7
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LIST OF APPENDICES

APPENDIX A.	STUDY SPECIFIC ABBREVIATIONS AND TERMS	18
APPENDIX B.	RESPONSIBILITIES OF THE INVESTIGATOR	20
APPENDIX C.	LIST OF PROTOCOL SIGNATORIES	21
APPENDIX D.	ACTIVITY SCHEDULE	22
APPENDIX E.	OPERATIONS MANUAL	24

1 SYNOPSIS

Title: Relative Bioavailability and Effect of Food on DSM265-TPGS 34% SDD Powder in Healthy Adult Subjects	
Background and Rationale:	The current clinical formulation requires reconstitution/administration with a 240 mL sucralose-based vehicle (for a 400 mg adult dose). The new formulation was selected to dissolve in a smaller volume with water (approximately 60 mL for 400 mg adult dose).
Objectives and Endpoints:	The primary objective of this study is to compare the relative bioavailability of the oral DSM265-TPGS 34% SDD powder with the 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.
Investigator(s):	David Carter, MD
Study Site(s):	AbbVie Clinical Pharmacology Research Unit (ACPRU)
Study Population and Number of Subjects to be Enrolled:	Approximately 42 healthy adult subjects
Investigational Plan:	This Phase 1, single-dose, open-label study will be conducted according to a randomized parallel group design in adult male and female subjects (3 groups of 14 subjects each). Subjects will be confined for 3 days with outpatient assessments through 21 days. Blood samples will be collected for 480 hours after dosing.
Key Eligibility Criteria:	Volunteers in general good health. Women must be of non-child bearing potential (WONCBP).
Study Drug and Duration of Treatment:	Single dose of 400 mg DSM265 25% SDD (Reference) Single dose of 400 mg DSM265 TPGS 34% SDD (Test)
Date of Protocol Synopsis:	13 August 2018

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

DSM265 is a new antimalarial drug candidate targeted for acute uncomplicated malaria (single dose cure) and possibly chemoprevention (repeated administration) being developed by Medicines for Malaria Venture (MMV). This new chemical entity is being evaluated in various Phase 1 studies and has been also tested in a Phase 2A trial in patients with acute uncomplicated malaria. The highest dose tested in the first-in-human study was 1200 mg and it has been shown to be well tolerated. Clinical data from a human malaria challenge model in healthy subjects as well as efficacy results from the Phase 2A trial suggests that efficacy in acute uncomplicated malaria with *Plasmodium falciparum* can be achieved with a single 400 mg dose of DSM265.

The median time to the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), was approximately 4 hours at a dose of 400 mg and the mean terminal phase elimination half-life ($t_{1/2}$) remained constant across doses, ranging from 85 to 112 hours. A major metabolite, DSM450, was identified with T_{max} of 96 to 144 hours after dosing, a mean $t_{1/2}$ ranging from 131 to 168 hours, and an area under the plasma concentration-time curve (AUC) of approximately 0.19 to 0.28 relative to that of DSM265.

This Phase 1 study is designed to evaluate the relative bioavailability of a single dose of a test formulation, DSM265-TPGS 34% SDD powder, with the reference DSM265 25% SDD powder for suspension formulation used in previous clinical trials. This Phase 1 study is also designed to evaluate the effect of food on the bioavailability of DSM265-TPGS 34% SDD powder.

2.2 Benefits and Risks to Subjects

There are no expected direct benefits for subjects who enroll in this healthy volunteer study. Study drugs may be associated with adverse effects as detailed in the subject informed consent form(s). Not all of the potential side effects of the study drugs may be known. In addition, subjects may experience discomfort or inconvenience related to study procedures.

For further details, reference findings from completed studies, including safety data in the DSM265 Investigator's Brochure.¹

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this study is to compare the relative bioavailability of the oral DSM265-TPGS 34% SDD powder to the 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.

3.2 Safety Endpoints

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

3.3 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 until the last measurable concentration (AUC_t), AUC from time 0 to 168 hours (AUC_{168}) and AUC 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, the blood samples may be used for other exploratory analysis.

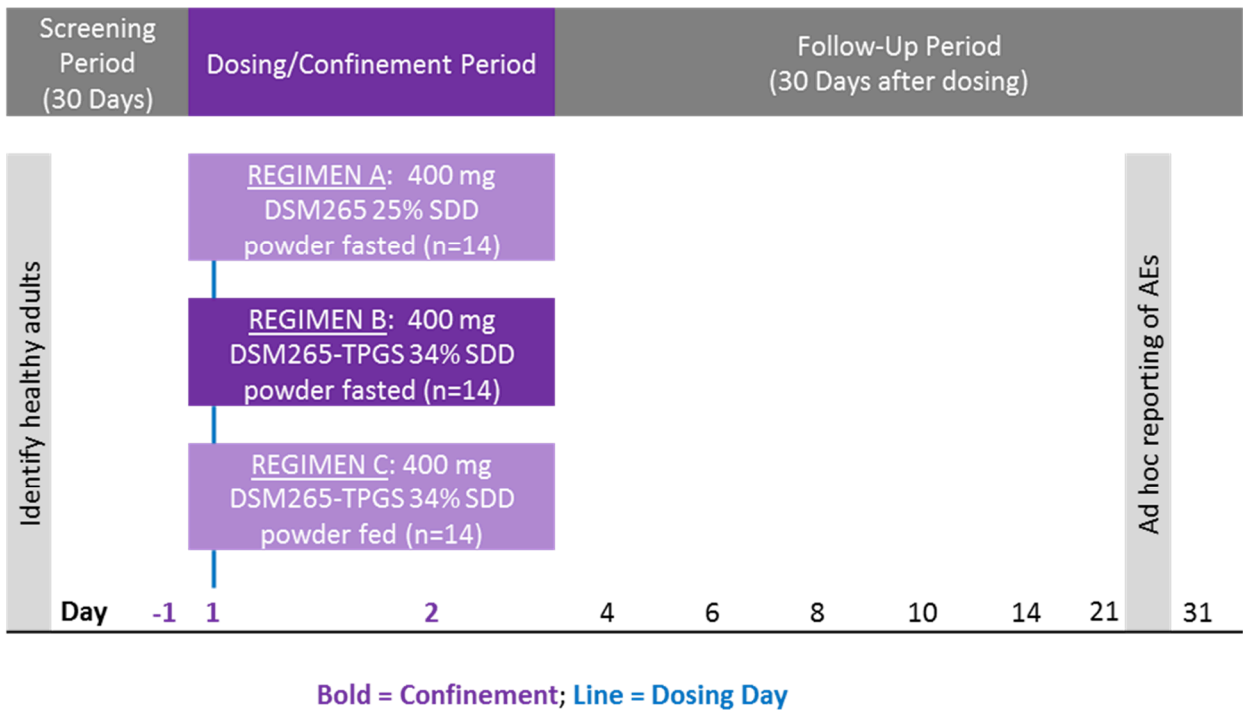
4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The schematic of the study is shown in [Figure 1](#). Further details regarding study procedures are located in the Operations Manual ([Appendix E](#)).

See Section [5.1](#) for information regarding eligibility criteria.

Figure 1. Single-Dose, Open-Label, Randomized Parallel Group Design in Healthy Volunteers



4.2 Discussion of Study Design

Discussion of Study Design and Choice of Control Groups

Each subject will be randomly assigned to one of the regimens to avoid bias. Parallel groups will be utilized as the half-life of DSM265 ranges from 85 to 112 hours.

Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study.

Suitability of Subject Population

The selection of subjects in general good health is standard for pharmacokinetic studies.

Selection of Doses in the Study

The dose of 400 mg was tested in the Phase 2A proof-of-concept clinical study and demonstrated the potential to be an efficacious dose for the treatment of uncomplicated malaria with *Plasmodium falciparum* with an acceptable safety profile.

Blinding

This is an open-label study.

Meals and Dietary Requirements

At least a ten-hour fast is required prior to dosing for Regimen A and Regimen B, a high-fat breakfast is required for Regimen C; otherwise, standard moderate-fat meals will be provided during confinement.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation. A subject who has failed screening may be re-screened at investigator's discretion.

Consent

- ✓ 1. Subjects or their legally authorized representative must voluntarily sign and date each informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic

- ✓ 2. Male or female between 18 and 55 years of age inclusive at the time of screening.
- ✓ 3. Body Mass Index (BMI) is ≥ 18.0 to ≤ 29.9 kg/m² after rounding to the tenths decimal. BMI is calculated as weight in kg divided by the square of height measured in meters.

Contraception Eligibility and Guidance

- ✓ 4. Females must be of Non-Childbearing Potential as defined below:
Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:
 - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an follicle stimulating hormone (FSH) level > 40 IU/L.
 - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
- ✓ 5. Female who is not pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 120 days after the last dose of study drug.
- ✓ 6. Male subjects who are sexually active with a female partner of childbearing potential, must agree to use condoms, even if the male subject has undergone a successful vasectomy, from Study Day 1 through 120 days after the last dose of study drug. His female partner(s) must also use at least one of the following methods of birth control:
 - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, injectable, transdermal) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.

- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
- bilateral tubal occlusion/ligation
- intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- ✓ 7. Male who is not considering fathering a child or donating sperm during the study or for approximately 120 days after the last dose of study drug.

Laboratory Assessments and ECG Criteria

- ✓ 8. Laboratory values meet the following criteria:
 - serum aspartate transaminase (AST) and alanine transaminase (ALT) \leq the upper limit of normal (ULN) at the Screening Visit and upon initial confinement.
 - negative test result for hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody (Ab) and human immunodeficiency virus (HIV) at screening visit.
 - negative screen for drugs of abuse, alcohol or cotinine at screening and upon initial confinement.
 - for non-postmenopausal female subjects, a negative urine pregnancy test at the screening visit and a negative serum pregnancy test upon initial confinement and prior to the first dose of study drug.
 - no other laboratory results that the investigator determines are clinically significant.
 - platelets greater than or equal to the lower limit of normal.
- ✓ 9. No clinically significant ECG abnormalities including
 - no evidence of 2nd or 3rd degree AV block at screening visit and upon initial confinement.
 - QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcf) is \leq 430 msec (males) or \leq 450 msec (females) at screening visit and upon initial confinement.

Subject History/Physical Exam and Vital Signs

- ✓ 10. A condition of general good health, based upon the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead ECG.
- ✓ 11. No history of: epilepsy, any clinically significant cardiac, respiratory (except mild asthma as a child), renal, hepatic, gastrointestinal, hematologic or psychiatric disease or disorder, or any uncontrolled medical illness.
- ✓ 12. No history of any clinically significant sensitivity or allergy to any medication or food.
- ✓ 13. No history of or active medical condition(s) or surgical procedure(s) that might affect gastrointestinal motility, pH, or absorption [e.g., Crohn's disease, celiac disease, gastroparesis, short bowel syndrome, gastric surgery (except pyloromyotomy for pyloric stenosis during infancy), cholecystectomy, vagotomy, bowel resection].

- ✓ 14. No evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma or localized carcinoma in situ of the cervix.
- ✓ 15. No history of any clinically significant illness/infection/major febrile illness, hospitalization, or any surgical procedure within 30 days prior to the first dose of study drug.
- ✓ 16. Has not donated blood (including plasmapheresis), lost ≥ 550 mL blood volume, or received a transfusion of any blood product within 8 weeks prior to study drug administration.
- ✓ 17. No consumption of alcohol, grapefruit products, Seville oranges, starfruit products or quinine/tonic water within the 72-hour period prior to study drug administration.
- ✓ 18. No use of tobacco or nicotine-containing products within 180 days prior to the first dose of study drug.
- ✓ 19. No history of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
- ✓ 20. Is not currently enrolled in another interventional clinical study.
- ✓ 21. Has not been previously enrolled in this study.
- ✓ 22. In the opinion of the investigator, this subject is a suitable candidate for enrollment in the study.

Concomitant Medications

- ✓ 23. Subjects must not have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug.
- ✓ 24. Subject must not have received any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.
- ✓ 25. Subject must not require any over-the-counter and/or prescription medication, vitamins and/or herbal supplements, with the exception of contraceptives or hormonal replacement therapies for females, on a regular basis.
- ✓ 26. Subject must not use any medications within the 2-week period prior to study drug administration.
- ✓ 27. Receipt of any drug by injection within 30 days or within a period defined by 5 half-lives, whichever is longer, prior to study drug administration.
- ✓ 28. No use of known inhibitors (e.g., ketoconazole) or inducers (e.g., carbamazepine) of cytochrome P450 3A (CYP3A) within 1 month prior to study drug administration.
- ✓ 29. No exposure to DSM265 within the past 90 days prior to first dose of study drug.

5.2 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medications) that the subject receives after enrollment into the study must be recorded through the last study visit.

5.3 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

AbbVie or MMV may terminate this study prematurely, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie or MMV terminates the study for safety reasons, AbbVie will promptly notify the Investigator.

5.4 Follow-Up for Subject Withdrawal from Study

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, ECG, laboratory analyses, and an assessment of adverse events will be performed as soon as possible after discontinuation from the study. Additional blood samples for drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to adverse events; the clock time, time in relation to dose, and date the sample was taken will be recorded.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

5.5 Study Drug

Information about the DSM265 formulations to be used in this study is presented in [Table 1](#).

Table 1. Identity of Investigational Products

	DSM265 Regimens	
	Reference	Test
Dosage Form	Powder for suspension	Powder for suspension
Formulation	25% SDD	TPGS 34% SDD
Strength (mg)	400	400
Drug Preparation	Reconstitute in 100 mL supplied vehicle; rinse twice with 70 mL supplied vehicle	Reconstitute in 40 mL water + 20 mL rinse water
Additional Information	Store at 2 to 8°C/35 to 46°F	Store at 2 to 8°C/35 to 46°F

5.6 Randomization/Drug Assignment

All subjects will be assigned a unique identification number prior to dosing. This number will encode the subject's assignment according to the randomization schedule generated by the statistics department at AbbVie.

5.7 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Medical Complaints/Adverse Events and Serious Adverse Events

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use

of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

If an adverse event meets any of the following criteria, it is to be reported to MMV/PrimeVigilance as a serious adverse event within 24 hours of the site being made aware of the serious adverse event:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 30 days or 5 half-lives after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signs the study-specific informed consent.

MMV/PrimeVigilance will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse Events of Special Interest (AESI)

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk.

All the abnormalities listed below should be reported as an AESI:

- Related to hematotoxicity:
 - A fall in hemoglobin of > 20 g/L or 25% from the baseline value,
 - A fall in absolute neutrophils count to $< 1000/\text{mm}^3$,
 - A fall in platelet level to $< 100,000/\text{mm}^3$.
- Related to hepatotoxicity:
 - ALT or AST $> 3 \times \text{ULN}$ with the appearance of worsening of fatigue, nausea, vomiting, fever, rash, or eosinophilia,
 - AST or ALT increase $> 8 \times \text{ULN}$,
 - ALT or AST rises rapidly to $> 5 \times \text{ULN}$ in less than 4 weeks or persists for more than 2 weeks,
 - ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ or INR $> 1.5 \times \text{ULN}$ (Hy's Law if ALP $< 2 \times \text{ULN}$), to also be reported as an SAE in case of Hy's Law.
- Related to cardiotoxicity:
 - QTcF prolongation from baseline of > 60 ms,
 - QTcF at any time > 450 ms,
 - T wave liability, or T wave morphologic changes during therapy,
 - Bundle branch block, complete or partial,
 - Any arrhythmia.
- Related to dermatotoxicity, clinical signs of possible cutaneous adverse reactions such as:
 - Dermatitis,
 - Rash,
 - Erythematous rash,
 - Macular rash,

- Papular rash,
- Maculo-papular rash,
- Pruritic rash,
- Pustular rash,
- Vesicular rash.
- Related to pregnancy:
 - Pregnancy in subject or in partner of a male subject.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each adverse event according to Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

The investigators will rate the severity of each adverse event as mild, moderate, or severe. The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to MMV/PrimeVigilance within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study procedures (Section 5.3). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. Pregnancy in a subject's partner will be collected from the date of the first dose through 120 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event (SAE) and must be reported to MMV/PrimeVigilance within 24 hours after the site becomes aware of the event.

6.2 Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Completed and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, NC, USA).

7.2 Statistical Analyses for Pharmacokinetics

Primary Analysis

For DSM265, an analysis of variance (ANOVA) will be performed for T_{max} , β , the natural logarithms of C_{max} , AUC, and C_{168} . Significant pharmacokinetic sample time deviations will be identified and listed.

Sample Size Estimation

Refer to the SAP for details on sample size determinations.

7.3 Statistical Analyses for Safety

Refer to the SAP for details on the safety analysis.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed

consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the Investigator are specified in 0.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

12 REFERENCES

1. MMV. DSM265 Investigator's Brochure Version 7.0. 31 July 2018.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
AUC _t	Area under the plasma concentration-time curve from time 0 until the last measurable concentration
AUC _{inf}	Area under the plasma concentration-time curve from time 0 to infinity
β	Apparent terminal phase elimination rate constant
BMI	Body mass index
C ₁₆₈	Plasma concentration at 168 hours
C _{max}	Time to the maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Event
ECG	Electrocardiogram
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HAV-IgM	Hepatitis A virus immunoglobulin M
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine device
MMV	Medicines for Malaria Venture
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
SAE	Serious adverse event

SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal phase elimination half-life
T_{\max}	Time to maximum observed plasma concentration (C_{\max})
ULN	Upper limit of normal
WONCBP	Women of Non-Child Bearing Potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol B19-227: Relative Bioavailability and Food Effect of DSM265

Protocol Date: 13 August 2018

Clinical research studies performed at AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
Joerg Moehrle	DSM265 Project Director	Clinical Program Development (MMV)
Stephan Chalon	Medical Director	Group MD or MA TA (MMV)
Stephan Duparc	Chief Medical Officer	Clinical Program Development (MMV)

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities and time-points. The individual activities are described in detail in the Operations Manual ([Appendix E](#)).

Study Activities Table

Activity	Screening	Day -1 Initial Confinement	Day 1	Day 2	Day 4	Day 6	Day 8	Day 10	Day 14 +/- 1 day	Day 21 +/- 1 day or Premature Discontinuation
INTERVIEWS & QUESTIONNAIRES										
Informed consent	✓									
Eligibility criteria	✓	✓								
Medical/surgical history (update only upon initial confinement)	✓	✓								
Drug alcohol and nicotine use	✓									
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓			✓	✓	✓	✓	✓	✓
LOCAL LABS & EXAMS										
HAV-IgM, HBsAg, HCV Ab, HIV Ab	✓									
Height (Screening and Initial confinement only) and weight	✓	✓								✓
Physical examination	✓	✓		✓						✓
Drug, Alcohol and Cotinine Screen	✓	✓								
12-lead ECG single	✓	✓	✓	✓						✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
FSH test (postmenopausal women)	✓									
Pregnancy test (non-postmenopausal women) (u = urine; s = serum)	✓ (u)	✓ (s)								✓ (s)
Blood Chemistry Hematology (CBC), and Urinalysis	✓	✓		✓			✓			✓
Blood samples for DSM265 assay			✓	✓	✓	✓	✓	✓	✓	✓
Administration										
DSM265 Administration			✓							
Confinement		✓	✓	✓						

Day 1

Day 1 Activity	Pre-Dose	0 Hour	0.5 Hour	1 Hour	2 Hour	4 Hour	6 Hour	8 Hour	12 Hour	24 Hour
Blood samples for DSM265 PK assay	✓		✓	✓	✓	✓	✓	✓	✓	✓
Study drug administration		✓								
12-lead ECG single						✓				
Vital signs	✓			✓		✓		✓	✓	✓

APPENDIX E. OPERATIONS MANUAL

**Operations Manual for Clinical Study Protocol B19-227
(MMV_DSM265_18_01)**

Malaria: Relative Bioavailability and Food Effect of DSM265

SPONSOR:	Medicines for Malaria Venture (MMV)	INVESTIGATIONAL PRODUCT:	DSM265, A-1400550
INVESTIGATOR:	David Carter, MD Medical Director AbbVie Clinical Pharmacology Research Unit 480 S. US Highway 45 Grayslake, IL 60030	Phone: (847) 937-8515 Fax: (847) 935-4402	

1 CONTACTS

Sponsor/ Emergency Contact and Safety Concerns:	Stephan Chalon, MD Medical Director MMV Route de Pre-Bois 20 Box 1826 1215 Geneva 15 Switzerland Email: chalons@mmv.org	Mobile: + 41-79-962-6244 Fax: + 41-22-555-0369
	EMERGENCY 24 hour Number: +1 (973) 784-6402	If not available: Phone: (973) 784-6402
Serious Adverse Event (SAE) Reporting	Email: MMV@primevigilance.com	FAX: +44 800 471 5694
Protocol Deviations and Product Complaints	Meredith McDonald Study Management Associate III One North Waukegan Road North Chicago, IL 60064	Mobile: +1 847-393-5792 Fax: +1 847-654-6836 Email: meredith.mcdonald@abbvie.com
	OR	OR
	Alyssa O'Neill Assistant Director One North Waukegan Road North Chicago, IL 60064	Office: +1 847-938-0387 Mobile: +1 847-513-2129 Email: alyssa.b.oneill@abbvie.abbvie.com
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TABLE OF CONTENTS

1	CONTACTS	2
2	INVESTIGATION PLAN	5
2.1	STUDY ACTIVITIES	5
3	STUDY PROCEDURES	5
3.1	STUDY INFORMATION AND INFORMED CONSENT	5
3.2	MEDICAL/SURGICAL HISTORY	5
3.3	HEPATITIS SCREEN	5
3.4	HIV SCREEN	6
3.5	DRUG, ALCOHOL AND COTININE SCREEN	6
3.6	12-LEAD ECG	6
3.7	HEIGHT AND WEIGHT	7
3.8	VITAL SIGNS	7
3.9	PHYSICAL EXAMINATION	8
3.10	CLINICAL LABORATORY TESTS	8
3.11	PREGNANCY TEST	9
3.12	PHARMACOKINETIC SAMPLING	9
3.13	MEALS	9
3.14	CONFINEMENT	10
3.15	OUTPATIENT VISITS	10
4	SAFETY MANUAL	10
4.1	METHODS AND TIMING OF SAFETY ASSESSMENT	10
4.2	RECORDING DATA AND ANALYSES OF SAFETY FINDINGS	11
4.3	REPORTING ADVERSE EVENTS	11
6	STUDY DRUG	12
6.1	TREATMENTS ADMINISTERED	12
6.2	PACKAGING AND LABELING	13
6.3	METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS	13

6.4	SELECTION AND TIMING OF DOSE FOR EACH SUBJECT	13
6.5	PREPARATION/RECONSTITUTION OF DOSAGE FORM	13

LIST OF APPENDICES

APPENDIX A.	STUDY SPECIFIC ABBREVIATIONS AND TERMS	14
APPENDIX B.	PHARMACOKINETIC HANDLING, PROCESSING AND SHIPMENT	15

2 INVESTIGATION PLAN

2.1 Study Activities

Information regarding specific procedures is provided in Section 3. The timing of the activities for this study is presented in tabular form in the Study Activities Tables attached to the protocol.

3 STUDY PROCEDURES

3.1 Study Information and Informed Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study. After the nature of the testing has been explained and the subject has had an opportunity to ask questions and questions have been answered to the subject's satisfaction, the subject will be presented the opportunity to sign the informed consent form(s). Each consent form must be voluntarily signed and dated before any related study activities are performed. Each informed consent form will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A signed copy of each informed consent will be given to the subject and each original will be placed in the subject's study record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

3.2 Medical/Surgical History

A complete medical/surgical history, including history of tobacco, alcohol and drug use, will be taken. The subject's medical history updated on initial confinement will serve as the baseline for clinical assessment.

Medication (prescription or over-the-counter, including vitamins and herbal supplements) use from 2 weeks prior to study drug administration through the end of the study will also be recorded.

3.3 Hepatitis Screen

HAV-IgM, hepatitis B surface antigen (HBsAg) and Hepatitis C virus antibody (HCV Ab) tests will be performed. The hepatitis test panel will be performed by a certified laboratory.

3.4 HIV Screen

Subjects will have blood tested by a certified laboratory for the presence of human immunodeficiency virus antibody (HIV Ab). Only those subjects negative for the presence of antibodies will be allowed to enroll in the study.

3.5 Drug, Alcohol and Cotinine Screen

Urine specimens will be tested for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed below. Any positive result must be assessed for clinical significance. These analyses will be performed by the certified laboratory chosen for the study. The cotinine test may be performed by the clinical site. Results of the cotinine test will be retained by the study site.

- Cannabinoids
- Opiates
- Barbiturates
- Amphetamines
- Cocaine
- Benzodiazepines
- Alcohol
- Phencyclidine
- Propoxyphene
- Methadone

3.6 12-Lead ECG

Resting single 12-lead ECGs will be obtained.

The ECG acquired prior to dosing will serve as the baseline measurements for clinical assessment.

When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection. ECGs occurring near meals will take place prior to meals.

ECGs will be acquired after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, subjects and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit electrical interference in the room.

ECG Safety Review

Each ECG will be evaluated by an appropriately qualified physician (preferably a cardiologist) at the study site (the "local reader"). The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event (AE) determination and management, and decision on whether a subject will be discontinued from the study.

The local reader will sign and date all the ECGs collected in this study and provide a global interpretation for each ECG using the following categories:

- Normal ECG
- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)
- Unable to evaluate

All local reader evaluations of ECGs will be entered into the source documents. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval corrected for heart rate using Fridericia's formula (QTcF) will be calculated and documented for all ECGs.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

3.7 Height and Weight

Height and weight will be measured in order to calculate body mass index (BMI). Body weight may be measured at additional timepoints throughout the study. The subject will wear lightweight clothing and no shoes during height measurement and weighing.

3.8 Vital Signs

Body temperature (oral), blood pressure and pulse will be measured. The vital signs measurements just prior to dosing on Study Day 1 will serve as the baseline measurements for clinical assessment.

Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes.

When measurements of vital signs are scheduled at the same time as a blood collection, the measurements of vital signs will be obtained prior to the blood collection.

Measurements of vital signs occurring near meals or dosing will take place prior to meals or dosing.

3.9 Physical Examination

Physical examinations will be performed. A symptom-directed physical examination will be performed when necessary. The last physical examination performed prior to the first dose will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after dosing will be recorded as adverse events.

3.10 Clinical Laboratory Tests

The blood samples for serum chemistry tests should be collected following a minimum 8-hour fast.

The site's local laboratory will be utilized to process and provide results for the clinical laboratory test. The laboratory must be certified and must provide laboratory reference ranges prior to the initiation of the study. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug. Follow-up safety labs may be performed by a certified lab other than the site's local laboratory. An out of range laboratory test at screening or check in may be repeated at the discretion of the investigator.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.
- A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an adverse event.

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Platelet count (estimate not acceptable) Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Reticulocyte count	Blood urea nitrogen (BUN) Creatinine Total bilirubin Albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Cholesterol Total protein Glucose Triglycerides Chloride Carbon Dioxide Lactate dehydrogenase (LDH)	Specific gravity Ketones pH Protein Glucose Blood Bilirubin Microscopic examination if the results are positive

3.11 Pregnancy Test

A urine pregnancy test and quantitative serum pregnancy tests will be performed for all non-postmenopausal women.

3.12 Pharmacokinetic Sampling

Blood Samples for DSM265 Assay

Blood samples for DSM265 will be collected at time points specified in Study Activities Table in the protocol.

Additional information on the disposition, handling and measurement methods can be found in [Appendix B](#).

3.13 Meals

At least a 10-hour fast is required prior to dosing for Regimen A and Regimen B, a high-fat breakfast is required for Regimen C; otherwise, standard moderate-fat meals will be provided during confinement.

Fasting: Subjects will receive a standardized diet. Subjects will fast for at least 10 hours prior to dosing in the fasting regimens (A and B). For Regimen C (non-fasting), subjects will start the high-fat breakfast approximately 30 minutes prior to dosing.

Non-fasting: With the exception of the high-fat breakfast for Regimen C, meals will be identical on the intensive pharmacokinetic sampling days (Study Day 1) except for the breakfast in Regimen C. The composition (protein, fat, carbohydrate, and total calories) of these meals will be determined by a dietician and a record will be kept with the source documents. For moderate fat meals, approximately 30% of the total caloric content of the meals must be from fat. For the high-fat breakfast, approximately 50% of the total caloric content of the meal must be from fat.

3.14 Confinement

Subjects will be confined to the study site and supervised for approximately 3 days. Confinement in each period will begin on Study Day –1 and end after the collection of the 24-hour blood samples and scheduled study procedures are completed on Study Day 2. Strenuous activity during confinement will not be permitted.

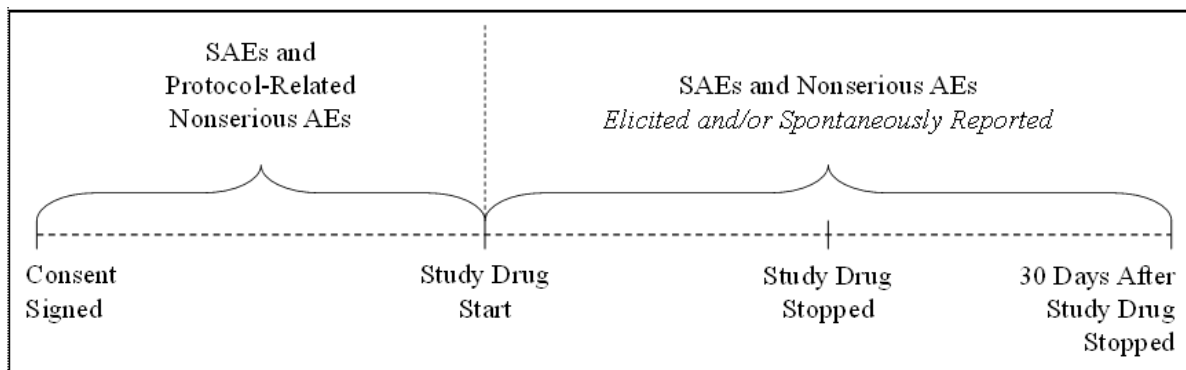
3.15 Outpatient Visits

Subjects will return to the study site in the morning of designated days for study procedures as indicated in the Study Activities Table.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious adverse events as well as protocol-related nonserious adverse events (e.g., occurrence during screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration and reported to the sponsor. From the time of study drug administration until 30 days or 5 half-lives whichever is longer following discontinuation of study treatment has elapsed, all adverse events and serious adverse events will be collected, whether solicited or spontaneously reported by the subject.



4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) with a breakdown by regimen. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 adverse event for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events

In the event of an SAE, whether associated with study drug or not, the Investigator will notify MMV Pharmacovigilance within 24 hours of the site being made aware of the SAE by email. The study specific SAE and AESI forms will be used by the Investigator.

Email: MMV@primevigilance.com

FAX to: +44 800 471 5694

For any subject safety concerns, please contact the physician listed below:

Stephan Chalon, MD

Medical Director

MMV

Route de Pre-Bois 20 Box 1826

1215 Geneva 15

Switzerland

Email: chalons@mmv.org

Mobile: + 41-79-962-6244

Fax: + 41-22-555-0369

HOTLINE: +1 (973) 784-6402

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., International

Conference on Harmonization (ICH) Expedited Reports or any additional reports required by local regulations) to the independent ethics committee (IEC)/Institutional Review Board (IRB) of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to MMV/PrimeVigilance.

For protocol-related non-serious adverse events in volunteers that sign the study specific informed consent, and are not randomized or dosed, provide to the monitor and the [TA] Safety Team (SafetyManagement_[TA]@abbvie.com) at minimum, the following information:

- a brief description of the adverse event, including onset and resolution dates
- a volunteer identifier
- the protocol-defined study procedure(s) and/or other factor(s) that caused the AE
- a brief description of the treatment or intervention

5 ADDITIONAL REQUIREMENTS

There are no additional requirements.

6 STUDY DRUG

6.1 Treatments Administered

Study drug will be administered in the morning on Study Day 1 as follows:

Regimen A	400 mg DSM265 25% SDD powder for suspension administered under fasting conditions (reference).
Regimen B	400 mg DSM265-TPGS 34% SDD powder administered under fasting conditions (test).
Regimen C	400 mg DSM265-TPGS 34% SDD powder administered under nonfasting conditions (test).

Regimen A will be taken orally with approximately 240 mL of vehicle (100 mL followed by 2 rinses of 70 mL each) after at least a 10-hour fast and approximately 4 hours before lunch. Regimen B will be taken orally with approximately 60 mL of water (40 mL followed by a rinse of 20 mL) after at least a 10-hour fast and approximately 4 hours before lunch. Regimen C will be taken orally with approximately 60 mL of water (40 mL followed by a rinse of 20 mL) approximately 30 minutes after starting breakfast. The time of each drug administration will be recorded to the minute. The subjects will be instructed to remain in a sitting or standing position for at least 2 hours after dosing.

6.2 Packaging and Labeling

All study drugs will be supplied in bags.

Each bag will be labeled as required per country requirements.

Storage and Disposition of Study Drug

DSM265 SDD powder must be stored at 5°C (2 to 8°C/35 to 46°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

As they are enrolled in the study, subjects will be assigned unique consecutive numbers beginning with 101. The subjects will be randomly assigned in equal numbers to receive one of the three regimens. The randomization schedule will be computer-generated before the start of the study by the Statistics Department, AbbVie.

6.4 Selection and Timing of Dose for Each Subject

The same dose will be administered to all subjects. Dosing will be accomplished in the morning of Study Day 1.

6.5 Preparation/Reconstitution of Dosage Form

The DSM265 drug product will be provided as a powder in bags. Each dose of DSM265 will be reconstituted following the specific dose preparation that will be provided to the site pharmacist in a pharmacy manual.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
ECG	Electrocardiogram
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibody
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred term
QTcF	QTc using Fridericia's correction formula
RBC	Red blood cell
SAE	Serious adverse event
SOC	System Organ Class

APPENDIX B. PHARMACOKINETIC HANDLING, PROCESSING AND SHIPMENT

Collection of Samples for Analysis

Blood samples for DSM265 analysis will be collected by venipuncture at the protocol specified times after dosing. The timing of blood collections will take priority over all other scheduled study activities except for dosing. The order of blood collections will be maintained to the minute such that the time intervals relative to the preceding dose will be the same for all subjects. The time that each blood sample is collected will be recorded to the minute.

The blood samples will be collected in 1 mL evacuated Lithium heparin-containing collection tubes. Sufficient blood will be collected to yield approximately 0.4 mL plasma from each sample. Immediately after collection, the blood samples will be inverted to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath.

Handling/Processing of Samples

The blood samples for DSM265 will be centrifuged at approximately 1400 x g for approximately 10 minutes using a refrigerated centrifuge to separate the plasma within 1 hour of collection. The plasma samples will be transferred using plastic pipettes into screw-capped polypropylene tubes labeled with the drug number name, type of sample (plasma), the protocol number, the subject number, the study day, and the planned time of sampling relative to dosing. The plasma samples will be placed in a freezer within 2 hours after collection and maintained at –20°C or colder until shipped to Swiss BioQuant.

Disposition of Samples

The frozen plasma samples for DSM265 will be packed in dry ice sufficient to last during transport. Pick-up and shipment of samples to Swiss BioQuant will be organized by MMV. An inventory of the samples included will accompany the package. Temperature excursions during transit will be tracked/recorded by the use of loggers included in the package.

Arrangements will be made with AbbVie for the shipment of samples to:

Swiss BioQuant/Anita Kress, Ph.D.

Kägenstrasse 18

4153 Reinach, Switzerland

Phone: +41 61 716 98 12

Fax: +41 61 716 98 15

E-mail: anita.kress@swissbioquant.com



Measurement Methods

Plasma concentrations of DSM265 will be determined using a validated method at:

Swiss BioQuant
Kägenstrasse 18
4153 Reinach, Switzerland

SIGNATURE PAGE

**Relative Bioavailability and Effect of Food on DSM265-TPGS 34% SDD
Powder in Healthy Adult Subjects
Medicines for Malaria Venture (MMV)
Protocol B19-227 (MMV_DSM265_18_01)**

Approved by:

Sponsor	Signature and Date
Stephan Chalon, MD, PhD VP-Head of Experiment Medicine DSM265 Medical Director	
Joerg Moehrle, PhD VP-Head of Translational Medicine DSM265 Project Director	
Stephan Duparc, MD Chief Medical Officer	

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