Official Title of Study:

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of Deucravacitinib (BMS-986165) in Participants with Active Discoid and/or Subacute Cutaneous Lupus Erythematosus (DLE/SCLE)

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CLINICAL PROTOCOL IM011132

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of Deucravacitinib (BMS-986165) in Participants with Active Discoid and/or Subacute Cutaneous Lupus Erythematosus (DLE/SCLE)

Brief Title:

A Phase 2 Clinical Study to Assess the Safety and Efficacy of Deucravacitinib in Participants with Active DLE and/or SCLE

Protocol Amendment 02

Incorporates Administrative Letter 02

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 02	15-Apr-2022	This protocol was amended to: [redacted] • Permit past use of frequently used second-line therapies that are prescribed to treat discoid lupus erythematous (DLE) and/or subcutaneous lupus erythematous (SCLE) to allow participants whose disease was inadequately controlled with these second-line therapies to participate in this Phase 2 study with deucravacitinib. [redacted] • Add details regarding serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2). • Incorporate changes from the approved Administrative Letter 02, which updates study contact information.
Administrative Letter 02	22-Jan-2021	The purpose of this letter is to change the Contact Information of the Medical Monitor
Revised Protocol 01	01-Dec-2020	[redacted] • Minor typographical errors and clarifications throughout.
Administrative Letter 01	11-Sept-2020	• Added EUDRACT Number and Universal Trial Number to the original protocol.
Original Protocol	28-Aug-2020	Not applicable.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02:

The overall rationale for Protocol Amendment 02 is:

[redacted]

- Added details regarding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

As this is a rare disease population, the following revisions are expected to increase the likelihood of enrollment of participants whose disease is inadequately controlled with standard of care treatment(s) and provide a more robust real world-like study population:

[redacted]

- Frequently used second-line therapies that are prescribed to treat discoid lupus erythematous (DLE) and/or subcutaneous lupus erythematous (SCLE) around the world were removed from the list of prohibited medications. This revision to the list of prohibited medications and the provision for a wash-out period prior to study screening will allow more participants whose disease was inadequately controlled with these therapies to be considered to participate in this study.

[redacted]

- This amendment incorporates the changes from the approved Administrative Letter 02, which is detailed in the Document History but not listed in the Summary of Key changes table below.
- Minor formatting and typographical corrections have been made, therefore, they have not been summarized.

This protocol amendment applies to all participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	• Changed Clinical Trial Physician - Medical Monitor [redacted]. • Changed Clinical Scientist [redacted].	To reflect updated personnel.
Section 1: Protocol Summary	Updated text.	To align the summary with updates made to the full protocol.
Table 2-1: Screening Procedural Outline (IM011132)	[redacted]	
	Added "eg." to packs per day under history of marijuana and tobacco use.	To clarify that packs per day is an example of how to measure tobacco use.
	Updated 'Serious Adverse Events Assessment' to 'Monitor for AEs and SAEs' and added AEs to notes.	To include AEs in addition to SAEs.
	Added to follicle stimulating hormone (FSH) testing that females under age 55 must have a serum FSH level > 40 mIU/mL to confirm menopause.	To require FSH testing for any woman reported to be postmenopausal who is under the age of 55, unless surgically sterile.
	Added hepatitis B surface antibody (anti-HBs) to serology testing and updated hepatitis B core antibody (HBc AB) to anti-HBc.	To ensure consistency with Appendix 14: Interpretation of Hepatitis B Serologic Test Results.
	[redacted]	

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
Table 2-2: Placebo-Controlled Treatment Period Procedural Outline Up to Week 16 (IM011132)	Added AEs to notes.	To include AEs in addition to SAEs.
Table 2-2: Placebo-Controlled Treatment Period Procedural Outline Up to Week 16 (IM011132)	[redacted]	
Table 2-3: Active Treatment Period Activities and Assessments (IM011132)		
Section 3.2.1: Disease Background	Removed belimumab.	This is a clarification as belimumab is approved for SLE and works by a different mechanism of action from the other medications noted in this section.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Table 4-1: Objectives and Endpoints	[redacted]	
Section 5.1.1: Screening Period		
Section 5.1.2: Placebo-controlled Treatment Period (Day 1 to Week 16)		
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6: Study Population	Added language for protocol waivers [redacted].	To clarify that protocol waivers or exemptions are not permitted [redacted].
Section 6.1: Inclusion Criteria	[redacted]	
	Added introductory text to inclusion criterion 4.	To add details on investigator role for WOCBP and regulations.
	Added inclusion criterion 4) j) to include that females under age 55 must have a serum FSH level > 40 mIU/mL to confirm menopause.	To require FSH testing for any woman reported to be postmenopausal who is under the age of 55, unless surgically sterile.
	Updated inclusion criterion 4) k) for egg donation.	To add details for WOCBP regarding egg donation following receiving study product.
Section 6.2: Exclusion Criteria	Updated exclusion criterion 3) f) to "not applicable" and added 3) h) to remove irritable bowel disease (IBD).	This is a correction as inflammatory bowel diseases are already excluded in criterion 2) b), which excludes any major illnesses or unstable gastrointestinal conditions. Irritable bowel syndrome (IBS) was never intended as exclusionary.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
	Updated exclusion criterion 3) d) to "not applicable" and added 3) j) to change topical corticosteroid from mild to moderate potency.	To be consistent with Appendix 12: Topical Steroid Potency Table.
	Updated exclusion criterion 3) h) to "not applicable" and added 3) i) to change from 90 days to 60 days for receiving a live vaccine.	To be consistent with SARS-CoV-2 guidance.
	Updated exclusion criterion 4) b) vi) to "not applicable" [redacted].	To allow for more eligible participants to be considered for participation [redacted].
	Updated numbering for exclusion criterion 3) to 5) b)	To rectify incorrect numbering.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
	and adjusted numbering for subsequent criteria.	
	Updated exclusion criterion 5) a) iv) to "not applicable" and added 5) a) v) for Latent Tuberculosis Infection (LTBI).	To clarify the exception for those participants who are receiving prophylactic treatment for LTBI and the Clinical Trial Physician/Medical Monitor should be consulted on all LTBI cases.
	Updated exclusion criterion 5) f) to "not applicable" and added additional new criteria with details for exclusionary infections prior to screening.	To clarify infections that should prevent enrollment.
	Updated exclusion criterion 5) f) i) to "not applicable" and added a new note at the end of 5) list of sub-criteria.	To clarify details regarding serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enrollment parameters.
Section 6.4.1: Retesting During Screening Period - Rescreening	Clarified that participants can be rescreened twice.	To increase the likelihood of enrollment.
Section 7.5: Preparation/Handling/ Storage/Accountability	Added details on investigator responsibility.	To clarify investigator responsibilities.
Section 7.7: Concomitant Therapy	Added topical medications.	This is a clarification as previous and current topical medications used for SCLE/DLE should be recorded in addition to the systemic medications.
	Added details on previous and current DLE/SCLE and SLE medications.	To clarify reporting requirements.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.7.1: Prohibited and/or Restricted Treatments	Removed reference to Section 6.2 and moved details to Section 7.7.1.1: Prohibited Treatments and Section 7.7.1.2: Restricted Treatments.	To clarify prohibited and restricted treatment.
Section 7.7.1.1: Prohibited Treatments	Added section.	To clarify which treatments are prohibited.
Section 7.7.1.2: Restricted Treatments	Added section.	To clarify which treatments are restricted.
Section 7.7.2: Permitted Background DLE/SCLE/SLE Therapies	Added "permitted" and "lupus" to section title.	To clarify therapies.
Section 7.7.2.1: Corticosteroid Therapy	[redacted]	
Section 7.7.3: Rescue Therapy	[redacted]	
Section 7.7.4: Permitted Vaccines (including COVID-19 Vaccine)	Added section.	To clarify which vaccines are permitted.
Section 8.3: Lost to Follow-Up	Added introductory language above bulleted list.	To clarify actions in bulleted list.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 9.2: Adverse Events	Removed reference to Appendix 3 for contacts on serious adverse event (SAE) reporting and added to refer to Appendix 3 for details on SAE reporting.	To specify where additional details can be found for SAE reporting.
Section 9.2.1: Time Period and Frequency for Collecting AE and SAE Information	Added that AEs will be collected from the time of signing the consent.	To clarify that AEs in addition to SAEs are collected.
	Removed that non-serious AEs should be collected from treatment initiation until safety follow-up visit.	To clarify that non-serious AEs are collected after informed consent is completed.
	Added SARS-CoV-2 language.	To clarify procedures for SARS-CoV-2 events.
Section 9.4.5: Clinical Safety Laboratory Assessments	Added anti-HBs to serology testing and updated HBc AB to anti-HBc.	To ensure consistency with Appendix 14: Interpretation of Hepatitis B Serologic Test Results.
[redacted]		

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
		[redacted]
Appendix 2: Study Governance Considerations	Updated language for Good Clinical Practice (GCP).	To reflect current GCP.
	Removed that investigator should provide investigator brochure or product labelling to the institutional review board (IRB) and added specific investigator responsibilities.	To reflect current processes.
	Updated investigator or representative process for informed consent.	To add details and clarify that the investigator or representative is responsible.
	Added definitions and details for source documents.	To provide additional clarifications.
	Updated first paragraph for monitoring to include remote monitoring.	To allow for remote monitoring.
	Added new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security, Study and Site Start and Closures, Dissemination of Clinical Study Data, Assessment of Intensity.	To provide details on how study start and closures will occur, how clinical study data will be made available, to provide guidance for assessing AEs/SAEs, to add details on commitment to diversity in clinical trials, and to comply with European Clinical Trials Register (EU-CTR) requirements.
Appendix 4: Women of Childbearing Potential	Added introductory paragraph.	To provide clarity on contents for Appendix 4.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Definitions and Methods of Contraception	Removed vaginal birth control suppositories, creams, and gels from intravaginal option.	To clarify that only rings are needed.
[redacted]		
Appendix 25: Core and Extended ADME Gene List	Added that section is not applicable per Protocol Amendment 02.	Examples of ADME related genes were provided in protocol [redacted]

TABLE OF CONTENTS

TITLE PAGE 1
DOCUMENT HISTORY 3
OVERALL RATIONALE FOR PROTOCOL AMENDMENT 02: 4
SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 02 5
TABLE OF CONTENTS 15
1 SYNOPSIS 19
2 SCHEDULE OF ACTIVITIES 26
3 INTRODUCTION 37
3.1 Study Rationale 37
3.2 Background 38
3.2.1 Disease Background 39
[redacted] 40
4 OBJECTIVES AND ENDPOINTS 44
5 STUDY DESIGN 47
5.1 Overall Design 47
5.1.1 Screening Period 49
5.1.2 Placebo-controlled Treatment Period (Day 1 to Week 16) 49
5.1.3 Active Treatment Period (Week 16 to Week 52) 49
5.1.4 Follow-up Period 50
5.1.5 Data Monitoring Committee and Other Committees 50
[redacted] 50
5.2 Number of Participants 50
5.3 End of Study Definition 50
5.4 Scientific Rationale for Study Design 50
[redacted] 52
6 STUDY POPULATION 53
6.1 Inclusion Criteria 53
6.2 Exclusion Criteria 56
6.3 Lifestyle Restrictions 61
6.3.1 Exposure to Sunlight 61
6.3.2 Meals and Dietary Restrictions 61
6.4 Screen Failures 61
6.4.1 Retesting During Screening Period - Rescreening 62
7 TREATMENT 62
7.1 Treatments Administered 65
7.2 Method of Treatment Assignment 65
7.3 Blinding 66
7.4 Dosage Modification 67
7.5 Preparation/Handling/Storage/Accountability 67
7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability 67
7.6 Treatment Compliance 67
7.7 Concomitant Therapy 68
7.7.1 Prohibited and/or Restricted Treatments 68

7.7.1.1 Prohibited Treatments 68
7.7.1.2 Restricted Treatments 68
7.7.2 Permitted Background DLE/SCLE/SLE Therapies 69
7.7.2.1 Corticosteroid Therapy 69
7.7.2.2 Antimalarial Therapy 69
7.7.2.3 Immunosuppressant Therapy 70
7.7.2.4 Nonsteroidal Anti-inflammatory Drugs and Narcotic Analgesics 70
7.7.3 Rescue Therapy 70
7.7.4 Permitted Vaccines (Including COVID-19 Vaccine) 71
[redacted] 71
8 DISCONTINUATION CRITERIA 71
8.1 Discontinuation from Study Treatment 71
8.1.1 Post Study Treatment Study Follow-up 72
8.2 Discontinuation from the Study 72
8.3 Lost to Follow-Up 73
9 STUDY ASSESSMENTS AND PROCEDURES 73
9.1 Efficacy Assessments 74
9.1.1 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) 74
[redacted] 74
75
75
9.1.4 Skin Biopsy 75
[redacted] 75
76
76
76
76
77
77
77
77
78
78
9.2 Adverse Events 78
9.2.1 Time Period and Frequency for Collecting AE and SAE Information 78
9.2.2 Method of Detecting AEs and SAEs 79
9.2.3 Follow-up of AEs and SAEs 79
9.2.4 Regulatory Reporting Requirements for SAEs 80
[redacted] 80
9.2.6 Pregnancy 80
9.2.7 Laboratory Test Result Abnormalities 81
9.2.8 Potential Drug Induced Liver Injury (DILI) 81
9.2.9 Other Safety Considerations 82
9.3 Overdose 82

9.4 Safety 82
9.4.1 Physical Examinations 82
9.4.2 Tuberculosis Screening and Chest X-ray 83
9.4.3 Vital signs 83
9.4.4 Electrocardiograms 83
9.4.5 Clinical Safety Laboratory Assessments 83
9.4.6 Imaging Safety Assessment 84
[redacted] 84
84
86
86
86
86
89
90
90
90
90
90
90
91
9.9 Health Economics OR Medical Resource Utilization and Health Economics . 91
10 STATISTICAL CONSIDERATIONS 91
[redacted] 91
10.2 Populations for Analyses 92
10.3 Statistical Analyses 92
10.3.1 Efficacy Analyses 93
10.3.2 Safety Analyses 94
[redacted] 94
10.3.4 Interim Analyses 94
11 REFERENCES 95
12 APPENDICES 99
APPENDIX 1 ABBREVIATIONS AND TRADEMARKS 100
APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS 105
APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING 116
APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION 120
[redacted] 124
125
127
APPENDIX 8 CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI) 130
APPENDIX 9 COMMONLY USED CORTICOSTEROID EQUIVALENTS 131

APPENDIX 10 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS IV 132
[redacted] 133
APPENDIX 12 TOPICAL STEROID POTENCY TABLE 135
[redacted] 136
APPENDIX 14 INTERPRETATION OF HEPATITIS B SEROLOGIC TEST RESULTS 137
[redacted] 139
[redacted] 140
[redacted] 142
[redacted] 150
[redacted] 152
[redacted] 153
[redacted] 154
[redacted] 155
[redacted] 156
[redacted] 157
APPENDIX 25 CORE AND EXTENDED ADME GENE LIST 158
APPENDIX 26 [redacted] DISCOID LUPUS CLASSIFICATION CRITERIA 167
APPENDIX 27 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY 168

1 SYNOPSIS

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of Deucravacitinib (BMS-986165) in Participants with Active Discoid and/or Subacute Cutaneous Lupus Erythematosus (DLE/SCLE)

Brief Title: A Phase 2 Clinical Study to Assess the Safety and Efficacy of Deucravacitinib in Participants with Active DLE and/or SCLE

Study Phase: 2

Rationale:

This Phase 2 study will assess if deucravacitinib (BMS-986165) is biologically active and potentially effective in the treatment of participants with moderate to severe discoid lupus erythematosus and/or subacute cutaneous lupus erythematosus (DLE/SCLE) with or without systemic lupus erythematosus (SLE), that is inadequately controlled with standard of care therapy.

Study Population:

Male and female participants (18 to 75 years of age) must have a biopsy-confirmed clinical diagnosis of DLE/SCLE, and inadequate response, defined as therapeutic failure or intolerance to an oral corticosteroid, and/or antimalarial and/or immunosuppressant.

Key Inclusion Criteria:

- Participants must have a diagnosis of DLE/SCLE for at least 3 months prior to Screening Visit.
- Participants must meet both clinical and histopathological diagnostic cutaneous lupus erythematosus (CLE) criteria per protocol.
- Participants are required to have active moderate to severe cutaneous disease based on the Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (CLASI-A) score ≥ 8 at Screening AND Baseline Visit (Day 1).
- Participants must currently be receiving treatment for DLE/SCLE with a stable regimen of at least one of the following medications: oral corticosteroid, and/or antimalarial, and/or immunosuppressant.

[redacted]

Key Exclusion Criteria:

- Participants with any of the following specific CLE subtypes in isolation: acute cutaneous lupus erythematosus (ACLE), lupus tumidus, lupus (profundus) panniculitis, chilblains.
- Participants with forms of drug-induced CLE and/or drug-induced SLE.
- Participants with active kidney disease, defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.7 m^2 and/or proteinuria > 0.5 g/24 h (spot urine protein/creatinine ratio [UPCR]: > 56.5 mg/mmol).
- Participants with antiphospholipid antibody syndrome (APS), serious thrombotic event (eg, pulmonary embolism, saddle embolism, stroke, deep vein thrombosis) or unexplained pregnancy loss within 1 year before the Screening Visit. Participants with a history of 3 or more unexplained consecutive pregnancy losses suspected due to APS.
- Participants with active severe or unstable neuropsychiatric SLE including, but not limited to, aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy); acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; and mononeuritis multiplex.
- Participants with other autoimmune diseases (eg, multiple sclerosis, psoriasis, inflammatory bowel disease [IBD], etc) with the exception of those with Type 1 autoimmune diabetes mellitus, thyroid autoimmune disease, celiac disease, or secondary Sjögren's syndrome.
- Participants with other non-SLE driven inflammatory joint or skin disease or overlap syndromes as primary disease (eg, dermatomyositis, fibromyalgia, polymyositis, scleroderma, mixed connective tissue disease, rosacea, sarcoidosis, Sjögren's syndrome) that in the opinion of the investigator will significantly impact the assessment of CLE/SLE disease manifestations and activity.

Objectives and Endpoints:

The objectives and endpoints for the primary and secondary analyses of this study are shown in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of two doses of deucravacitinib (3 mg BID and 6 mg BID) compared with placebo on CLASI-A score at Week 16.	Percentage change from baseline in CLASI activity (CLASI-A) score at Week 16.
Secondary	
To evaluate additional clinical measures of cutaneous disease manifestations with two doses of deucravacitinib (3 mg BID and 6 mg BID) compared with placebo at Week 16.	• Percentage of participants with an improvement of ≥ 50% from baseline in the CLASI-A score (CLASI-50). • Percentage of participants who have disease improvement as defined by a reduction in CLASI-A of ≥ 4 points from baseline. • Mean change from baseline in CLASI-A score. • Percentage of participants who have a Complete Response (CR) on CLASI-A defined as a score of "0".
Safety	
To assess the safety and tolerability of two doses of deucravacitinib (3 mg BID and 6 mg BID) compared with placebo.	• Number and proportion of participants experiencing SAEs, AEs (with severity and relationship of AEs), and abnormalities in laboratory testing, vital signs, and 12-lead ECGs.
[redacted]	

Abbreviations: AEs = adverse events; BID = twice a day; CLASI = cutaneous lupus erythematosus disease area and severity index; CLASI-50 = improvement of ≥ 50% from baseline in the CLASI-A score; CLASI-A = cutaneous lupus erythematosus disease area and severity index-activity; CR = complete response; ECGs = electrocardiograms; SAEs = serious adverse events.

Overall Design:

This is a Phase 2 randomized, placebo-controlled, double-blind, multicenter study to evaluate the safety and efficacy of deucravacitinib 3 mg BID and 6 mg BID given orally in participants with moderate to severe active DLE/SCLE, which may or may not be associated with SLE.

Participants must have a biopsy-confirmed clinical diagnosis of DLE/SCLE, and inadequate response, defined as therapeutic failure or intolerance to an oral corticosteroid, and/or antimalarial and/or immunosuppressant.

Participants must be on stable background DLE/SCLE therapy, which includes one oral corticosteroid, and/or one antimalarial and/or one immunosuppressant, taken alone or in combination. [redacted]

The study consists of 4 Periods:

1) Screening Period: up to 4 weeks (28 days).
2) Placebo-controlled Treatment Period: 16 weeks (Day 1 to Week 16).

3) Active Treatment Period: 36 weeks (Week 16 to Week 52).
4) Follow-up Period: 4 weeks from last dose of study treatment (28 days).

[redacted]

All randomized participants will be encouraged to participate in an additional [redacted].

[redacted]

Screening Period:

After signing the Informed Consent Form (ICF), participants are considered "enrolled" in the study, and will enter the Screening Period. During the 28-day screening period, participants will complete the study procedures and screening assessments as outlined in the Schedule of Activities to determine if they continue to meet eligibility criteria. If eligibility parameters cannot be obtained within the 28-day period, the Screening Period may be extended by up to 7 calendar days, if approved by the Clinical Trial Physician/Medical Monitor.

[redacted]

Placebo-Controlled Treatment Period (Day 1 to Week 16):

CLASI-A assessment must be performed for eligibility at Screening and Baseline (Day 1) prior to randomization for confirmation of minimally required disease activity (CLASI-A ≥8). Following confirmation of enrolment eligibility by the PI [redacted], participants will be randomized at a 1:1:1 ratio to receive:

- Deucravacitinib 3 mg BID
- Deucravacitinib 6 mg BID
- Deucravacitinib-matching Placebo BID.

[redacted]

[redacted]

Participants will be evaluated at study visits every 4 weeks through Week 16.

Active Treatment Period (Week 16 to Week 52):

Participants who complete the placebo-controlled treatment period will continue into an active treatment period for an additional 36 weeks of treatment.

At Week 16, participants receiving placebo during the placebo-controlled treatment period will be re-randomized 1:1 in a blinded-fashion to receive active treatment with either deucravacitinib 3 mg BID or 6 mg BID until Week 52. Participants receiving deucravacitinib 3 mg BID or 6 mg BID through Week 16 will continue the originally randomized treatment in a blinded manner through Week 52.

Post-Treatment Follow-up Period:

All participants will be followed for 28 days (± 3 days) after the last dose of study treatment for safety monitoring.

Number of Participants:

Approximately 75 participants are expected to be randomized.

Treatment Arms and Duration:

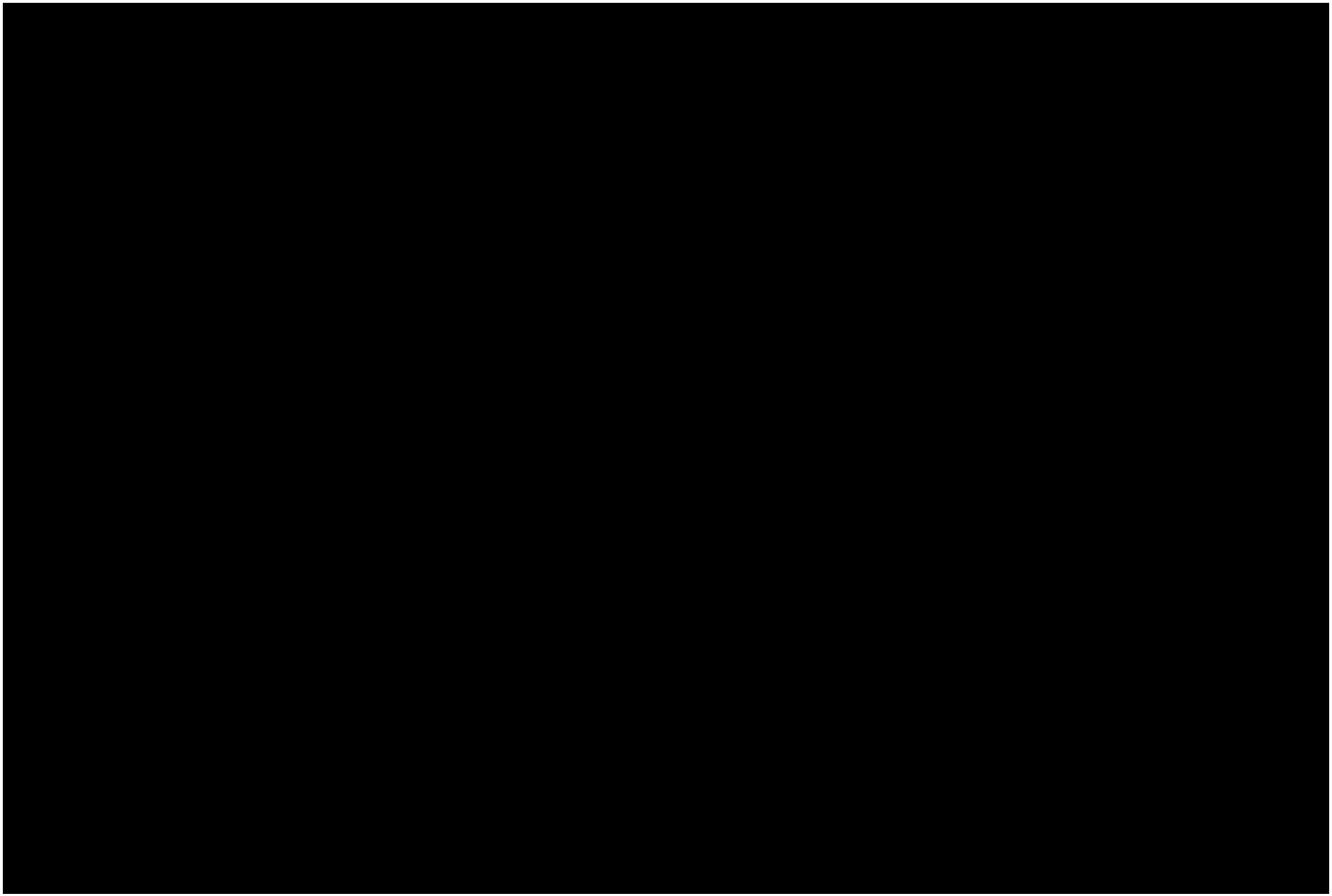
Study treatment: Participants in all treatment groups will take oral doses of investigational product (IP) for the 52-week treatment period as presented in Table 2.

Table 2: Study Treatments

Medication	Dose	IP/Non-IP
deucravacitinib **BID**	3 mg or 6 mg	IP
Placebo BID	Not applicable	IP

Abbreviations: BID = twice a day; IP = Investigational Product; Non-IP = Non-investigational Product.

Notes: In all treatment groups, participants will take their randomly assigned treatment twice daily. No titration or modification of IP doses is permitted.



Data Monitoring Committee:

A Data Monitoring Committee (DMC) with multi-disciplinary representation will be established to evaluate safety data (eg, AEs, laboratory parameters) on a periodic basis to ensure the ongoing safety of study participants and the overall benefit/risk for the study is maintained. The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

2 SCHEDULE OF ACTIVITIES

Schedules of assessments and procedures are described in Table 2-1 for the screening period, Table 2-2 for the placebo-controlled treatment period up to Week 16, and Table 2-3 for the active treatment period (up to Week 52), End of Treatment (EOT) Visit, and Safety Follow-up.

Table 2-1: Screening Procedural Outline (IM011132)

Procedure[a]	Screening Visit (28 days[b])	Notes
Eligibility Assessments		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Study allows for re-enrollment of a participant that has discontinued the study as a pretreatment failure. If re-enrolled, the participant must be re-consented and assigned a new participant number from IRT. See Section 6.4.
Eligibility Assessment	X	[redacted]
[redacted]		
Inclusion/Exclusion Criteria	X	See full inclusion/exclusion criteria (see Sections 6.1 and 6.2).
DLE, SCLE, SLE Medical History	X	Disease-specific history will include a detailed CLE and SLE history including previous laboratory results and histopathology.
Prior/Concomitant Medications	X	Documentation of background therapy. Restricted medications are detailed [redacted]. Medications restricted at screening are described in Section 6.2.
General Medical History	X	Include any toxicities or allergy related to previous treatments.
History of Tobacco and Marijuana Use	X	Type(s) of substance; nonsmoker, light or heavy smoker, volume (eg, packs per day) and duration, and state if actively using substance or year discontinued (if inactive).
Prior/Surgeries and Procedures	X	Include prior surgeries and procedures.
Safety Assessments		
Complete Physical Examination	X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, and musculoskeletal.
Vital Signs, Height, Weight	X	Body temperature, blood pressure and heart rate should be measured seated after at least 5 minutes of rest.
BMI	X	Calculated based on weight and height.
12-lead ECG	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.

Table 2-1: Screening Procedural Outline (IM011132)

Procedure[a]	Screening Visit (28 days[b])	Notes
Chest X-ray (PA and Lateral)	X	Can be performed within 6 months prior to the Screening Visit with documentation on file.
Monitor for AEs And SAEs	X	AE and SAE collection begins from the signing of the informed consent.
Laboratory Tests		
Pregnancy Test (Urine)	X	For WOCBP only.
FSH	X	Women only, if needed to confirm postmenopausal status. Females under the age of 55 years must have a serum follicle stimulating hormone level > 40 mIU/mL to confirm menopause.
Chemistry, Hematology, Urinalysis, and Coagulation Tests	X	Includes blood and urine samples. See Section 9.4.5.
Spot Urine for Protein:Creatinine Ratio	X	See Section 6.2, *Exclusion Criteria*, 1), c).
Tuberculosis screening	X	See Section 9.4.2.
Serology	X	Hepatitis C antibody, anti-HBs, HBsAg, anti-HBc, HIV-1, and HIV-2 antibody.
C3, C4, Anti-dsDNA	X	
[redacted]		
Disease Assessment		
[redacted]		
CLASI	X	Refer to Appendix 8.

Table 2-1: Screening Procedural Outline (IM011132)

Procedure[a]	Screening Visit (28 days[b])	Notes
[redacted]		

Abbreviations: anti-dsDNA =anti-double stranded deoxyribonucleic acid (antibody); anti-HBs = anti-hepatitis B surface antibody; BMI = body mass index; C3 = complement 3; C4 = complement 4; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLE = cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; [redacted] ECG(s) = electrocardiograms; [redacted] anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; [redacted] HIV = human immunodeficiency virus; [redacted] IRT = Interactive Response Technology; PA = posterioranterior; [redacted] SAE = serious adverse event; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; [redacted] WOCBP = women of childbearing potential.

[a] Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations. Some of the safety assessments intended to be used as safety monitoring by the treating physician may not be captured as data in the CRF.

[b] Screening procedures should be performed within the 28 day window prior to Day 1. If eligibility parameters cannot be obtained within this time period, the screening period may be extended by up to 7 calendar days if approved by the Clinical Trial Physician/Medical Monitor.

Table 2-2: Placebo-Controlled Treatment Period Procedural Outline Up to Week 16 (IM011132)

Procedure[a]	D1 (Baseline)	W4 D29 (±3d)	W8 D57 (±3d)	W12 D85 (±3d)	W16 D113 (±3d)	Notes: Participants who discontinue treatment at any time prior to Week 52 should proceed to the EOT/ET visit Table 2-3). The Safety Follow-up visit will occur 28 days ±3 days after last treatment visit (Table 2-3).
Eligibility Assessments						
Eligibility / Randomization	X					Confirm eligibility criteria and complete Baseline assessments prior to randomization.
Re-randomized for Active Treatment Period					X	Only participants on placebo will be re-randomized, but IRT will be contacted for all participants to maintain the blind.
Safety Assessments						
Complete Physical Examination	X				X	General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal.
Targeted Physical Examination		X	X	X		As clinically indicated.
Concomitant Medications	X	X	X	X	X	
Vital Signs	X	X	X	X	X	Includes body temperature, body weight, respiratory rate, and blood pressure and heart rate.
12-lead ECG	X				X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Pregnancy Test (Urine)	X	X	X	X	X	For WOCBP only.
Monitor for AEs and SAEs	Continuously					AE and SAE collection begins from the signing of the informed consent.
Laboratory Tests						
Hematology, Serum Chemistry Panel	X	X	X	X	X	See Section 9.4.5.

Table 2-2: Placebo-Controlled Treatment Period Procedural Outline Up to Week 16 (IM011132)

Procedure[a]	D1 (Baseline)	W4 D29 (±3d)	W8 D57 (±3d)	W12 D85 (±3d)	W16 D113 (±3d)	Notes: Participants who discontinue treatment at any time prior to Week 52 should proceed to the EOT/ET visit Table 2-3). The Safety Follow-up visit will occur 28 days ±3 days after last treatment visit (Table 2-3).
[redacted] Lipid Panel and Glucose	X		X		X	Predose, after at least [redacted]. See Section 9.4.5.
Spot Urine for Protein:Creatinine Ratio	X	X	X	X	X	See Section 9.4.5.
Urinalysis	X	X	X	X	X	
C3, C4, Anti-dsDNA	X	X	X	X	X	Anti-dsDNA will be collected only for participants with antibodies elevated above normal at Screening.
Efficacy Assessments						
[redacted]						
CLASI	X	X	X	X	X	Refer to Appendix 8.
[redacted]						

Table 2-2: Placebo-Controlled Treatment Period Procedural Outline Up to Week 16 (IM011132)

Procedure[a]	D1 (Baseline)	W4 D29 (±3d)	W8 D57 (±3d)	W12 D85 (±3d)	W16 D113 (±3d)	**Notes:** Participants who discontinue treatment at any time prior to Week 52 should proceed to the EOT/ET visit Table 2-3). The Safety Follow-up visit will occur 28 days ±3 days after last treatment visit (Table 2-3).
[redacted]						

Table 2-2: Placebo-Controlled Treatment Period Procedural Outline Up to Week 16 (IM011132)

Procedure[a]	D1 (Baseline)	W4 D29 (±3d)	W8 D57 (±3d)	W12 D85 (±3d)	W16 D113 (±3d)	Notes: Participants who discontinue treatment at any time prior to Week 52 should proceed to the EOT/ET visit Table 2-3). The Safety Follow-up visit will occur 28 days ±3 days after last treatment visit (Table 2-3).
Clinical Drug Supplies						
Dispense IP	X	X	X	X	X*	*If a participant will continue to the Active Treatment Period, study drug will be dispensed at Week 16/D113.
IP Accountability/ Study Treatment Compliance		X	X	X	X	Unused IP collected.

Abbreviations: AEs = adverse events; anti-dsDNA = anti-double stranded deoxyribonucleic acid (antibody); C3 = complement 3; C4 = complement 4; [redacted] CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; [redacted] ECG(s) = electrocardiogram(s); [redacted] IP = Investigational Product; IRT = Interactive Response Technology; [redacted] SAEs = serious adverse events; [redacted] WOCBP = women of child bearing potential.

[a] Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations. Some of the safety assessments intended to be used as safety monitoring by the treating physician may not be captured as data in the CRF.

Table 2-3: Active Treatment Period Activities and Assessments (IM011132)

Procedure[a]	W20 D141 (±3d)	W24 D169 (±3d)	W28 D197 (±3d)	W40 D281 (±3d)	EOT/ET[b,c] W52 D365 (±3d)	Safety FU[b,c.] W56 D393 (±3d)	Notes
Safety Assessments							
Complete Physical Examination	X				X		General, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdominal, extremities, neurologic, psychiatric, skin, musculoskeletal.
Targeted Physical Examination		X	X	X		X	General, extremities, skin, musculoskeletal, and others as clinically indicated.
Concomitant Medications	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	Includes body temperature, body weight, respiratory rate, and seated blood pressure and heart rate.
12-lead ECG	X				X		ECGs should be recorded after the participant has been supine for at least 5 minutes.
Pregnancy Test (Urine)	X	X	X	X	X	X	For WOCBP only.
Monitor for AEs and SAEs	Continuously						See Section 9.2.
Laboratory Tests							Predose.
Hematology, Serum Chemistry Panel	X	X	X	X	X	X	See Section 9.4.5.
[redacted] Lipid Panel and Glucose	X	X	X	X	X	X	Predose, after at least [redacted]. See Section 9.4.5.
Urinalysis	X	X	X	X	X	X	See Section 9.4.5.
Spot Urine for Protein:Creatinine Ratio	X	X	X	X	X	X	See Section 9.4.5.

Table 2-3: Active Treatment Period Activities and Assessments (IM011132)

Procedure[a]	W20 D141 (±3d)	W24 D169 (±3d)	W28 D197 (±3d)	W40 D281 (±3d)	EOT/ET[b,c] W52 D365 (±3d)	Safety FU[b,c.] W56 D393 (±3d)	Notes
C3, C4, Anti-dsDNA	X	X	X	X	X	X	Anti-dsDNA will be collected only for participants with antibodies elevated above normal at Screening.
Efficacy Assessments							
[redacted]							
CLASI	X	X	X	X	X	X	Refer to Appendix 8.
[redacted]							

Table 2-3: Active Treatment Period Activities and Assessments (IM011132)

Procedure[a]	W20 D141 (±3d)	W24 D169 (±3d)	W28 D197 (±3d)	W40 D281 (±3d)	EOT/ET[b,c] W52 D365 (±3d)	Safety FU[b,c.] W56 D393 (±3d)	Notes
[redacted]							
Clinical Drug Supplies							
Dispense IP	X	X	X*	X*			*IP dispensed at Week 28 and Week 40 will cover a 12 week duration.
IP Accountability/ Study Treatment Compliance	X	X	X	X	X		Unused IP collected.

Abbreviations: AEs = adverse events; anti-dsDNA = anti-double stranded deoxyribonucleic acid (antibody); C3 = complement 3; C4 = complement 4; [redacted] CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; [redacted] ECG(s) = electrocardiograms; EOT = end of treatment; ET = early termination; FU = follow-up (period); IP = Investigational Product; [redacted] SAEs = serious adverse events; [redacted] WOCBP = women of child bearing potential.

a Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations. Some of the safety assessments intended to be used as safety monitoring by the treating physician may not be captured as data in the CRF.

b EOT/ET visit for participants who discontinue treatment any time prior to completing Week 52 of active treatment period. Safety FU visit occurs 28 days ±3 days after the last dose of study treatment.

c [redacted]

3 INTRODUCTION

Deucravacitinib (BMS-986165) is the first, potent, orally bioavailable small molecule, selective tyrosine kinase 2 (TYK2) inhibitor with a novel, unique mechanism of action that is being proposed as a therapy to modulate the dysregulated immune response in autoimmune diseases. TYK2 activates signal transducer and activator of transcription (STAT)-dependent transcription and functional responses downstream of critical immune mediators, such as interleukin (IL)-12, IL-23, and Type I and III interferons (IFNs). Deucravacitinib inhibits TYK2 through a novel allosteric mechanism, binding to the unique pseudokinase Janus kinase (JAK) homology 2 (JH2) domain, rather than binding directly to the active site on the kinase domain, which differentiates deucravacitinib from other inhibitors of the closely related JAK 1-3 of kinases. Deucravacitinib mechanism of action (MOA) results in the blockade of receptor-mediated activation of TYK2 and inhibition of downstream pathways (IL-23, IL-12, and Type I IFNs), and the cytokine networks they modulate (eg, IL-17, IL-22, IFN-γ). [1] Genetic evidence implicates TYK2 in the pathophysiology of multiple immune-mediated diseases. Those most relevant to this protocol are Systemic Lupus Erythematosus (SLE) and Cutaneous Lupus Erythematosus (CLE), specifically Subacute Cutaneous Lupus (SCLE) and Discoid Lupus Erythematosus (DLE).[2]

Lupus Erythematosus (LE) is a multi-organ autoimmune disease of unknown etiology that can have clinical manifestations ranging from mild, localized cutaneous involvement to systemic involvement with severe, life threatening internal organ damage. The prevalence of SLE in the United States (US) is about 102 to 150 cases per 100,000.[3] CLE includes a broad range of dermatologic manifestations, which may or may not be associated with SLE, and the prevalence of CLE in the US is about 70 to 73 cases per 100,000. The skin is involved in 70% to 85% of LE cases and may be the only organ system involved in isolated CLE.[4] Epidemiologically, CLE is consistently more prevalent in females than males, and there appears to be racial differences among CLE patients, with African Americans having a 5.4-fold higher risk for DLE than Caucasians.[5,6] Factors that aggravate CLE include sun exposure, cigarette smoking, hormone fluctuation, viral infection, and certain drug exposures. The diagnosis of CLE is made using a combination of clinical assessments, serologic testing, and histopathologic findings. Gilliam and Sontheimer proposed the classification of LE lesions into specific lesions, which are further categorized into acute cutaneous lupus erythematosus (ACLE), SCLE, and/or chronic cutaneous lupus erythematosus (CCLE).[7,8]

3.1 Study Rationale

Tyrosine kinase 2 activates intracellular STAT -dependent transcription and functional responses downstream of receptors for critical immune mediators, such as interleukin (IL)-12, IL-23, IL-10, and Type I and III IFNs.[9,10,11] [redacted].

These immune and inflammatory signaling pathways are critical in the pathophysiology of various immune-mediated diseases including psoriasis, lupus, spondyloarthritis, inflammatory bowel disease (IBD), dermatomyositis, and Type I interferonopathies.[12,13] Deucravacitinib potently

inhibits IL-23-, IL-12-, IL-10-, and Type I/III IFN-driven responses and has demonstrated proof of mechanism in mouse models of autoimmunity (psoriasis, colitis, and SLE) and in healthy humans.[13,14]

There is increased expression of type I IFN-regulated proteins in the blood and target tissues of patients with CLE and SLE. A polymorphism in IFN regulatory factor 5 (IRF5) is seen in SLE, SCLE and DLE skin biopsy samples.[2] It has been documented that patients with SCLE and DLE have elevated IFN-I scores (expression level of the five genes are expressed as a cumulative IFN score) compared with healthy controls regardless of concomitant SLE. The IFN-I score of participants with SCLE or DLE with and without concomitant SLE have been shown to correlate with Cutaneous Lupus Area and Severity Index (CLASI) activity score.[15] These finding support a shared pathogenesis of DLE and/or SCLE (DLE/SCLE) with SLE. Based on the demonstration of elevated type I IFN-regulated gene expression in DLE/SCLE, TYK2 inhibitors may be useful for the treatment of DLE/SCLE with and without SLE.

[redacted]

This Phase 2 study will assess if deucravacitinib is biologically active and potentially effective in the treatment of patients with moderate to severe DLE/SCLE (with or without SLE), that is inadequately controlled with standard of care therapy.

3.2 Background

TYK2, a member of the JAK family, catalyzes the phosphorylation of STAT-proteins downstream of the receptors for the p40-containing cytokines IL-12 and IL-23 as well as the Type I IFN receptor, resulting in the activation of STAT-dependent transcription and functional responses specific for those receptors. Deucravacitinib is a first-in-class orally administered small molecule inhibitor of TYK2 that has been shown to be superior to blockade of the Type I IFN receptor in an IFN-dependent mouse model of SLE. TYK2-dependent cytokines (eg, IL-12, IL-23 and Type I IFNs) are distinct from those dependent on closely related JAK family members JAK1, JAK3 (eg, IL-2, IL-15, IL-7, IL-6) or JAK2 (eg, erythropoietin, thrombopoietin, and granulocyte-monocyte colony-stimulating factor). Consequently, a TYK2 inhibitor is expected to have a highly differentiated profile from inhibitors of closely related JAK 1-3 kinases.

Deucravacitinib has a unique mode of binding that provides the high selectivity over the other members of the JAK family of non-receptor tyrosine kinases. Deucravacitinib binds to the regulatory pseudokinase domain of TYK2, stabilizing an inhibitory interaction between the pseudokinase and the catalytic domains of the enzyme, the result of which is blockade of receptor-mediated activation of TYK2 and inhibition of downstream functions in cells and in vivo. The

binding mode of deucravacitinib takes advantage of unique structural features of the TYK2 pseudokinase domain compared with other kinases and pseudokinases to provide high biochemical and cellular functional selectivity. This approach differentiates deucravacitinib from nonselective inhibitors of the JAK family of kinases that target the highly conserved active site of the kinase domain. Deucravacitinib is an orally administered selective TYK2 inhibitor. In vitro and in vivo data for deucravacitinib supports the development of this compound in humans.

[redacted]

3.2.1 Disease Background

The clinical spectrum of CLE is broad, ranging from isolated discoid plaques to widespread skin lesions. Histological, skin lesions present as interface dermatitis (inflammation of the skin in the dermal-epidermal junction mediated by anti-epidermal responses), which is orchestrated by both innate and adaptive immune pathways that are strongly activated in the formation of skin lesions.

Cutaneous LE is comprised of 3 different subtypes based on clinical presentation and histopathology: ACLE, SCLE and CCLE. CCLE is further subdivided and includes DLE, LE profundus (LEP), chilblain LE (CHLE), and LE tumidus (LET).[20]

ACLE may present in a localized or generalized form and is frequently (~90%) associated with active SLE. Malar rashes have been reported to be present in up to 52% of SLE patients at the time of diagnosis, with clinical activity of the rash paralleling that of the systemic disease.[21] The localized form is the malar or butterfly rash and the generalized, photosensitive maculopapular rash occurs above and below the neck.

SCLE lesions typically occur on visible sun exposed areas of the body, including the upper thorax, upper back, and the extensor surfaces of arms and forearms, and the lesions are highly light sensitive. There are two morphologic variants of SCLE, annular and papulosquamous. The annular type is characterized by scaly annular erythematous plaques, which tend to coalesce and produce a polycyclic array. The papulosquamous variant can resemble eczema or psoriasis, as well as pityriasis in some instances.[21] An estimated 50% of SCLE patients meet criteria for SLE.

DLE is the most common form of CCLE, which can be either localized or generalized. The localized form, characterized by the limited cutaneous involvement of the head and scalp, usually accounts for 70% of DLE, and the generalized form (characterized by the extension to more than

the head-body area)[22] accounts for 30% of DLE. DLE lesions appear as a well-demarcated, scaly, erythematous macule or papule, which gradually develops into an indurated discoid plaque with an adherent scale. Treatment resistant discoid lesions cause scarring of the affected skin areas and permanent scarring alopecia, which can lead to significant disfigurement. Over time, these lesions typically become atrophic, with hyperpigmentation peripherally and depigmentation centrally. Approximately 50% of DLE patients are classified as having DLE without SLE; of these, approximately 25% have moderate to severe skin disease.[22]

As UV light has been implicated in the initiation and exacerbation of lesions, photo-protective measures including the use of broad-spectrum sunscreens, protective clothing, and wigs are highly recommended to prevent exacerbation of lesions.

Along with lifestyle changes, treatment with topical corticosteroids are frequently used; however, long term use is discouraged due to recognized adverse effects such as atrophy, telengiactasiae, striae, and purpura.

Topical calcineurin inhibitors (such as tacrolimus ointment and pimecrolimus cream) are not approved for the treatment of CLE, but are an established therapeutic alternative to corticosteroids in CLE. Unlike corticosteroids, these inhibitors do not induce skin atrophy as an adverse effect, but they are also less effective.

Antimalarials, such as hydroxychloroquine, chloroquine, and quinacrine represent first-line systemic CLE treatment. Hydroxychloroquine is the only systemic treatment approved for DLE. Antimalarials have varied levels of effectiveness (up to 45% of patients treated with antimalarials require an additional treatment) and 25% of patients remain refractory to available therapies.[22,23,24] Other unapproved systemic treatments utilized include prednisone, tacrolimus, mycophenolate mofetil, methotrexate, azathioprine, and other cytokine-blocking agents.

Effective control of DLE/SCLE is difficult due to the disease heterogeneity among individuals and variability in skin manifestations. There have been few double-blind placebo controlled studies in the DLE/SCLE patient population where the lack of safe, effective, well-tolerated medications clearly remains an unmet need. The immunosuppressive and immunomodulatory agents have varied levels of effectiveness and are associated with serious adverse reactions and dose-limiting toxicities. Given the limitations associated with currently used unapproved therapies for active DLE/SCLE, there remains an unmet medical need for effective and safe agents.

[redacted]

[redacted]

[redacted]

[redacted]

4 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the primary, secondary, [redacted] analyses of this study are shown in Table 4-1.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of two doses of deucravacitinib (3 mg BID and 6 mg BID) compared with placebo on CLASI-A score at Week 16.	Percentage change from baseline in CLASI activity (CLASI-A) score at Week 16.
Secondary	
To evaluate additional clinical measures of cutaneous disease manifestations with two doses of deucravacitinib (3 mg BID and 6 mg BID) compared with placebo at Week 16.	• Percentage of participants with an improvement of ≥ 50% from baseline in the CLASI-A score (CLASI-50). • Percentage of participants who have disease improvement as defined by a reduction in CLASI-A of ≥ 4 points from baseline. • Mean change from baseline in CLASI-A score. • Percentage of participants who have a Complete Response (CR) on CLASI-A defined as a score of "0".
Safety	
To assess the safety and tolerability of two doses of deucravacitinib (3 mg BID and 6 mg BID) compared with placebo.	• Number and proportion of participants experiencing SAEs, AEs (with severity and relationship of AEs), and abnormalities in laboratory testing, vital signs, and 12-lead ECGs.
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: AEs = adverse events; BID = twice a day; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-50 = 50% improvement from baseline in CLASI-A score; CLASI-A = CLASI activity; CR = complete response; ECGs = electrocardiograms; SAEs = serious adverse events;

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 2 randomized, placebo-controlled, double-blind, multicenter study to evaluate the safety and efficacy of deucravacitinib 3 mg BID and 6 mg BID given orally in participants with moderate to severe active DLE/SCLE, which may or may not be associated with SLE.

Participants must have a biopsy-confirmed clinical diagnosis of DLE/SCLE, and inadequate response, defined as therapeutic failure or intolerance to an oral corticosteroid, and/or antimalarial and/or immunosuppressant.

Participants must be on stable background DLE/SCLE therapy, which includes one oral corticosteroid, and/or one antimalarial and/or one immunosuppressant, taken alone or in combination. [redacted]

The study consists of 4 Periods:

1) Screening Period: up to 4 weeks (28 days; see Section 2).
2) Placebo-controlled Treatment Period: 16 weeks (Day 1 to Week 16; see Section 5.1.2).
3) Active Treatment Period: 36 weeks (Week 16 to Week 52; see Section 2).
4) Follow-up Period: 4 weeks from last dose of study treatment (28 days; see Section 5.1.4).

[redacted]

All randomized participants will be encouraged to participate in an optional substudy, evaluating biomarkers based on skin biopsies obtained during the study.

Eligible participants will be randomized 1:1:1 to receive one of the following treatments for the first 16 weeks:

- Deucravacitinib 3 mg BID
- Deucravacitinib 6 mg BID
- Deucravacitinib-matching Placebo BID

[redacted]

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events throughout the study. [redacted].

5.1.1 Screening Period

After signing the Informed Consent Form (ICF), participants are considered "enrolled" in the study, and they enter the screening period. During the 28-day screening period, participants will complete the study procedures and screening assessments as outlined in the Schedule of Activities (Table 2-1) to determine if they continue to meet eligibility criteria. If eligibility parameters cannot be obtained within the 28-day period, the screening period may be extended by up to 7 calendar days, if approved by the Clinical Trial Physician/Medical Monitor.

Eligibility will be based on specified inclusion and exclusion criteria (Section 6). [redacted]

[redacted]

5.1.2 Placebo-controlled Treatment Period (Day 1 to Week 16)

CLASI-A assessment must be performed for eligibility at Screening and Baseline (Day 1) prior to randomization for confirmation of minimally required disease activity (CLASI-A ≥ 8). Following confirmation of enrolment eligibility by the PI [redacted] participants will be randomized at a 1:1:1 ratio to receive:

- Deucravacitinib 3 mg BID
- Deucravacitinib 6 mg BID
- Deucravacitinib-matching Placebo BID.

[redacted]

Participants will be evaluated at study visits every 4 weeks through Week 16 (Table 2-2).

5.1.3 Active Treatment Period (Week 16 to Week 52)

Participants who complete the placebo-controlled treatment period will continue into an active treatment period for an additional 36 weeks of treatment.

At Week 16, participants receiving placebo during the placebo-controlled treatment period will be re-randomized 1:1 in a blinded-fashion to receive active treatment with either deucravacitinib 3 mg BID or 6 mg BID until Week 52. Participants receiving deucravacitinib 3 mg BID or 6 mg BID through Week 16 will continue on the originally randomized treatment in a blinded manner through Week 52 (Table 2-3).

5.1.4 Follow-up Period

All participants will be followed for 28 days (± 3 days) after the last dose of study treatment for safety monitoring (Table 2-3).

5.1.5 Data Monitoring Committee and Other Committees

A Data Monitoring Committee (DMC) with multi-disciplinary representation will be established to evaluate safety data (eg, AEs, laboratory parameters, etc.) and a favorable benefit/risk for the study is maintained. The DMC responsibilities, authorities, and procedures will be documented and followed according to the DMC charter.

[redacted]

5.2 Number of Participants

Approximately 75 participants will be randomized in a 1:1:1 ratio to receive deucravacitinib 3 mg BID, deucravacitinib 6 mg BID, or deucravacitinib-matching Placebo BID. Sample size considerations are described [redacted].

5.3 End of Study Definition

The start of the trial is defined as the first visit for first participant screened. End of trial is defined as the last visit or scheduled procedure shown in the Schedule of Activities for the last participant. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

5.4 Scientific Rationale for Study Design

The primary purpose of the study is to estimate the treatment effect of deucravacitinib in participants with DLE/SCLE. CLASI will be the key efficacy assessment to provide clinical evidence of response to deucravacitinib in the CLE population. The primary endpoint will be the percent change from baseline in CLASI-A score at Week 16.

CLASI is a validated instrument that is used in lupus clinical trials to quantify disease activity and damage in CLE. CLASI was assessed for content validity, inter-rater validity and intra-rater validity, and performed well in all of these aspects.[29] CLASI can be used to categorize patients into severity groups and to identify clinically significant improvements in disease activity.

CLASI consists of two separate scores to allow for descriptions of both disease activity (CLASI-A) and damage (CLASI-D). This differentiation permits easily quantifiable assessments of activity in short-term studies, as well as assessments of disease-induced damage in longer-term studies. CLASI-A has been used in large Phase 2 and 3 SLE trials to document efficacy in cutaneous disease manifestations in participants with lupus.[19,30,31] Randomized, double-blind, placebo-controlled studies in DLE/SCLE and SLE have included percent change from baseline in CLASI-A as a primary efficacy measures.[39]

[redacted]

A placebo control is included up to Week 16 to allow the effects of treatment, both desired and adverse, to be appropriately attributed to treatments received, taking into account that all participants must be on a stable dose of background therapy for DLE/SCLE consisting of antimalarial and/or an immunosuppressant and /or oral corticosteroids [redacted].

The 16 weeks placebo-controlled treatment duration of this study is considered optimal to assess potential clinical benefits of deucravacitinib in DLE/SCLE while minimizing the duration of treatment with placebo. This duration is consistent with other studies that evaluated the effect of investigational treatment in CLE such as the Phase 2 LILAC Study of BIIB059 in Participants with Active Cutaneous Lupus Erythematosus.[39]

The overall treatment duration of 52 weeks is considered necessary to assess the durability of therapy benefits, taking into account the chronic nature of CLE and its waxing and waning course, and to obtain 1-year safety data with deucravacitinib.

To study a broader and "real-world" CLE patient population, the study will enroll participants who have active disease despite exposure to one or more of a large spectrum of CLE therapies, such as oral steroids, antimalarial and/or immunosuppressant. [redacted]

[redacted]

The eligibility and randomization criteria and procedures [redacted] are designed to ensure that participants have the correct diagnosis and expected level of cutaneous lupus disease activity that could benefit from additional treatment with investigational drug. [redacted]

[redacted]

[redacted]

6 STUDY POPULATION

Eligibility criteria for this study have been carefully considered to ensure the safety of the study participants.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. [redacted] However, all laboratory testing must be performed by the study-specific central laboratory.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

For entry into the study, the following criteria MUST be met.

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Participants must be willing to participate in the study and sign the ICF.

b) Participants must be willing and able to complete all study-specific procedures and visits.

2) Type of Participant and Target Disease Characteristics

a) Participants must have a diagnosis of DLE/SCLE for at least 3 months prior to Screening Visit.

b) Participants must meet <u>both</u> clinical and histopathological diagnostic CLE criteria:

i) <u>Clinical diagnosis of active DLE/SCLE</u> [redacted] <u>Participants with or without concurrent SLE diagnosis are eligible.</u> [redacted]

- AND -

ii) **Not applicable per Protocol Amendment 02:** <u>Biopsy-proven histology consistent with DLE/SCLE (based on Gilliam classification</u> [redacted] <u>), confirming the clinical diagnosis.</u> [redacted]

[redacted]

c) Participants are required to have active moderate to severe cutaneous disease [redacted]

3) Background Therapies/Concomitant Medications for DLE/SCLE

a) Participants must currently be receiving treatment with a stable regimen of at least one of the following medications: an oral corticosteroid, and/or an antimalarial, and/or an immunosuppressant per the protocol (see Section 7.7.2 for Background Medications).

[redacted]

4) Age and Reproductive Status

a) Men and women aged 18 (or age of majority) to 75 years at screening.

- Investigators shall counsel women of childbearing potential (WOCBP) participants, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraception methods.

Female Participants:

b) Women who are not of childbearing potential (as defined in Appendix 4) are exempt from contraceptive requirements.

c) Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study treatment. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In

such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

d) Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Assessments.

e) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

f) Women must not be pregnant, lactating, breastfeeding or be planning pregnancy during the study period

g) **Not applicable per Protocol Amendment 02:** Women of childbearing potential (WOCBP) must agree to use highly effective (with a failure rate of <1% per year) method(s) of contraception, preferably with low user dependency, as described in Appendix 4, during the study period until the end of the study.

Note:

(1) **Not applicable per Protocol Amendment 02:** Local laws and regulations may require use of alternative and/or additional contraception methods; additionally, alternative and/or additional contraceptive may be required eg, based on background DMARDS the participant may be taking, such as methotrexate, mycophenolate mofetil, etc.

(2) **Not applicable per Protocol Amendment 02:** WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this section.

h) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

Male Participants:

i) Male participants should maintain their usual practice with regard to contraception (if any); however, no specific contraceptive measures are required.

Note:

Local laws and regulations may require use of alternative and/or additional contraception methods; additionally, alternative and/or additional contraceptive may be required eg, based on background DMARDS the participant may be taking, such as methotrexate, mycophenolate mofetil, etc.

j) Females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

k) WOCBP must agree to use a contraceptive method that is highly effective (with a failure rate of < 1% per year), with low user dependency, as described in Appendix 4 during the intervention period and for at least 33 days and agree not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period.

Note:

(1) Local laws and regulations may require use of alternative and/or additional contraception methods; additionally, alternative and/or additional contraceptive may be required (eg, based on background DMARDS the participant may be taking, such as methotrexate, mycophenolate mofetil, etc).

(2) WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements, but must still undergo pregnancy testing as described in this section.

6.2 Exclusion Criteria

The presence of any of the following will exclude a participant from enrollment.

1) Target Disease Exclusion

a) Participants with any of the following specific CLE subtypes in isolation: ACLE, lupus tumidus, lupus (profundus) panniculitis, chilblains.

b) Participants with forms of drug-induced CLE and/or drug-induced SLE

c) Participants with active kidney disease, defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.7 m2 and/or proteinuria > 0.5 g/24 h (spot urine protein/creatinine ratio [UPCR]: > 56.5 mg/mmol).

d) Participants with antiphospholipid antibody syndrome, serious thrombotic event (eg, pulmonary embolism, saddle embolism, stroke, deep vein thrombosis) or unexplained pregnancy loss within 1 year before the Screening Visit. Participants with a history of 3 or more unexplained consecutive pregnancy losses.

e) Participants with active severe or unstable neuropsychiatric SLE including, but not limited to, aseptic meningitis; cerebral vasculitis; myelopathy; demyelination syndromes (ascending, transverse, acute inflammatory demyelinating polyradiculopathy); acute confusional state; impaired level of consciousness; psychosis; acute stroke or stroke syndrome; cranial neuropathy; status epilepticus; cerebellar ataxia; and mononeuritis multiplex.

f) **Not applicable per Protocol Amendment 02:** Participants with other autoimmune diseases (eg, multiple sclerosis, psoriasis, irritable bowel disease [IBD], etc) with the exception of those with Type 1 autoimmune diabetes mellitus, thyroid autoimmune disease, celiac disease, or secondary Sjögren's syndrome.

g) Participants with other non-SLE driven inflammatory joint or skin disease or overlap syndromes as primary disease (eg, dermatomyositis, fibromyalgia, polymyositis, scleroderma, mixed connective tissue disease, rosacea, sarcoidosis, Sjögren's syndrome) that in the opinion of the investigator will significantly impact the assessment of CLE/SLE disease manifestations and activity.

h) Participants with other autoimmune diseases (eg, multiple sclerosis, psoriasis, etc) with the exception of those with Type 1 autoimmune diabetes mellitus, thyroid autoimmune disease, celiac disease, or secondary Sjögren's syndrome.

2) Other Medical History and Conditions

a) Women who are pregnant or breastfeeding.

b) Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric) or local active infection/infectious illness that, as determined by investigator, will substantially increase the risk to the participant if he or she participates in the study.

c) Any major surgery within the last 30 days before the first dose of study treatment, or any surgery planned during the course of the study.

d) Participants with cancer or history of cancer or lymphoproliferative disease within the previous 5 years except for:

   i) treated (eg, cured) basal cell or squamous cell in situ skin carcinomas

   ii) treated (eg, cured) cervical intraepithelial neoplasia or carcinoma in situ of the cervix with no evidence of recurrence within 5 years of the Screening Visit.

e) Class III or IV congestive heart failure as defined by the New York Heart Association (NYHA) or any recent onset of heart failure resulting in NYHA Class III/IV symptoms.

f) Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before Screening Visit.

g) Current or recent (within 3 months before Screening Visit) gastrointestinal disease, including gastrointestinal surgery, that could impact the absorption of study treatment.

h) Participant with non-SLE concomitant illness, as determined by investigator, who is likely to require additional systemic glucocorticosteroid therapy during the study (eg, asthma).

i) Significant blood loss (> 500 mL) or blood transfusion within 4 weeks before Screening Visit.

j) Inability to take medication orally.

k) Inability to undergo venipuncture and/or tolerate venous access.

l) Any other sound medical, psychiatric, and/or social reason as determined by investigator.

m) Recent (within 6 months before randomization) drug or alcohol abuse as defined by the Diagnostic Criteria for Drug and Alcohol Abuse in the Diagnostic and Statistical Manual of Mental Disorders IV (Appendix 10).

n) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

o) History of congenital or acquired immunodeficiency.

3) Prior and Concomitant Therapy

[redacted]

b) Required discontinuation periods to allow previous exposure to other immunomodulatory or biologic drugs are provided [redacted]. If a drug is not specifically listed, consult the medical monitor for guidance. Participant has enrolled in a clinical trial and has

received an investigational product within 5 pharmacokinetic half-lives or one month, whichever is longer, prior to the Screening Visit.

c) Inability to comply with restrictions and prohibited treatments (Section 7.7.1); inability to comply with medication discontinuation requirements listed [redacted].

d) **Not applicable per Protocol Amendment 02:** Participant has used high or mild potency topical corticosteroids (WHO Class 1-5) [refer to Appendix 12], intralesional CS topical immunosuppressants (calcineurin inhibitors), or topical retinoids within 2 weeks prior to Screening Visit.

e) Participant has used intramuscular, intralesional/intradermal, intra-articular, intrabursal, and/or intravenous (IV) CS within 6 weeks prior to Screening Visit.

f) Participants using modified-release oral CS formulations.

g) Participants using drugs inducing cutaneous lupus erythematosus [redacted].

h) **Not applicable per Protocol Amendment 02:** Participants that have received a live vaccine within 90 days or an inactivated vaccine within 30 days before Screening Visit.

i) Participants that have received live vaccine within 60 days prior to Screening Visit.

j) Participant has used high or moderate potency topical corticosteroids (WHO Class 1-5; refer to Appendix 12), topical immunosuppressants (calcineurin inhibitors), or topical retinoids within 2 weeks prior to Screening Visit.

4) Physical and Laboratory Test Findings

a) Clinically significant abnormalities on chest X-ray or ECG at Screening Visit.

b) Clinically significant abnormalities in laboratory tests at Screening Visit including the following:

i) Serum alanine aminotransferase (ALT) > 2× ULN or serum aspartate aminotransferase (AST) > 2× ULN.

ii) Serum total bilirubin > 1.5× ULN, unless due to documented Gilbert's syndrome.

iii) Hemoglobin < 9 g/dL (90 g/L).

iv) Estimated glomerular filtration rate < 60 mL/min.

v) Absolute white blood cell count < 2.0 × 103/µL (2.0 × 109/L).

[redacted]

vii) Any other significant laboratory or procedure abnormalities, as determined by investigator that might pose unacceptable risk to the participant during the study.

[redacted]

5) Findings Related to Possible Infection

a) Participants with any of the following tuberculosis (TB) criteria:

i) History of active TB prior to Screening Visit, regardless of completion of adequate treatment.

ii) Signs or symptoms of active TB (eg, fever, cough, night sweats, and weight loss) during Screening as judged by the investigator.

iii) Any imaging of the chest (eg, chest x-ray, chest computed tomography scan) obtained during the Screening period or anytime within 6 months prior to Screening with documentation, showing evidence of current active or history of active pulmonary TB.

iv) **Not applicable per Protocol Amendment 02:** Latent TB infection (LTBI) defined as positive IGRA, by QuantiFERON-TB Gold testing at Screening, in the absence of clinical manifestations.

Not applicable per Protocol Amendment 02: Note: Participants are eligible if:

There are no current signs or symptoms of active TB.

-AND-

(1) **Not applicable per Protocol Amendment 02:** Participant has received adequate documented treatment for LTBI within 5 years of Screening.

-OR-

(2) **Not applicable per Protocol Amendment 02:** Participant has initiated prophylactic treatment for LTBI per local guidelines.

(a) **Not applicable per Protocol Amendment 02:** Participants not currently on prophylactic treatment per local guidelines, including participants that have documented completed treatment within 5 years of Screening: indeterminate results of initial IGRA with no signs or symptoms of active TB must be retested for confirmation.

(i) **Not applicable per Protocol Amendment 02:** If the second test is again indeterminate, the participant will be excluded from the study. If the retest is positive, the participant will be excluded. If the retest is negative, the participant may be eligible provided no other exclusion criteria for TB are met.

(b) **Not applicable per Protocol Amendment 02:** Participants that are on prophylactic treatment for LTBI per local guidelines, and there are no current signs or symptoms of active TB, retesting of an initial positive or indeterminate result is not required and participants may be eligible provided no other exclusion criteria for TB are met, and participants continue to complete treatment for LTBI per local guidelines

v) Latent TB infection (LTBI) defined as positive IGRA, by QuantiFERON-TB Gold testing at Screening, in the absence of clinical manifestations, or known positive Quantiferon-TB Gold testing by history

Note: Participants may be eligible if:

(1) There are no current signs or symptoms of active TB

-AND-

(2) Participant has received adequate documented treatment for LTBI within 5 years of screening

OR

(3) Participant has initiated prophylactic treatment for LTBI per local guidelines and is rescreened after 1 month of treatment. To continue in the study, the participant must agree to complete a locally recommended course of treatment for LTBI. The

BMS Clinical Trial Physician/Medical Monitor should be consulted on all LTBI cases.

Note: An IGRA test that is indeterminate with no signs or symptoms of active TB must be retested for confirmation. If the second result is indeterminate, the participant will be excluded from the study. If the retest is negative, the participant may be eligible provided no other exclusion criteria for TB are met. If the retest is positive, the participant may be treated as having LTBI with initiation of prophylactic treatment (as above).

(4) **Not applicable per Protocol Amendment 02:** Participants with evidence of hepatitis B or hepatitis C infection determined by serologic testing (described in Section 9.4.5) at Screening Visit will be excluded. Participants with isolated positive hepatitis B surface antibody are not excluded (refer to Appendix 14).

b) **Not applicable per Protocol Amendment 02:** Positive for human immunodeficiency virus (HIV) by antibody testing (HIV-1 and -2 Ab) at Screening Visit. **Note**: Participants who are newly found to be HIV-positive should be directed to appropriate follow-up care.

c) **Not applicable per Protocol Amendment 02:** Currently on any therapy for chronic infection (eg, pneumocystis, cytomegalovirus, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria).

d) **Not applicable per Protocol Amendment 02:** Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (intramuscular or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic agents) within 30 days of randomization, or completion of oral antimicrobial agents within 2 weeks of randomization.

e) **Not applicable per Protocol Amendment 02:** Previous history of herpes zoster, herpes simplex, or influenza infection within 12 weeks before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia).

f) **Not applicable per Protocol Amendment 02:** Severe infection within 4 weeks prior to screening.

i) **Not applicable per Protocol Amendment 02:** Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment in consultation with the clinical trial physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.

g) Participants with evidence of hepatitis B or hepatitis C infection determined by serologic testing (described in Section 9.4.5) at Screening Visit will be excluded. Participants with isolated positive hepatitis B surface antibody are not excluded (refer to Appendix 14).

h) Positive for human immunodeficiency virus (HIV) by antibody testing (HIV-1 and -2 Ab) at Screening Visit. **Note**: Participants who are newly found to be HIV positive should be directed to appropriate follow-up care.

i) Currently on any therapy for chronic infection (eg, pneumocystis, cytomegalovirus, herpes simplex, herpes zoster, invasive bacterial or fungal infections, or atypical mycobacteria).

j) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (intramuscular or IV) antimicrobial agents (eg, antibiotics,

antiviral, antifungal, or antiparasitic agents) within 30 days of randomization, or completion of oral antimicrobial agents within 2 weeks of randomization.

k) Previous history of herpes zoster, herpes simplex, or influenza infection within 12 weeks before randomization or a history of disseminated/complicated herpes zoster infection (multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia).

l) Known active infection, or any major episode of infection requiring hospitalization or treatment with parenteral (intramuscular or IV) antimicrobial agents (eg, antibiotics, antiviral, antifungal, or antiparasitic within 4 weeks prior to screening.

Note: In the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and based on investigator assessment, that could place the participant at risk when receiving IP. SARS-CoV 2 testing may be conducted prior to randomization if required by and in accordance with national, local, or institutional guidelines.

6) Other Exclusion Criteria

a) Inability to abstain from the use of tanning salons or prolonged intentional sun exposure from Screening to Week 52. Usual and reasonable sunlight exposure during daily activities is acceptable.

b) Prisoners or participants who are involuntarily incarcerated. (Note: under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

c) Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

6.3 Lifestyle Restrictions

6.3.1 Exposure to Sunlight

Every precaution needs to be taken to limit excessive sun exposure though out the duration of the study. General skin care measures are recommended that are standard for patients with CLE and SLE, as follows: use of broad spectrum sunscreen (minimum sun protection factor 30 and with inorganic ingredients (zinc oxide, titanium dioxide), avoiding sun exposure, wearing sun-protective clothing, avoidance of alcohol-based emollients, avoidance of over-the-counter anti-acne medications and alcohol-based skin care products, and avoidance of perfumed soaps and detergents, and similar measures. Participants should avoid tanning (including tanning salons), sunbathing, and outdoor activities that require prolonged or extensive sun exposure.

6.3.2 Meals and Dietary Restrictions

Not applicable.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure

participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening Period - Rescreening

For laboratory parameters and/or assessments that initially do not meet eligibility requirements, a single retest within the 28 day screening period is permitted in an effort to find all possible well--qualified participants. Consultation with the Clinical Trial Physician/Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

The study permits the rescreening (after the end of the initial 4-week Screening Period) of a participant who discontinues the study as a pretreatment failure (ie, the participant fails screening or randomization and has not been treated). The participant must be re-consented and will be assigned a new identification number, and a full Screening Visit must be performed again.

A participant can be rescreened twice (ie, if the participant fails 2 rescreening attempts, no additional rescreening is allowed). Depending on the timing of rescreening, repetition of some assessments may not be required. Duration of existing treatments and required discontinuation periods shall be considered relative to the given Screening Visit and/or randomization.

Laboratory parameters and/or assessments that are included in Table 2-1, *Screening Procedural Outline*, may be repeated in an effort to find all possible well-qualified participants. Consultation with the Clinical Trial Physician/Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational- [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following: deucravacitinib, background medications, and placebo. Information about the pharmacology and previous experience with deucravacitinib is provided in Section 3.2.

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Study treatment descriptions including dosage form, potency, IP/non-IMP, and storage conditions are presented in Table 7-1.

Table 7-1: Study Treatments for IM011132

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Deucravacitinib Oral Tablet	3 mg or 6 mg	IP	Blinded	[redacted]	Store 15 to 25°C; Protect from light; Store in original container.
Deucravacitinib-matching Placebo Oral Tablet	Not applicable	IP	Blinded		Store 15 to 25°C; Protect from light; Store in original container.

Note: Background therapies will be obtained as per participant's local standard of care.

7.1 Treatments Administered

The selection and timing of dose for each participant are presented in Table 7.1-1.

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s) / Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
Deucravacitinib (3 mg tablet)	3 mg BID	1 active and 1 placebo tablet in the morning and 1 active and 1 placebo tablet in the evening.	Oral
Deucravacitinib (6 mg tablet)	6 mg BID	1 active and 1 placebo tablet in the morning and 1 active and 1 placebo tablet in the evening.	Oral
Deucravacitinib-matching Placebo (oral tablet)	BID	2 placebo tablets in the morning and 2 placebo tablets in the evening.	Oral

Abbreviation: BID = twice a day.

Blinded study treatment will be supplied [redacted] at each study visit. The tablets will be arranged into sets to be taken in the morning and in the evening, approximately 12 hours apart. The participant should be instructed to take 2 tablets in the morning and 2 tablets in the evening. Study treatment may be taken with or without food. If a scheduled dose of study drug is missed and the participant remembers within 4 hours of the scheduled dose time, the dose should be taken as soon as possible. If the missed dose is remembered later than 4 hours after the scheduled dose time, the dose should be skipped and the next dose taken at the appropriate time. Any missed doses should be returned at the next study visit.

[redacted]

7.2 Method of Treatment Assignment

At the time of the Screening Visit, immediately after informed consent is obtained and before any study-related procedures are performed, the investigative site will access the enrollment option utilizing Interactive Response Technology (IRT) for assignment of a participant number (including participants not subsequently randomized or treated). This number will be unique across all sites. Enrolled participants, including those not dosed, will be assigned sequential participant numbers. The participant number may not be used for any other participant. If a potential participant is rescreened, they will be given a new identification number.

Eligible participants will be centrally randomized using IRT to receive oral treatment with deucravacitinib 3 mg BID, 6 mg BID, or deucravacitinib-matching Placebo BID in accordance with stratification criteria (see Section 5.1). At the Week 16 study visit, the participants initially

assigned to receive Placebo and who agree to continue study participation will be re-randomized by the IRT to receive oral treatment with either deucravacitinib 3 mg BID or 6 mg BID until Week 52. Re-randomized participants will receive a new randomization number prior to dosing.

Before the study is initiated, each user (at investigative sites) will receive log-in information and directions on how to access the IRT. Treatment codes will be assigned prior to dosing.

7.3 Blinding

This is a randomized, double-blind, placebo-controlled study. During the placebo-controlled period and the active treatment period, the IP will remain blinded, to prevent study personnel and participants from knowing the IP assignment. For the [redacted] database lock, BMS personnel who have access to the unblinded data are not to discuss or make materials available that would unblind individual participant data to the personnel involved in the study conduct [redacted]. A separate blinding charter will detail the unblinding process. Access to treatment codes will be restricted from all participants and site personnel prior to final database lock, with exceptions as specified below.

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual participant in which knowledge of the investigational product is critical to the participant's management, the blind for that participant may be broken by the investigator. The participant's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual participant's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the participant's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the participant is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Clinical Trial Physician/Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The actual TASK of unblinding can be delegated by the investigator to a designee assigned the task on the Delegation of Authority. The Principal Investigator or appointed designee should access IRT for emergency unblinding AFTER the decision to unblind the participant has been documented.

For this study, the method of unblinding for emergency purposes is IRT. The method of unblinding for emergency purposes is described in the IRT manual. In cases of accidental unblinding, contact the Clinical Trial Physician/Medical Monitor and ensure every attempt is made to preserve the blind. Any request to unblind a participant for non-emergency purposes should be discussed with the Clinical Trial Physician/Medical Monitor.

Designated staff of Bristol-Myers Squibb Research & Development may be unblinded (obtain the randomization codes) prior to database lock [redacted].

7.4 Dosage Modification

There is no provision for dose modification of study treatment.

If a participant interrupts treatment due to an AE, study treatment may be restarted following consultation with the Clinical Trial Physician/Medical Monitor.

In the event a participant requires a surgical or invasive procedure during the course of the study, the Clinical Trial Physician/Medical Monitor must be contacted to discuss whether or not the participant is eligible to continue study participation.

7.5 Preparation/Handling/Storage/Accountability

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2, *Study Governance Considerations*.

7.5.1 Retained Samples for Bioavailability / Bioequivalence / Biocomparability

Not applicable.

7.6 Treatment Compliance

Study treatment compliance will be monitored as indicated in the Schedule of Activities (Section 2) using standard drug accountability procedures (comparing the number of tablets returned with number dispensed, considering the expected regimen and any reported missed doses). Drug accountability will be reviewed by the investigative site staff at each visit to confirm

treatment compliance. Site staff will discuss any discrepancies with the participant and remind the participant of the importance of compliance with the assigned regimen.

7.7 Concomitant Therapy

All previous and current systemic and topical medications taken for DLE/SCLE and SLE must be reported.

Current medications and medications taken within 4 weeks prior to study drug administration for conditions other than DLE/SCLE and SLE must be recorded on the case report form (CRF).

Over the course of the study, changes in concomitant medications or additional medications may be required to manage aspects of the disease state of the participants or side effects from treatments.

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications during the study are described below.

7.7.1.1 Prohibited Treatments

- Use of [redacted].
- [redacted]
- Phototherapy; use of tanning booths or therapeutic sunbathing.
- Topical formulations of high or moderate potency topical corticosteroids (WHO Class 1-5; (refer to Appendix 12), topical immunosuppressants (calcineurin inhibitors), or topical retinoids.
- Non-oral routes of CS administration: intramuscular, intralesional/intradermal, intra-articular, intrabursal, and/or intravenous (IV) CS.
- Modified-release oral CS formulations.
- Investigational COVID-19 vaccines that are not authorized or approved by relevant Health Authorities.
- Live vaccines during the study and within 60 days after the last dose of study treatment. Heat-killed or otherwise inactivated or protein vaccines (ie, influenza and pneumococcal) may be received at any time on study. Other inactivated vaccines may be used according to local guidelines.

7.7.1.2 Restricted Treatments

- NSAIDs or narcotic analgesics on an as needed basis are permitted, except for 12 hours prior to any study visit with disease activity assessments.

[redacted]

[redacted]

- Use of medications/therapy that could induce or exacerbate cutaneous lupus erythematosus [redacted], unless considered necessary for subject's welfare or treatment of adverse events.

In addition, the following applies:

- Live vaccines are prohibited 60 days prior to the Screening Visit during the study treatment period and within the 60 days after the last dose of study treatment. Heat-killed or otherwise inactivated or protein vaccines (ie, influenza and pneumococcal) may be received at any time on study. Other inactivated vaccines may be used according to local guidelines.

7.7.2 Permitted Background DLE/SCLE/SLE Therapies

[redacted]

Usual monitoring for background medications should continue as per local standard of care guidelines. Dosing information, including any modifications to dosing of these medications must be recorded in the concomitant medication section of the CRF.

7.7.2.1 Corticosteroid Therapy

[redacted]

7.7.2.2 Antimalarial Therapy

Participants are permitted to take one antimalarial medication alone, or in combination with either OCS and/or an immunosuppressant. [redacted]

[redacted]

7.7.2.3 Immunosuppressant Therapy

[redacted]

7.7.2.4 Nonsteroidal Anti-inflammatory Drugs and Narcotic Analgesics

[redacted] Participants may take NSAIDs or narcotic analgesics on an as needed basis, but not 12 hours prior to a scheduled visit.

7.7.3 Rescue Therapy

[redacted]

Rescue therapy [redacted] may include topical corticosteroids, including high and moderate potency (WHO Class 1-5). The steroid must be tapered [redacted]. Any course of OCS or topical steroid above the baseline dose must not extend beyond Week 8, regardless of when the course was started.

7.7.4 Permitted Vaccines (Including COVID-19 Vaccine)

Administration of a non-live vaccine is allowed during the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving deucravacitinib is unknown. The following are examples of non-live vaccines: inactivated vaccines (eg, heat-killed and formalin-killed vaccines), subunit vaccines (eg, influenza and pneumococcal vaccines), toxoid vaccines, nucleic acid vaccines that do not encode potentially infectious virus (eg, Pfizer/BioNTech and Moderna COVID-19 vaccines), and replication-incompetent recombinant vector vaccines (eg, AstraZeneca/University of Oxford COVID-19 vaccine).

For COVID-19 vaccines requiring more than 1 dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment when feasible and when a delay in enrollment would not put the study subject at risk. Ideally, AEs attributable to a vaccine should have resolved prior to enrollment.

If a participant has received a specific COVID-19 vaccination, details such as type and date of vaccine received should be recorded on the concomitant medication page, if given during the study, or the past history page, if given prior to enrollment.

Please contact the Clinical Trial Physician/Medical Monitor with any questions related to COVID-19 vaccines.

[redacted]

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

Participants MUST discontinue investigational product for any of the following reasons:

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws

consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by Bristol-Myers Squibb (BMS).
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Unblinding of a participant's treatment assignment for any reason (emergency or nonemergency).
- Pregnancy.

Refer to the Schedule of Activities in Section 2 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

In the case of pregnancy, the investigator must immediately, within 24 hours of awareness of the pregnancy, notify the Clinical Trial Physician/Medical Monitor/designee of this event. Refer to Section 9.2.6, *Pregnancy*.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. Participants who discontinue study treatment prior to Week 52 will proceed to the EOT/ET and Follow-Up visits as described in Table 2-3. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion between the investigator and the Clinical Trial Physician/Medical Monitor must occur.

If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate case report form (CRF) page.

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment should be followed as outlined in the schedule of assessments for the Safety Follow-up Period (see Table 2-3).

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. Participants who discontinue study treatment prior to Week 52 will proceed to the EOT/ET and Follow-up visits as described in Table

2-3. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **three** documented phone calls, faxes, or emails as well as lack of response by participant to one registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant's contact information or other public vital status data necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information.
- If after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.

- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations and any applicable Baseline assessments must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Screening and baseline assessments must be performed per protocol (standard of care assessments may not be used for baseline).

9.1 Efficacy Assessments

Protocol-specific training and assessments must be successfully completed so that investigators or designees can be qualified to perform assessments using the CLASI, [redacted]. Every effort must be made to ensure that the same evaluator(s) complete the assessment for each participant. If the evaluator(s) is unable to complete the evaluation, then a qualified individual with overlapping experience may perform the evaluation. Documentation of who performed the evaluation is to be recorded in source documents. Assessments are to be performed at approximately the same time of day throughout the duration of the study.

The following sections describe the procedures or tools to be used to assess participants' SLE disease activity during the study (also refer to the Schedule of Activities in Section 2).

9.1.1 Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

Refer to Appendix 8. The CLASI is a validated scale used to assess cutaneous manifestations of SLE consisting of 2 scores. The first (CLASI-A) summarizes the activity of the disease while the second is a measure of the damage done by the disease. Activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and nonscarring alopecia. CLASI-A will be the key efficacy assessment to provide clinical evidence of response to deucravacitinib in the active DLE/SCLE population. The second scale (CLASI-D) assesses damage and is scored in terms of dyspigmentation and scarring, including scarring alopecia. Literature suggests that a 4-point or 20% decrease in the CLASI-A score from baseline is considered an improvement in disease activity.[32]

[redacted]

[redacted]

9.1.4 Skin Biopsy

DLE and SCLE lesion biopsy is a standard histopathological diagnostic test performed for cutaneous lupus disease. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Appendix 1 of the IB represents the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

All AEs and SAEs, including those related to SARS-CoV-2, must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 30 days of discontinuation of dosing.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure, [redacted].

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the CRF module.

- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

In participants who are exhibiting symptoms consistent with COVID-19, the Sponsor advises the investigator to consider holding dosing of investigational product and consult the Clinical Trial Physician/Medical Monitor. If a participant has a positive test for COVID-19, or participants with suspected COVID post contact if no testing is available, the Sponsor advises the investigator to consider holding participant dosing until such time as symptoms resolve. If a positive COVID-19 test result is reported, please consult with the Clinical Trial Physician/Medical Monitor on whether resolution of symptoms alone is sufficient to resume dosing of the IP (Section 3.1). Upon a positive test result for SARS-CoV-2 infection, the infection should be reported to the Sponsor within 24 hours.

COVID-19-related AEs/SAEs will be captured in specific clinical safety program eCRF pages.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known adverse events, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (refer to Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.
- SARS-CoV-2-related AEs/SAEs will be captured in specific clinical safety program (CSP) case report form (CRF) pages.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

Participants will be followed for all SAEs, non-serious AEs of special interest (as defined in Section 9.2), and SARS-CoV-2 related AEs until resolution, the condition stabilizes, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

[redacted]

9.2.6 Pregnancy

In the event a **participant** becomes pregnant during the trial, the study treatment must be discontinued immediately. If the **participant** becomes pregnant during the study period until the end of study, the investigator must immediately notify the Clinical Trial Physician/Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

In all cases, the study treatment will be permanently discontinued.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS Drug Safety. For the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

9.2.7 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE.
- Any laboratory test result abnormality that required the participant to have study treatment discontinued or interrupted.
- Any laboratory test result abnormality that required the participant to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.8 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

- AT (ALT or AST) elevation > 3× ULN

  - AND -

- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

  - AND -

- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.2.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.3 Overdose

For this study, any dose of deucravacitinib greater than 24 mg within a 24-hour time period will be considered an overdose. However, if a participant takes a higher dose than assigned (even if < 24 mg in a 24-hour period), this deviation should be documented appropriately.

In the event of an overdose, the investigator should carry out all of the following actions:

1) Contact Clinical Trial Physician/Medical Monitor immediately.
2) Closely monitor the participant for AEs, SAEs, and laboratory abnormalities until BMS-986165 can no longer be detected systemically (at least 3 days).
3) Obtain a plasma sample [redacted] within 3 days from the date of the last dose of study treatment if requested by the Clinical Trial Physician/Medical Monitor (determined on a case-by-case basis).
4) Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

All urgent safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment. Safety evaluations that will be performed in addition to AE monitoring are physical examinations (Section 9.4.1), TB screening (Section 9.4.2), vital signs, ECGs, concomitant medication use, and laboratory tests (Section 9.4.5).

9.4.1 Physical Examinations

Schedules for physical examinations are provided in Section 2. Complete and/or targeted PEs may be performed by a Doctor of Medicine (MD), or someone who is authorized to perform the examinations by training and has been delegated this task by the principal investigator. While the targeted examination may not be as comprehensive as the initial full examination, key aspects should evaluate important body systems as clinically indicated. These body systems can include lymph nodes, liver, spleen, and breast at the discretion of the examiner. A targeted examination may note any changes in the participant's condition (body systems) since the last assessment and does not preclude examination of any of the other body systems as clinically indicated. Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

9.4.2 Tuberculosis Screening and Chest X-ray

A chest X-ray and PE are part of the process to assess a participant's eligibility as defined in Section 6.2, *Exclusion Criteria*, 6) a), and outlined in Section 2. A chest X-ray at the Screening Visit is required if not already performed within 6 months of obtaining written informed consent.

In addition to a complete PE and medical history to evaluate exposure to TB, all participants will have a screening test, an IGRA (eg, T-spot® or QuantiFERON®), preferably performed centrally. If unable to obtain central laboratory results (eg, repeated test due to indeterminate result), an IGRA test could be obtained locally, after consultation with the Clinical Trial Physician/Medical Monitor.

9.4.3 Vital signs

Refer to Schedule of Activities in Section 2.

9.4.4 Electrocardiograms

Refer to Schedule of Activities in Section 2.

9.4.5 Clinical Safety Laboratory Assessments

A central laboratory will perform assessments of safety laboratory assessments (except pregnancy tests) and provide reference ranges and laboratory reports. Investigators must document their review of each laboratory safety report. Any laboratory test result that the investigator considers clinically relevant is to be recorded on the appropriate AE page of the CRF (Section 9.2.7). Results of clinical laboratory tests performed during screening must be available prior to randomization.

The laboratory parameters to be assessed are as follows:

- Hematology: hemoglobin, hematocrit, total leukocyte count (including differential), platelet count, red blood cell count, and manual differential (separate smear).
- Chemistry: AST, ALT, gamma glutamyltransferase, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, creatinine, blood urea nitrogen, uric acid, [redacted] glucose, total protein, albumin, sodium, potassium, chloride, calcium, phosphorus, magnesium, creatine kinase, creatinine clearance (Screening only).
- Coagulation (Screening only): prothrombin time, international normalized ratio, and either partial thromboplastin time or activated partial thromboplastin time.
- Lipid Panels (Placebo-controlled and Active Treatment Only) tests performed [redacted]: lipid panel (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides).
- Urinalysis: protein, glucose, blood, leukocyte esterase, specific gravity, pH; microscopic examination of the sediment if blood, protein, or leukocyte esterase are positive on dipstick; spot urine will be assessed for urine protein and urine creatinine.
- Serology to be performed at screening: Hepatitis C antibody, anti-HBs, HBsAg, anti-HBc, HIV-1 and HIV-2 antibody.
- TB (screening only).

- C3, C4, Anti-dsDNA: At Screening for all participants, and subsequent collections only for participants with antibodies elevated above normal at Screening.

In addition, urine pregnancy testing will be performed for WOCBP, and follicle-stimulating hormone will be measured to confirm postmenopausal status (as applicable; at screening only). Additional safety assessments may be performed at local laboratories at the investigator's discretion.

9.4.6 Imaging Safety Assessment

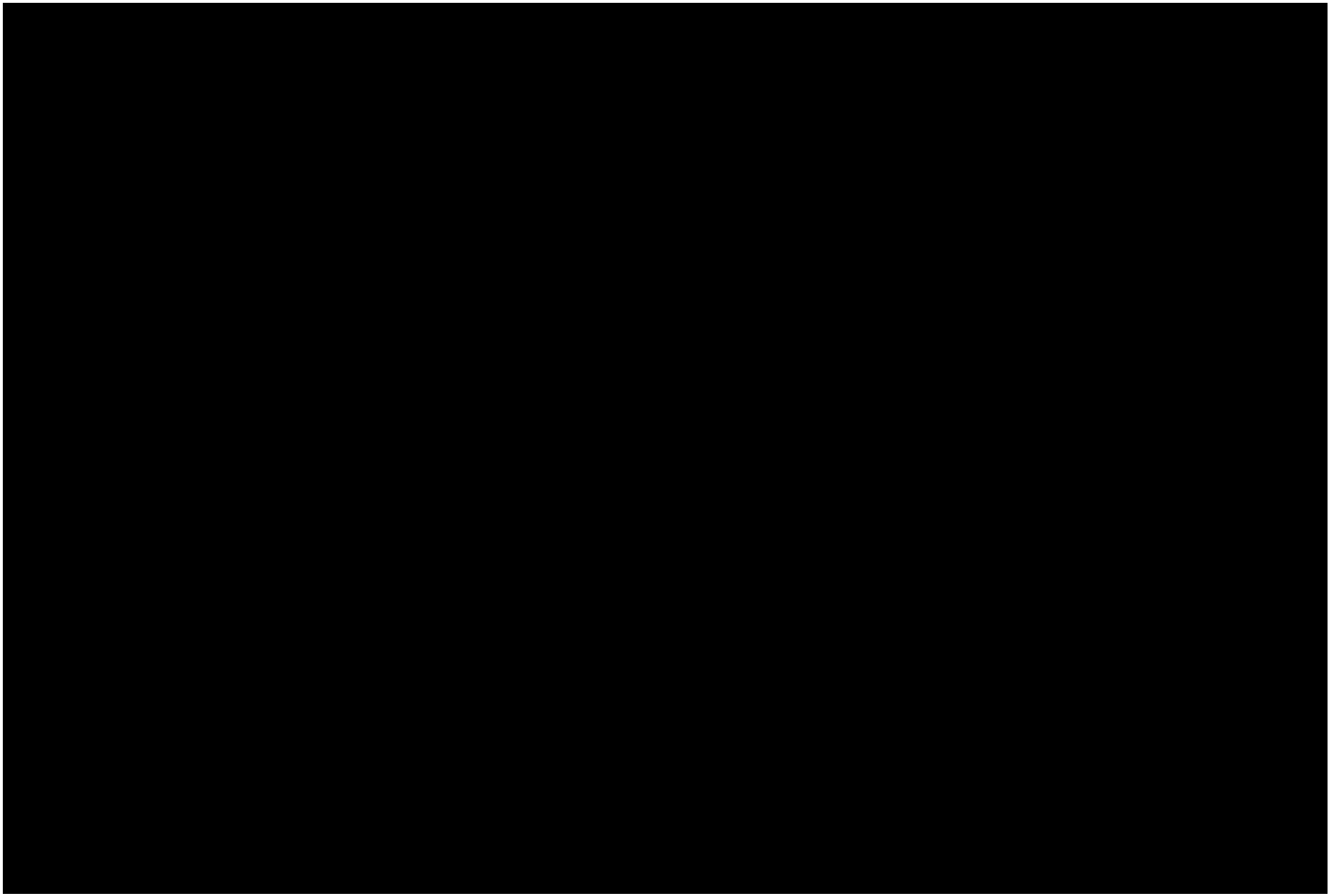
Not applicable.

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

[redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign informed consent.
Randomized	All participants who are randomized to a treatment. Participants will be grouped according to the treatment to which they are randomized according to IRT at the start of the treatment period.
As Treated	All participants who took at least 1 dose of double blind study treatment in the placebo-controlled part of the study. The treatment group "as treated" will be the same as the treatment group "as randomized" by IRT, except in the following cases: • If a participant took the same incorrect treatment throughout the study, then the participant will be analyzed based on the treatment received. • If a participant took study drug from more than one treatment group, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment taken.
As-Treated (Active Treatment Period)	All randomized participants who took at least 1 dose of double-blind study treatment in the active treatment period. Participants will be included in the treatment path they were randomized, except in the following cases: • If a participant took the same incorrect treatment throughout a respective treatment period, then the participant will be analyzed based on the treatment received in each treatment period. • If a participant took study drug from more than one treatment group within a treatment period, and none of the administrations were consistent with the assigned randomized treatment group, then the participant will be analyzed based on the first treatment taken within each treatment period. Participants will be grouped according to the following treatment sequences: • Deucravacitinib 3 mg BID ☐deucravacitinib 3 mg BID • Deucravacitinib 6 mg BID ☐deucravacitinib 6 mg BID • Placebo ☐:deucravacitinib 3 mg BID - OR - • Placebo ☐deucravacitinib 6 mg BID.

Abbreviations: BID = twice a day; IRT = Interactive Response Technology.

10.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Below is a summary of planned statistical analyses of the primary and secondary endpoints. See Table 4-1 for the list of endpoints.

A description of the participant population will be included in a statistical output report, including subgroups of age, gender and race.

10.3.1 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Percent change from baseline over time for CLASI-A score will be analyzed using a longitudinal repeated measures analysis on the randomized population. [redacted] Adjusted mean % changes (LSMEANS) and unadjusted mean % changes with corresponding SE and 95% CI per treatment arm will be provided. The difference in LSMEANS and corresponding 90% and 95% CIs will be provided for the difference between the 2 combined active arms and the placebo arm and for the difference between the individual active arms and the placebo arm at the different time points. [redacted] Nominal p-values will be provided for the difference between the 2 combined active arms and the placebo arm and for the difference between the individual active arms and the placebo arm at Week 16. No adjustment for multiplicity will be applied. If warranted, transformations will be considered. [redacted] [redacted] Additional sensitivity analyses of the primary endpoint, including the handling of intercurrent events, may be defined in the statistical analysis plan.
Secondary	Continuous secondary efficacy endpoints will be analyzed similarly to the primary efficacy endpoint using a longitudinal repeated measures model. For the binary secondary efficacy endpoints (e.g., CLASI-50 response) a logistic regression analysis at Week 16 will be provided on the randomized population. [redacted] The estimated odds ratio of the 2 combined active arms versus the placebo arm and of the individual active arms versus the placebo arm with the corresponding 2-sided 90% CI and 95% CI will be presented. In addition, the estimated treatment differences and corresponding 90% CI and 95% CI will be provided for the difference in response rate between the 2 combined active arms and the placebo arm and for the difference in response rate between the individual active arms and the placebo arm at the different time points. The handling of missing values and intercurrent events will be described in the SAP. No adjustments for multiplicity will be done for the secondary endpoints. Nominal p-values will be provided for the Week 16 timepoint.
[redacted]	

Abbreviations: CI = confidence interval; CLASI-50 = 50% improvement from baseline in CLASI-A score; CLASI-A = cutaneous lupus erythematosus disease area and severity index activity; LSMEANS = adjusted mean % changes; [redacted] SAP = statistical analysis plan; [redacted]

10.3.2 Safety Analyses

All safety analyses will be performed on the As-treated analysis population.

Endpoint	Statistical Analysis Methods
Primary	Not applicable as all safety assessments and variables are considered secondary.
Secondary	Safety assessments and variables during the 16-week placebo-controlled treatment period (TP), as specified in Table 4-1, will be summarized descriptively by treatment group (combined BMS doses, each BMS dose, and placebo). Adverse events will be listed and tabulated by System Organ Class (SOC) and Preferred Term (PT). Categorical data will be summarized as frequency counts and percentages. Continuous data for absolute and change from baseline values will be summarized using n, mean, standard deviation, median, minimum, and maximum, unless otherwise specified.
[redacted]	

Abbreviations: n = number of samples; PT = Preferred Term; SOC = System Organ Class; TP = treatment period.

[redacted]

10.3.4 Interim Analyses

Not applicable.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
ACLE	acute cutaneous lupus erythematosus
ACR	American College of Rheumatology
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
anti-dsDNA	anti-double stranded deoxyribonucleic acid (antibody)
anti-HBs	anti-hepatitis B surface antibody
APS	antiphospholipid antibody syndrome
[redacted]	[redacted]
AST	aspartate aminotransferase
[redacted]	[redacted]
BID	twice a day
BMI	body mass index
BMS	Bristol-Myers Squibb (Company)
C3	complement 3
C4	complement 4
CCLE	chronic cutaneous lupus erythematosus
CI	confidence interval
[redacted]	[redacted]
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-50	50% improvement from baseline in CLASI-A score
CLASI-A	CLASI activity (score)
CLASI-D	CLASI damage (score)
CLE	cutaneous lupus erythematosus
[redacted]	[redacted]
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease of 2019

Term	Definition
CR	complete response
CS	corticosteroid(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DLE	discoid lupus erythematosus
DMC	Data Monitoring Committee
[redacted]	[redacted]
ECG	Electrocardiogram
EOT	End of Treatment
[redacted]	[redacted]
ET	Early Termination
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FU	Follow-up (Period)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
IEC	Independent Ethics Committee

Term	Definition
IFN(α, β, γ)	interferon (alpha, beta, gamma)
[redacted]	[redacted]
IGRA	interferon-gamma release assay
IL	Interleukin
IMP	Investigational Medicinal Product
IP	Investigational Product
IRB	Institutional Review Board
[redacted]	[redacted]
IRT	Interactive Response Technology
[redacted]	[redacted]
IU	international unit
IV	Intravenous
JAK	Janus kinase
[redacted]	[redacted]
LE	Lupus Erythematosus
LET	lupus erythematosus tumidus
[redacted]	[redacted]
LSMEANS	least-squares mean
[redacted]	[redacted]
MD	Doctor of Medicine
[redacted]	[redacted]
[redacted]	[redacted]
MOA(s)	mechanism(s) of action
[redacted]	[redacted]
[redacted]	[redacted]
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OCS	oral corticosteroid(s)
PA	Posterioranterior

Term	Definition
[redacted]	[redacted]
[redacted]	[redacted]
PE	physical examination
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Serious acute respiratory syndrome coronavirus 2
SCLE	subacute cutaneous lupus erythematosus
[redacted]	[redacted]
SLE	systemic lupus erythematosus
[redacted]	[redacted]
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
SPSD	Site Process and Source Documentation
STAT	signal transducer and activator of transcription
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TB	Tuberculosis
[redacted]	[redacted]
TP	Treatment Period
TYK2	tyrosine kinase 2
ULN	upper limit of normal

Term	Definition
UPCR	urine protein/creatinine ratio
US	United States
UV	Ultraviolet
[redacted]	[redacted]
[redacted]	[redacted]
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the CRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation, etc) that is likely to affect, to a significant degree one or more of the following: (1) the physical, safety or mental integrity of one or more subjects/participants; (2) the scientific value of the trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP Regulation(s) or Trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, participant recruitment materials (eg, advertisements), and any other written information to be provided to subjects/participants.

The investigator, Sponsor or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects/participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects/participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects/participants prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that subjects/participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given by subjects/participants, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the participant volunteers to participate.

Sponsor or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects/participants, prior to the beginning of the study, and after any revisions are completed for new information.

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or his/her legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects'/participants' signed ICF and, in the US, the subjects'/participants' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

Subjects/participants unable to give their written consent (eg, stroke or subjects/participants with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

The rights, safety, and well-being of the study subjects/participants are the most important considerations and should prevail over interests of science and society.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in the Site Process and Source Documentation (SPSD) form.

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs),

adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

BMS or designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

The confidentiality of records that could identify subjects/participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS, a vendor or sourced by the investigator) such as partially used study treatment containers, vials and syringes may be destroyed on site.

If	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non-study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

For sites that will not destroy study treatment on-site, it is the investigator's or designee's responsibility to arrange for disposal of all empty study treatment containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of full or partially used study treatments supplied by BMS or its vendors will be arranged by the responsible Study Monitor.

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the clinical study report.

For each CSR related to this protocol, the following criteria will be used to select the signatory investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTAg) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTAg.

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable subjects with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:
An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment.
An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) • elective surgery, planned prior to signing consent • admissions as per protocol for a planned medical/surgical procedure • routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) • medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases • admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.6 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

- End of relevant systemic exposure is the time point where the IMP or any active major metabolites has decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed adverse effect level (NOAEL) or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral (birth control pills) – intravaginal (rings) – transdermal • Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy
• Progestogen-only hormonal contraception associated with inhibition of ovulation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] – oral – injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol)[b] • Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS) (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol) [b,c]
- Bilateral tubal occlusion

- Vasectomized partner

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

A vasectomy is a highly effective contraception method provided that the participant is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence
- Periodic abstinence (including but not limited to calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

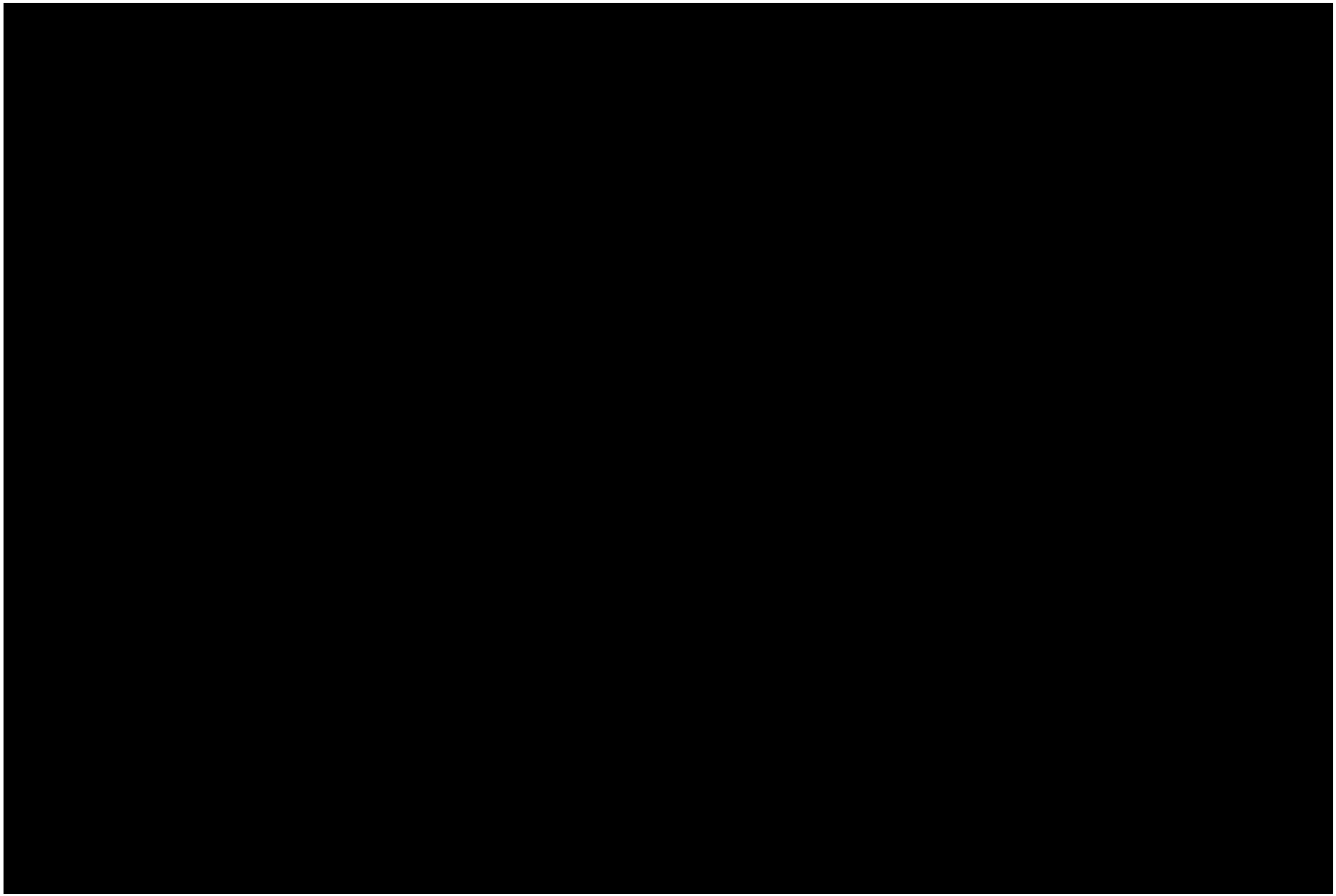
[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.6 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting



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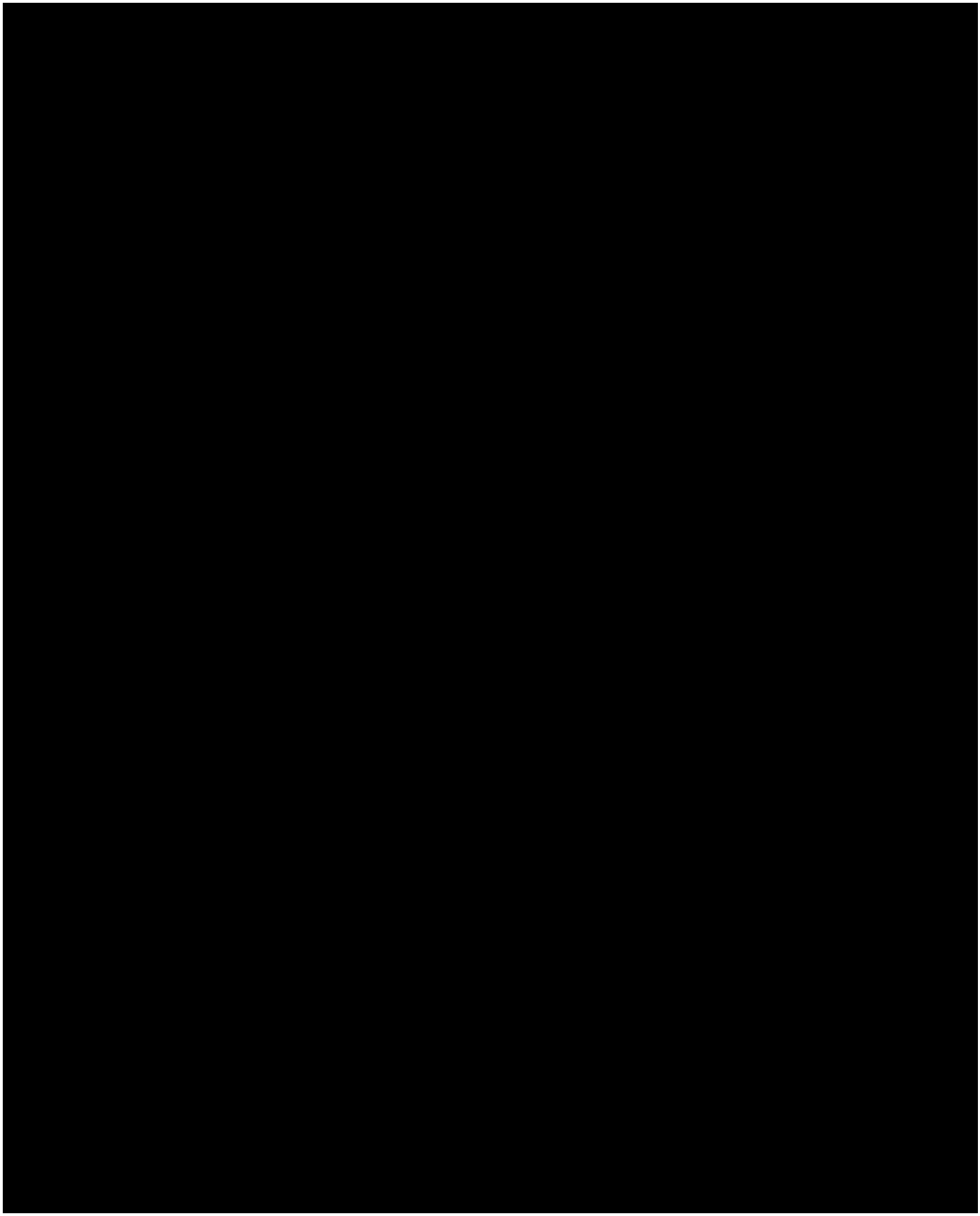

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APPENDIX 8 CUTANEOUS LUPUS ERYTHEMATOSUS DISEASE AREA AND SEVERITY INDEX (CLASI)

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient) 1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

Albrecht and Werth, J. Invest. Derm, 125:889, 2005

APPENDIX 9 COMMONLY USED CORTICOSTEROID EQUIVALENTS

Medication	Dose Equivalence
Prednisone	20 mg
Cortisone	100 mg
Hydrocortisone	80 mg
Prednisolone	20 mg
Methylprednisolone	16 mg
Triamcinolone	16 mg
Budesonide	4 mg
Dexamethasone	3 mg
Betamethasone	2.4 mg
Deflazacort	26 mg

APPENDIX 10 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS IV

Alcohol abuse:

In the past year, have you:

- Found that drinking – or being sick from drinking – often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- More than once gotten arrested, been held at a police station, or had other legal problems because of your drinking?
- Continued to drink even though it was causing trouble with your family or friends?

The presence of any 1 of the above is considered indicative of alcohol abuse.

Alcohol dependence:

In the past year, have you:

- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing hear, or a seizure? Or sensed things that were not there?
- Had times when you ended up drinking more, or longer, than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over other aftereffects?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?

The presence of any 3 of the above is considered indicative of alcohol dependence.

National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism. Alcohol use disorder: a comparison between DSM-IV and DSM-5. NIH Publication No. 13-7999. Reviewed July 2016.

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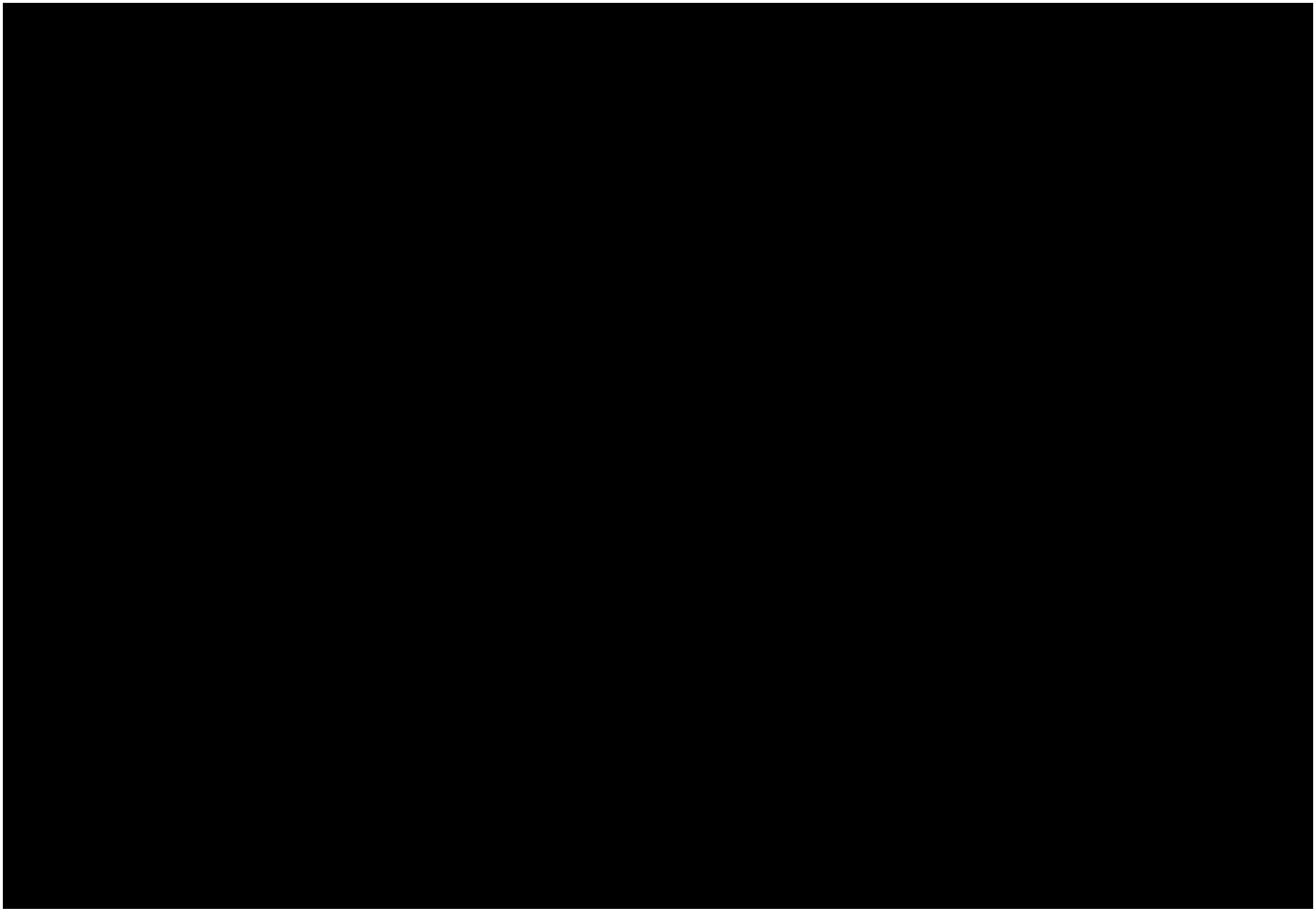
APPENDIX 12 TOPICAL STEROID POTENCY TABLE

Medscape® www.medscape.com

Class	Generic Name	Formulation
Class 1 Very High Potency		
	Betamethasone dipropionate	0.05% G O (diprolene)
	Clobetasol	0.05% C F G L O
	Diflorasone diacetate	0.05% O
	Halobetasol propionate	0.05% C O
Class 2 High Potency		
	Amcinonide	0.1% O
	Betamethasone dipropionate	0.05% C (diprolene)
	Desoximetasone	0.05% G, 0.25% C O
	Fluocinonide	0.05% C G O S
	Halcinonide	0.1% C
	Mometasone furoate	0.1% O
Class 3 High Potency		
	Amcinonide	0.1% C L
	Betamethasone dipropionate	0.05% C (non-diprolene)
	Betamethasone valerate	0.1% O
	Desoximetasone	0.05% C
	Diflorasone diacetate	0.05% C
	Fluticasone propionate	0.005% O
	Halcinonide	0.1% O S
	Triamcinolone	0.1% O
Class 4 Mid Potency		
	Betamethasone valerate	0.12% F
	Flucinolone acetonide	0.025% O
	Flurandrenolide	0.05% O
	Hydrocortisone valerate	0.2% O
	Mometasone furoate	0.1% C
	Triamcinolone	0.1% C
Class 5 Mid Potency		
	Betamethasone dipropionate	0.05% L
	Betamethasone valerate	0.1% C
	Flucinolone acetonide	0.025% C
	Fluticasone propionate	0.05% C
	Flurandrenolide	0.05% C
	Hydrocortisone butyrate	0.1% C
	Hydrocortisone valerate	0.2% C
Class 6 Low Potency		
	Alcometasone dipropionate	0.05% C O
	Betamethasone valerate	0.1% L
	Desonide	0.05% C L O
	Flucinolone acetonide	0.01% C S
Class 7 Low Potency		
	Hydrocortisone acetate	0.5% C L O, 1% C O F
	Hydrocortisone hydrochloride	0.25% C L, 0.5% C L O S, 1% C L O S, 2% L, 2.5% C L O S

C = Cream, F = Foam, G = Gel, L = Lotion, O = Ointment, S = Solution



APPENDIX 14 INTERPRETATION OF HEPATITIS B SEROLOGIC TEST RESULTS

As study treatment in this study is expected to demonstrate immunosuppressive effects, it is imperative to carefully evaluate and exclude participants with potentially active hepatitis B infection. For this reason, in order to fully evaluate a participant's eligibility for enrollment, the exclusion criterion (see Section 6.2) requires interpretation of data from 3 standard tests for hepatitis B, ie, measurement of hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs).

Participant's eligibility for enrollment should be assessed as described below. Participants that are:

- Hepatitis B serological test negative (neg) for all results may be included in the study
- HBsAg (neg), anti-HBc (neg), and anti-HBs positive (POS) may be included in the study (immunized due to hepatitis B vaccination)
- HBsAg (neg), anti-HBc (POS), and anti-HBs (POS) are to be excluded from the study (immune due to natural infection exposure)
- Participants that are HBsAg (POS) are excluded from the study (acute or chronic infection)
- Participants that are anti-HBc (POS) are excluded from the study (acute or chronic infection)
- Participants that are HBsAg (neg), anti-HBc (POS), and anti-HBs (neg) are to be excluded from the study (interpretation unclear)

Please refer to the below "Interpretation of Hepatitis B Serologic Test Results" provided by the Department of Health and Human Services, Centers for Disease Control and Prevention.

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

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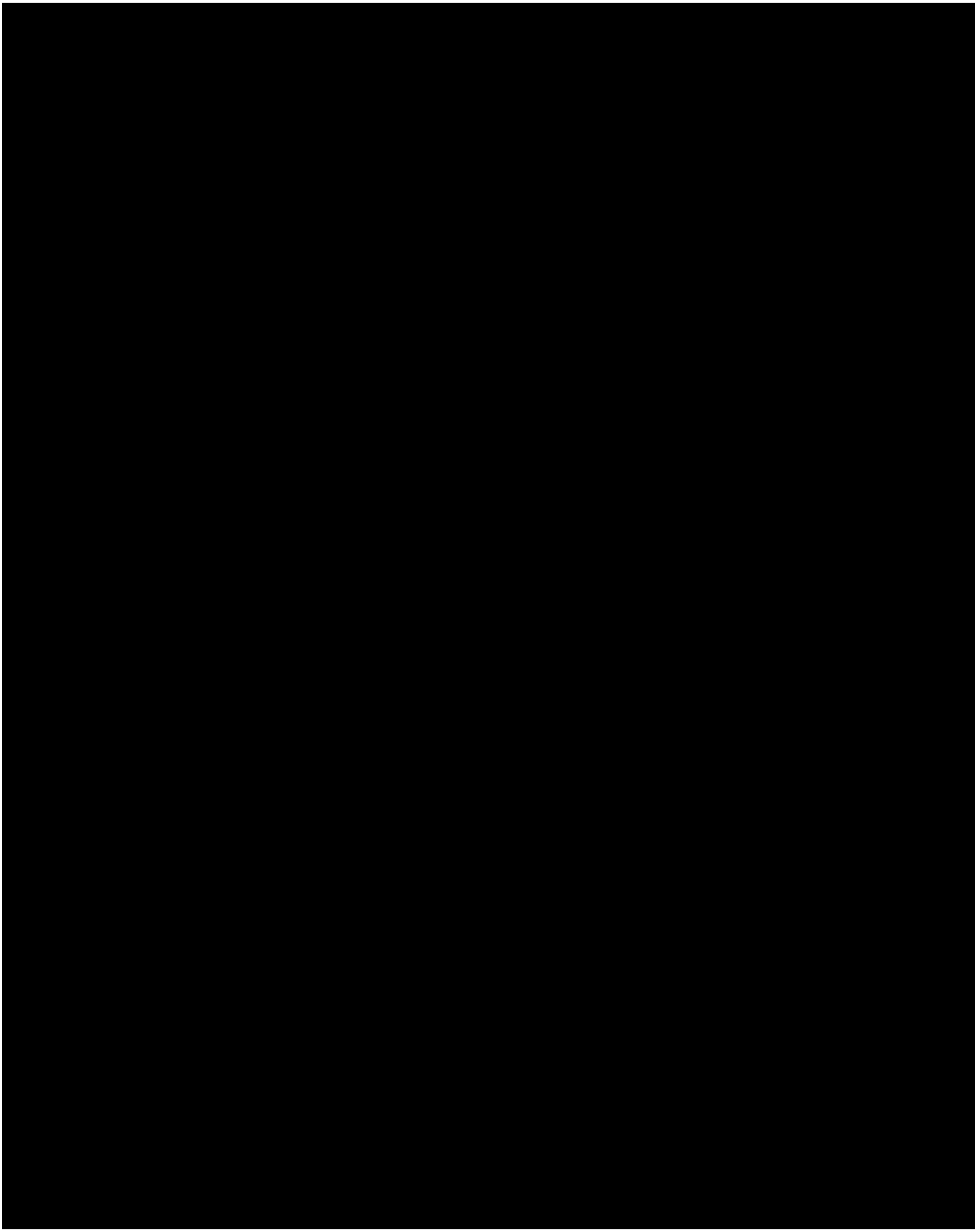

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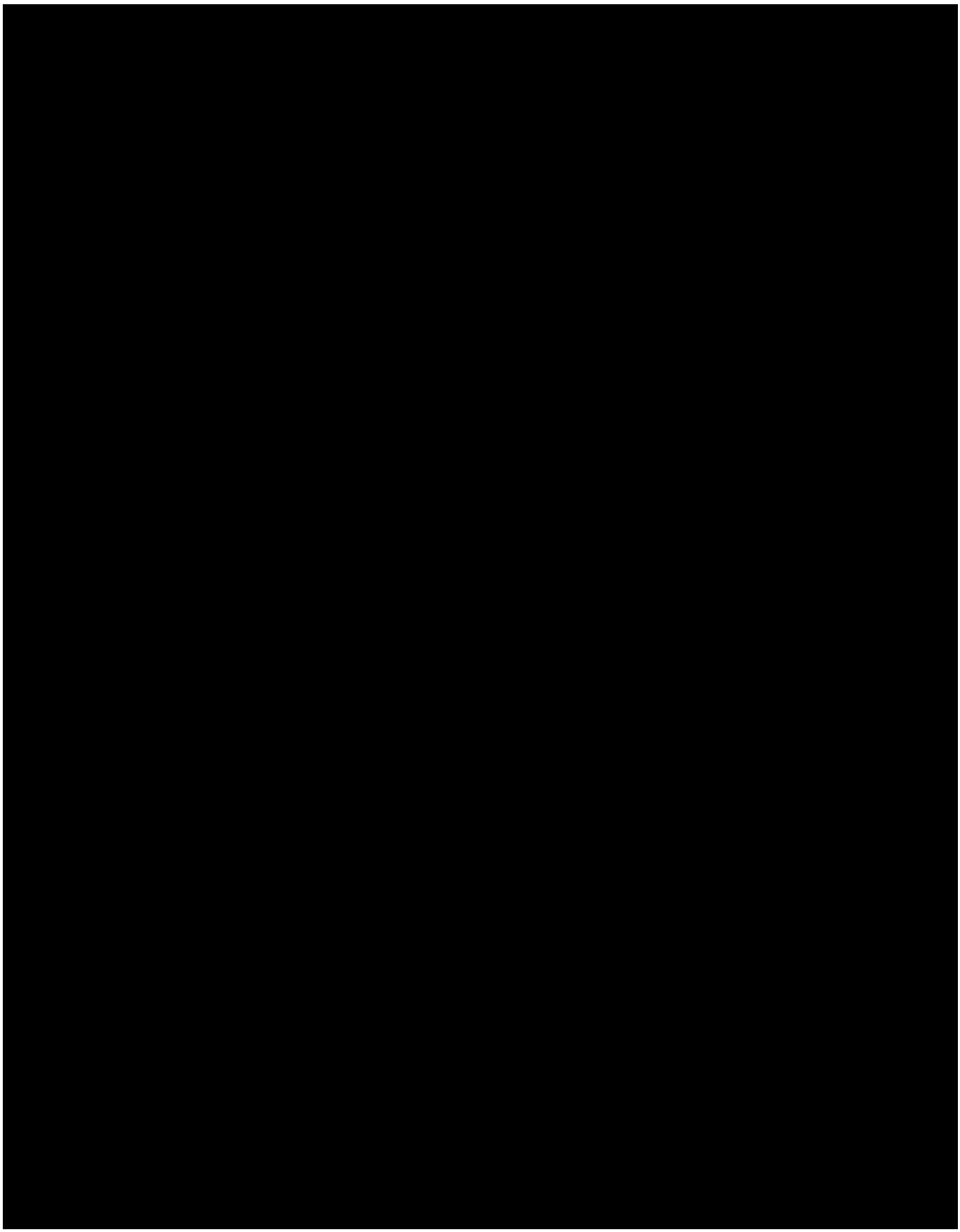

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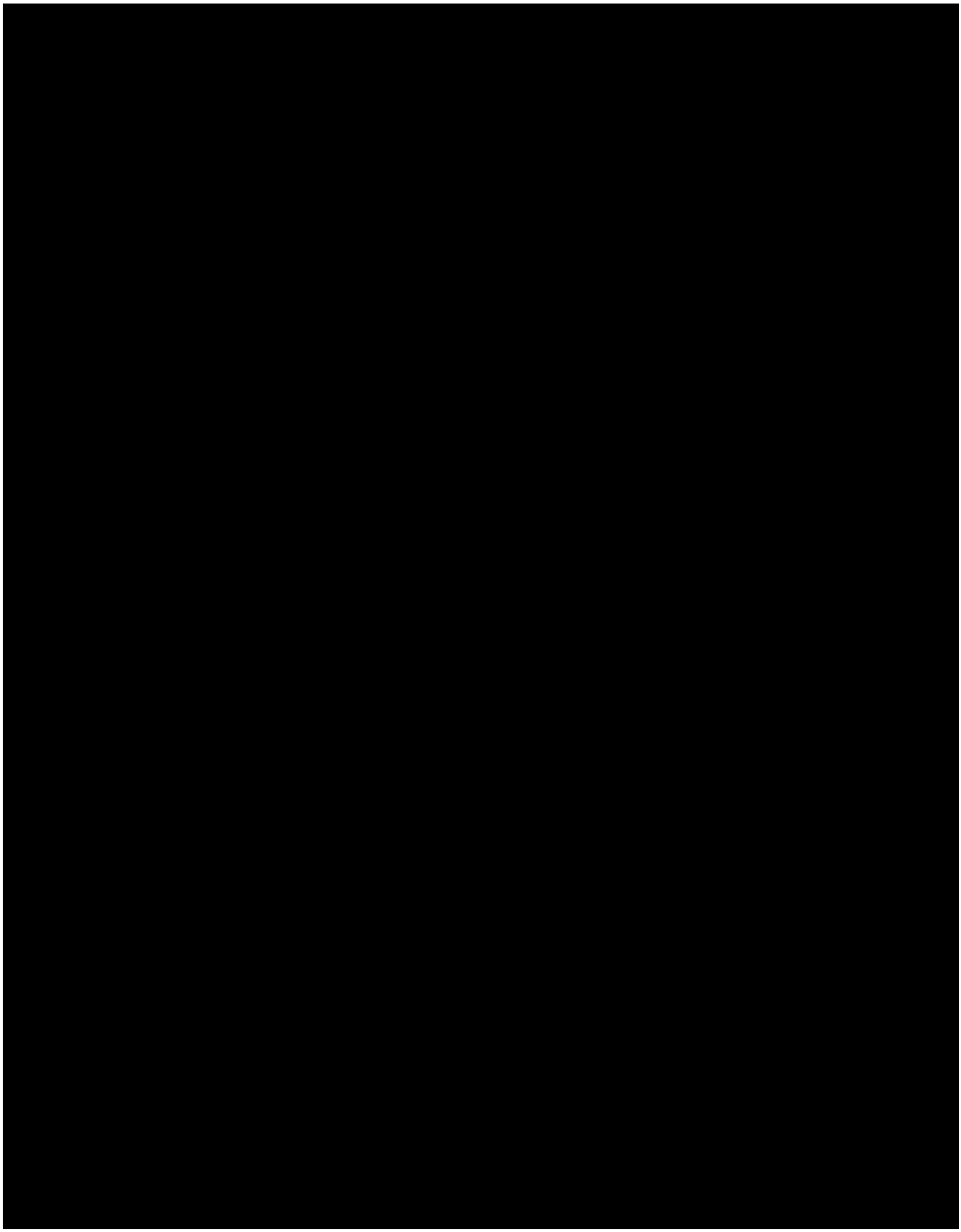

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APPENDIX 25 CORE AND EXTENDED ADME GENE LIST

Appendix 25 is not applicable per Protocol Amendment 02.

Core ADME Gene List:

Gene Symbol	Full Gene Name	Class
ABCB1	ATP-binding cassette, sub-family B (MDR/TAP), member 1	Transporter
ABCC2	ATP-binding cassette, sub-family C (CFTR/MRP), member 2	Transporter
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2	Transporter
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	Phase I
CYP1A2	cytochrome P450, family 1, subfamily A, polypeptide 2	Phase I
CYP2A6	cytochrome P450, family 2, subfamily A, polypeptide 6	Phase I
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6	Phase I
CYP2C19	cytochrome P450, family 2, subfamily C, polypeptide 19	Phase I
CYP2C8	cytochrome P450, family 2, subfamily C, polypeptide 8	Phase I
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9	Phase I
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	Phase I
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1	Phase I
CYP3A4	cytochrome P450, family 3, subfamily A, polypeptide 4	Phase I
CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5	Phase I
DPYD	dihydropyrimidine dehydrogenase	Phase I
GSTM1	glutathione S-transferase M1	Phase II
GSTP1	glutathione S-transferase pi	Phase II
GSTT1	glutathione S-transferase theta 1	Phase II
NAT1	N-acetyltransferase 1 (arylamine N-acetyltransferase)	Phase II
NAT2	N-acetyltransferase 2 (arylamine N-acetyltransferase)	Phase II
SLC15A2	solute carrier family 15 (H+/peptide transporter), member 2	Transporter
SLC22A1	solute carrier family 22 (organic cation transporter), member 1	Transporter
SLC22A2	solute carrier family 22 (organic cation transporter), member 2	Transporter
SLC22A6	solute carrier family 22 (organic anion transporter), member 6	Transporter
SLCO1B1	solute carrier organic anion transporter family, member 1B1	Transporter
SLCO1B3	solute carrier organic anion transporter family, member 1B3	Transporter
SULT1A1	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1	Phase II
TPMT	thiopurine S-methyltransferase,	Phase II
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Phase II
UGT2B15	UDP glucuronosyltransferase 2 family, polypeptide B15	Phase II
UGT2B17	UDP glucuronosyltransferase 2 family, polypeptide B17	Phase II
UGT2B7	UDP glucuronosyltransferase 2 family, polypeptide B7	Phase II

Extended ADME Gene List:

Gene Symbol	Full Gene Name	Class
ABCB8	ATP-binding cassette, sub-family B (MDR/TAP), member 8	Transporter
ABCC12	ATP-binding cassette, sub-family C (CFTR/MRP), member 12	Transporter
ABCC3	ATP-binding cassette, sub-family C (CFTR/MRP), member 3	Transporter
ABCC4	ATP-binding cassette, sub-family C (CFTR/MRP), member 4	Transporter
AHR	aryl hydrocarbon receptor	Modifier
ALDH4A1	aldehyde dehydrogenase 4 family, member A1	Phase I
ALDH5A1	aldehyde dehydrogenase 5 family, member A1	Phase I
ALDH6A1	aldehyde dehydrogenase 6 family, member A1	Phase I
CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)	Phase I
CES2	carboxylesterase 2 (intestine, liver)	Phase I
CYP7A1	cytochrome P450, family 7, subfamily A, polypeptide 1	Phase I
EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)	Phase I
FMO3	flavin containing monooxygenase 3	Phase I
GSTA1	glutathione S-transferase A1	Phase II
GSTA2	glutathione S-transferase A2	Phase II
GSTA3	glutathione S-transferase A3	Phase II
GSTA4	glutathione S-transferase A4	Phase II
GSTA5	glutathione S-transferase A5	Phase II
GSTM2	glutathione S-transferase M2 (muscle),glutathione S-transferase M4	Phase II
GSTM3	glutathione S-transferase M3 (brain)	Phase II
GSTM4	glutathione S-transferase M4	Phase II
GSTO1	glutathione S-transferase omega 1,glutathione S-transferase omega 2	Phase II
GSTO2	glutathione S-transferase omega 2	Phase II
GSTT2	glutathione S-transferase theta 2	Phase II
SLC10A1	solute carrier family 10 (sodium/bile acid cotransporter family), member 1	Transporter
SLC15A1	solute carrier family 15 (oligopeptide transporter), member 1	Transporter
SLC22A11	solute carrier family 22 (organic anion/cation transporter), member 11	Transporter
SLC22A8	solute carrier family 22 (organic anion transporter), member 8	Transporter
SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	Transporter
SLCO1A2	solute carrier organic anion transporter family, member 1A2	Transporter
SLCO2B1	solute carrier organic anion transporter family, member 2B1	Transporter
SULT1A2	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 2	Phase II
SULT1A3	sulfotransferase family, cytosolic, 1A, phenol-preferring, member 3	Phase II
SULT1B1	sulfotransferase family, cytosolic, 1B, member 1	Phase II

Gene Symbol	Full Gene Name	Class
UGT1A3	UDP glucuronosyltransferase 1 family, polypeptide A3	Phase II
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Phase II
UGT1A7	UDP glucuronosyltransferase 1 family, polypeptide A7	Phase II
UGT1A8	UDP glucuronosyltransferase 1 family, polypeptide A8	Phase II
UGT1A9	UDP glucuronosyltransferase 1 family, polypeptide A9	Phase II
UGT2A1	UDP glucuronosyltransferase 2 family, polypeptide A1	Phase II
UGT2B11	UDP glucuronosyltransferase 2 family, polypeptide B11	Phase II
UGT2B28	UDP glucuronosyltransferase 2 family, polypeptide B28	Phase II
UGT2B4	UDP glucuronosyltransferase 2 family, polypeptide B4	Phase II
ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	Transporter
ABCA4	ATP-binding cassette, sub-family A (ABC1), member 4	Transporter
ABCB11	ATP-binding cassette, sub-family B (MDR/TAP), member 11	Transporter
ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	Transporter
ABCB5	ATP-binding cassette, sub-family B (MDR/TAP), member 5	Transporter
ABCB6	ATP-binding cassette, sub-family B (MDR/TAP), member 6	Transporter
ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	Transporter
ABCC1	ATP-binding cassette, sub-family C (CFTR/MRP), member 1	Transporter
ABCC10	ATP-binding cassette, sub-family C (CFTR/MRP), member 10	Transporter
ABCC11	ATP-binding cassette, sub-family C (CFTR/MRP), member 11	Transporter
ABCC5	ATP-binding cassette, sub-family C (CFTR/MRP), member 5	Transporter
ABCC6	ATP-binding cassette, sub-family C (CFTR/MRP), member 6	Transporter
ABCC8	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	Transporter
ABCC9	ATP-binding cassette, sub-family C (CFTR/MRP), member 9	Transporter
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Transporter
ADH1A	alcohol dehydrogenase 1A (class I), alpha polypeptide	Phase I
ADH1B	alcohol dehydrogenase IB (class I), beta polypeptide	Phase I
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	Phase I
ADH4	alcohol dehydrogenase 4 (class II), pi polypeptide	Phase I
ADH5	alcohol dehydrogenase 5 (class III), chi polypeptide,methionyl aminopeptidase 1	Phase I
ADH6	alcohol dehydrogenase 6 (class V)	Phase I
ADH7	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide	Phase I
ALDH1A1	aldehyde dehydrogenase 1 family, member A1	Phase I
ALDH1A2	aldehyde dehydrogenase 1 family, member A2	Phase I
ALDH1A3	aldehyde dehydrogenase 1 family, member A3	Phase I
ALDH1B1	aldehyde dehydrogenase 1 family, member B1	Phase I
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	Phase I

Gene Symbol	Full Gene Name	Class
ALDH3A1	aldehyde dehydrogenase 3 family, memberA1	Phase I
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	Phase I
ALDH3B1	aldehyde dehydrogenase 3 family, member B1	Phase I
ALDH3B2	aldehyde dehydrogenase 3 family, member B2	Phase I
ALDH7A1	aldehyde dehydrogenase 7 family, member A1	Phase I
ALDH8A1	aldehyde dehydrogenase 8 family, member A1	Phase I
ALDH9A1	aldehyde dehydrogenase 9 family, member A1	Phase I
AOX1	aldehyde oxidase 1	Phase I
ARNT	aryl hydrocarbon receptor nuclear translocator	Modifier
CBR1	carbonyl reductase 1	Phase I
CBR3	carbonyl reductase 3	Phase I
CDA	cytidine deaminase	Modifier
CYB5R3	cytochrome b5 reductase 3	Phase I
CYP11A1	cytochrome P450, family 11, subfamily A, polypeptide 1	Phase I
CYP11B1	cytochrome P450, family 11, subfamily B, polypeptide 1	Phase I
CYP11B2	cytochrome P450, family 11, subfamily B, polypeptide 2	Phase I
CYP17A1	cytochrome P450, family 17, subfamily A, polypeptide 1	Phase I
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP20A1	cytochrome P450, family 20, subfamily A, polypeptide 1	Phase I
CYP21A2	cytochrome P450, family 21, subfamily A, polypeptide 2	Phase I
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	Phase I
CYP26A1	cytochrome P450, family 26, subfamily A, polypeptide 1	Phase I
CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Phase I
CYP2A13	cytochrome P450, family 2, subfamily A, polypeptide 13	Phase I
CYP2A7	cytochrome P450, family 2, subfamily A, polypeptide 7	Phase I
CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18	Phase I
CYP2F1	cytochrome P450, family 2, subfamily F, polypeptide 1	Phase I
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	Phase I
CYP39A1	cytochrome P450, family 39, subfamily A, polypeptide 1	Phase I
CYP3A43	cytochrome P450, family 3, subfamily A, polypeptide 43	Phase I
CYP3A7	cytochrome P450, family 3, subfamily A, polypeptide 7	Phase I
CYP4B1	cytochrome P450, family 4, subfamily B, polypeptide 1	Phase I
CYP4F11	cytochrome P450, family 4, subfamily F, polypeptide 11	Phase I
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Phase I
EPHX2	epoxide hydrolase 2, cytoplasmic	Phase I

Gene Symbol	Full Gene Name	Class
FMO1	flavin containing monooxygenase 1	Phase I
FMO2	flavin containing monooxygenase 2	Phase I
FMO4	flavin containing monooxygenase 4	Phase I
FMO5	flavin containing monooxygenase 5	Phase I
GPX2	glutathione peroxidase 2 (gastrointestinal)	Phase I
GPX3	glutathione peroxidase 3 (plasma)	Phase I
GPX7	glutathione peroxidase 7	Phase I
GSR	glutathione reductase	Phase I
GSTK1	glutathione S-transferase kappa 1	Phase II
GSTM5	glutathione S-transferase M5	Phase II
GSTZ1	glutathione transferase zeta 1 (maleylacetoacetate isomerase)	Phase II
NNMT	nicotinamide N-methyltransferase	Phase II
NR1I2	nuclear receptor subfamily 1, group I, member 2	Modifier
NR1I3	nuclear receptor subfamily 1, group I, member 3	Modifier
PNMT	phenylethanolamine N-methyltransferase	Phase II
PON1	paraoxonase 1	Phase I
PON2	paraoxonase 2	Phase I
PON3	paraoxonase 3	Phase I
POR	P450 (cytochrome) oxidoreductase	Modifier
PPARD	peroxisome proliferative activated receptor, delta	Modifier
PPARG	peroxisome proliferative activated receptor, gamma	Modifier
RXRA	retinoid X receptor, alpha	Modifier
SLC10A2	solute carrier family 10 (sodium/bile acid cotransporter family), member 2	Transporter
SLC13A1	solute carrier family 13 (sodium/sulfate symporters), member 1	Transporter
SLC13A2	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 2	Transporter
SLC13A3	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3	Transporter
SLC16A1	solute carrier family 16 (monocarboxylic acid Transporter), member 1	Transporter
SLC19A1	solute carrier family 19 (folate transporter), member 1	Transporter
SLC22A10	solute carrier family 22 (organic anion/cation transporter), member 10	Transporter
SLC22A12	solute carrier family 22 (organic anion/cation transporter), member 12	Transporter
SLC22A13	solute carrier family 22 (organic cation transporter), member 13	Transporter
SLC22A14	solute carrier family 22 (organic cation transporter), member 14	Transporter
SLC22A15	solute carrier family 22 (organic cation transporter), member 15	Transporter
SLC22A16	solute carrier family 22 (organic cation transporter), member 16	Transporter

Gene Symbol	Full Gene Name	Class
SLC22A17	solute carrier family 22 (organic cation transporter), member 17	Transporter
SLC22A18	solute carrier family 22 (organic cation transporter), member 18	Transporter
SLC22A18AS	solute carrier family 22 (organic cation transporter), member 18 antisense	Transporter
SLC22A3	solute carrier family 22 (extraneuronal monoamine transporter), member 3	Transporter
SLC22A4	solute carrier family 22 (organic cation transporter), member 4	Transporter
SLC22A5	solute carrier family 22 (organic cation transporter), member 5	Transporter
SLC22A7	solute carrier family 22 (organic anion transporter), member 7	Transporter
SLC22A9	solute carrier family 22 (organic anion/cation transporter), member 9	Transporter
SLC27A1	solute carrier family 27 (fatty acid transporter), member 1	Transporter
SLC28A1	solute carrier family 28 (sodium-coupled nucleoside transporter), member 1	Transporter
SLC28A2	solute carrier family 28 (sodium-coupled nucleoside transporter), member 2	Transporter
SLC28A3	solute carrier family 28 (sodium-coupled nucleoside transporter), member 3	Transporter
SLC29A1	solute carrier family 29 (nucleoside Transporter), member 1	Transporter
SLC29A2	solute carrier family 29 (nucleoside Transporter), member 2	Transporter
SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	Transporter
SLC2A5	solute carrier family 2 (facilitated glucose/fructose transporter), member 5	Transporter
SLC5A6	solute carrier family 5 (sodium-dependent vitamin transporter)	Transporter
SLC6A6	solute carrier family 6 (neurotransmitter transporter, taurine), member 6	Transporter
SLC7A8	solute carrier family 7 (cationic amino acid transporter, y+ system), member 8	Transporter
SLCO1C1	solute carrier organic anion transporter family, member 1C1	Transporter
SLCO2A1	solute carrier organic anion transporter family, member 2A1	Transporter
SLCO3A1	solute carrier organic anion transporter family, member 3A1	Transporter
SLCO4A1	solute carrier organic anion transporter family, member 4A1	Transporter
SLCO4C1	solute carrier organic anion transporter family, member 4C1	Transporter
SLCO5A1	solute carrier organic anion transporter family, member 5A1	Transporter
SLCO6A1	solute carrier organic anion transporter family, member 6A1	Transporter
SULT1C1	sulfotransferase family, cytosolic, 1C, member 1	Phase II
SULT1C2	sulfotransferase family, cytosolic, 1C, member 2	Phase II
SULT1E1	sulfotransferase family 1E, estrogen-preferring, member 1	Phase II
SULT2A1	sulfotransferase family, cytosolic, 2A, DHEA preferring, member 1	Phase II
SULT2B1	sulfotransferase family, cytosolic, 2B, member 1	Phase II

Gene Symbol	Full Gene Name	Class
TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT1A10	UDP glucuronosyltransferase 1 family, polypeptide A10	Phase II
UGT1A4	UDP glucuronosyltransferase 1 family, polypeptide A4	Phase II
UGT1A5	UDP glucuronosyltransferase 1 family, polypeptide A5	Phase II
UGT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10	Phase II
ABCC13	ATP-binding cassette, sub-family C (CFTR/MRP), member 13	Transporter
ARSA	arylsulfatase A	Modifier
CAT	catalase	Modifier
CHST8	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 8	Phase II
CYP19A1	cytochrome P450, family 19, subfamily A, polypeptide 1	Phase I
CYP26C1	cytochrome P450, family 26, subfamily C, polypeptide 1	Phase I
CYP27B1	cytochrome P450, family 27, subfamily B, polypeptide 1	Phase I
CYP2R1	cytochrome P450, family 2, subfamily R, polypeptide 1	Phase I
CYP2S1	cytochrome P450, family 2, subfamily S, polypeptide 1	Phase I
CYP46A1	cytochrome P450, family 46, subfamily A, polypeptide 1	Phase I
CYP4A11	cytochrome P450, family 4, subfamily A, polypeptide 11	Phase I
CYP4F12	cytochrome P450, family 4, subfamily F, polypeptide 12	Phase I
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2	Phase I
CYP4F3	cytochrome P450, family 4, subfamily F, polypeptide 3	Phase I
CYP4F8	cytochrome P450, family 4, subfamily F, polypeptide 8	Phase I
CYP4Z1	cytochrome P450, family 4, subfamily Z, polypeptide 1	Phase I
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1	Phase I
CYP8B1	cytochrome P450, family 8, subfamily B, polypeptide 1	Phase I
DHRS13	dehydrogenase/reductase (SDR family) member 13	Phase I
DHRS2	dehydrogenase/reductase (SDR family) member 2	Phase I
GPX1	glutathione peroxidase 1	Phase I
GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)	Phase I
GPX5	glutathione peroxidase 5 (epididymal androgen-related protein)	Phase I
GPX6	glutathione peroxidase 6 (olfactory)	Phase I
GSS	glutathione synthetase	Phase I
GSTCD	glutathione S-transferase, C-terminal domain containing	Phase II
HNF4A	hepatocyte nuclear factor 4, alpha	Modifier
HNMT	histamine N-methyltransferase	Phase II
HSD11B1	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B11	hydroxysteroid (17-beta) dehydrogenase 11	Phase I
HSD17B14	hydroxysteroid (17-beta) dehydrogenase 14	Phase I

Gene Symbol	Full Gene Name	Class
LOC731356	similar to dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
MGST1	microsomal glutathione S-transferase 1	Phase II
MGST2	microsomal glutathione S-transferase 2	Phase II
MGST3	microsomal glutathione S-transferase 3	Phase II
MPO	myeloperoxidase	Modifier
NOS1	nitric oxide synthase 1 (neuronal)	Phase I
NOS2A	nitric oxide synthase 2A (inducible, hepatocytes)	Phase I
NOS3	nitric oxide synthase 3 (endothelial cell)	Phase I
PPARA	peroxisome proliferator-activated receptor alpha	Modifier
SERPINA7	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 7	Modifier
SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	Transporter
SOD1	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	Modifier
SOD2	superoxide dismutase 2, mitochondrial	Modifier
SOD3	superoxide dismutase 3, extracellular precursor	Modifier
SULF1	sulfatase 1	Phase I
SULT4A1	sulfotransferase family 4A, member 1	Phase II
TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	Transporter
UGT8	UDP glycosyltransferase 8 (UDP-galactose ceramide galactosyltransferase)	Phase II
XDH	xanthine dehydrogenase	Phase I
ADHFE1	alcohol dehydrogenase, iron containing, 1	Phase I
CHST1	carbohydrate (keratan sulfate Gal-6) sulfotransferase 1	Phase II
CHST10	carbohydrate sulfotransferase 10	Phase II
CHST11	carbohydrate (chondroitin 4) sulfotransferase 11	Phase II
CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Phase II
CHST13	carbohydrate (chondroitin 4) sulfotransferase 13	Phase II
CHST2	carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2	Phase II
CHST3	carbohydrate (chondroitin 6) sulfotransferase 3	Phase II
CHST4	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	Phase II
CHST5	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 5	Phase II
CHST6	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	Phase II
CHST7	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 7	Phase II
CHST9	carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9	Phase II
CYP2D7P1	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	Phase I
DDO	D-aspartate oxidase	Phase I

Gene Symbol	Full Gene Name	Class
DHRS1	dehydrogenase/reductase (SDR family) member 1	Phase I
DHRS12	dehydrogenase/reductase (SDR family) member 12	Phase I
DHRS3	dehydrogenase/reductase (SDR family) member 3	Phase I
DHRS4	dehydrogenase/reductase (SDR family) member 4	Phase I
DHRS4L1	dehydrogenase/reductase (SDR family) member 4 like 1	Phase I
DHRS4L2	dehydrogenase/reductase (SDR family) member 4 like 2	Phase I
DHRS7	dehydrogenase/reductase (SDR family) member 7	Phase I
DHRS7B	dehydrogenase/reductase (SDR family) member 7B	Phase I
DHRS7C	dehydrogenase/reductase (SDR family) member 7C	Phase I
DHRS9	dehydrogenase/reductase (SDR family) member 9	Phase I
DHRSX	dehydrogenase/reductase (SDR family) X-linked	Phase I
DPEP1	dipeptidase 1 (renal)	Phase I
FMO6P	flavin containing monooxygenase 6	Phase I
HAGH	hydroxyacylglutathione hydrolase	Phase I
IAPP	islet amyloid polypeptide	Modifier
KCNJ11	potassium inwardly-rectifying channel, subfamily J, member 11	Modifier
LOC728667	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
LOC731931	similar to dehydrogenase/reductase (SDR family) member 2 isoform 1	Phase I
MAT1A	methionine adenosyltransferase I, alpha	Modifier
METAP1	methionyl aminopeptidase 1	Phase I
PDE3A	phosphodiesterase 3A, cGMP-inhibited	Phase I
PDE3B	phosphodiesterase 3B, cGMP-inhibited	Phase I
PLGLB1	plasminogen-like B1	Phase I
ATP7A	ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome)	Modifier
ATP7B	ATPase, Cu++ transporting, beta polypeptide	Modifier
CFTR	cystic fibrosis transmembrane conductance regulator	Modifier

APPENDIX 26 [redacted] DISCOID LUPUS CLASSIFICATION CRITERIA

Instructions:

- The investigator should identify the presence or absence of each candidate morphological characteristic for DLE once at screening visit and a second time at baseline visit.
- The clinical features and the points-based system should be scored according to Table 3 and recorded.
- Assign the appropriate score for each feature that is observed for the participant at the visit. **Only one location score, either the conchal bowl or head and neck can be applied.** Tally up the points to generate a total score.
- Note: A maximum score of 8 points can be given.

Table 3. Final Model for DLE Classification Criteria

Clinical feature	Points assigned[a]
Atrophic scarring	3
Location in the conchal bowl	2
Preference for head and neck	2
Dyspigmentation	1
Follicular hyperkeratosis/plugging	1
Erythematous to violaceous in color	1

Abbreviation: DLE, discoid lupus erythematosus.

[a] A score of ≥5 points yields classification as DLE with 84.1% sensitivity and 75.9% specificity. A score of ≥7 points yields 73.9% sensitivity and 92.9% specificity.

Source: Elman SA, Joyce C, Braudis K, et al. Creation and validation of classification criteria for discoid lupus erythematosus. JAMA Dermatol. 2020 Jun 17;156(8):1-6.

APPENDIX 27 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Revised Protocol 01, 01-Dec-2020

The rationale for the IM011-132 protocol revision 01:

[redacted]

4) An unscheduled visit for participants experiencing flare outside of visit window has been added, along with assessments to be completed at that visit.

In addition, minor clarifications and corrections have been made throughout. This revised protocol also incorporates changes from Administrative Letter 01.

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2, Table 2-2: Placebo-Controlled Treatment Period Outline Up to Week 16; Table 2-3: Active Treatment Period Activities and Assessments (IM011132); Section 4: Table 4-1 Objectives and Endpoints; [redacted]	• [redacted] • DLQI [redacted] Assessments have been removed. • DLQI Appendix replaced [redacted]. • [redacted] Appendix replaced [redacted].	• [redacted] has been replaced [redacted] due to licensing complications. These assessments combined will provide comparable information [redacted] • DLQI has been replaced [redacted] to support qualification of CLASI [redacted].
Section 2, Table 2-2: Placebo-Controlled Treatment Period Outline Up to Week 16; Table 2-3: Active Treatment Period Activities and Assessments (IM011132); [redacted].	• Added that participants [redacted] should come to the site for an unscheduled visit. Details regarding assessments at an unscheduled visit [redacted].	• [redacted] the participant must come to an unscheduled visit for verification of meeting the oral corticosteroid rescue therapy criteria. • •
	[redacted]	
Table 9.2.1: Time Period and Frequency for Collecting AE and SAE Information;	• Revised to reflect collection and follow-up of SARS-CoV-2 events with AE collection.	• Clarified that all AEs related to SARS-CoV-2 should be followed until

Summary of Key Changes for Revised Protocol 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.2.3: Follow-up of AEs and SAEs.		resolution as an SAE or an AE of special interest.
[redacted]		
All	• Minor formatting and typographical corrections.	• Minor, therefore have not been summarized.