Official Protocol Title:	A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-6194 in Adult Participants With Systemic Lupus Erythematosus
NCT number:	NCT06161116
Document Date:	20-Feb-2024

TITLE PAGE

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Protocol Title: A Phase 2a, Multic**enter**, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-6194 in Adult Participants With Systemic Lupus Erythematosus

Protocol Number: 006-02

Compound Number: MK-6194

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	06161116
EU CT	2023-505520-61
EudraCT	Not applicable
JRCT	jRCT2041230137
WHO	Not applicable
UTN	U1111-1291-8716
IND	163334

Approval Date: 20 February 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	20-FEB-2024	This amendment was created to enhance HBV safety monitoring.
Amendment 01	03-OCT-2023	This amendment was created to fulfill a health authority request.
Original Protocol	21-AUG-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

This amendment was created to enhance HBV safety monitoring.

Summary of Changes Table:

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for the Amendment		
Section 8.3.8 HBV, HCV, and HIV Testing	Comprehensive description of HBV testing and test result interpretation was added.	Strategic update to enhance HBV safety monitoring and clarity in the requirements for study entry.

Additional Changes		
Section Number and Name	**Description of Change**	**Brief Rationale**
Title Page	NCT and JRCT numbers were added.	Regulatory agency identifying numbers are now available.
Section 1.3, Schedule of Activities	Day row was added to all subsections of the SoA.	To ensure clarity and avoid scheduling issues.
Section 1.3, Schedule of Activities	Test type of QFT was updated in all subsections of the SoA.	To allow for testing flexibility.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.1, Main Study Schedule of Activities – Week 0 to Week 52	Reference to Section 8.3.8 was added to the HIV, HBV, and HCV testing row.	See rationale for Section 8.3.8.
	A row for HBV-DNA testing was added.	See rationale for Section 8.3.8.
	TB testing note was shortened. Readers are directed to Section 8.3.6 and Section 5.2.	Note directing readers to updated TB testing information.
	Directed physical examination was added to Visit 2.	Inadvertently omitted during original protocol creation.
	Photography note was updated. Readers are directed to Section 8.3.9.	Follow-up photography downgraded to recommended to allow flexibility.
Section 1.3.2, Main Study Schedule of Activities – Week 0 to Week 52 (continued)	A row for HBV-DNA testing was added.	See rationale for Section 8.3.8.
Section 1.3.3 Long-term Extension Schedule of Activities – Week 52 to Week 106	Participant Reminder Log: review/collect was removed from the Week 106 Visit.	Log will not be collected as participants do not return to the clinic on Week 106.
	A row for HBV-DNA testing was added.	See rationale for Section 8.3.8.
Section 5.2, Exclusion Criteria	Added reference to Appendix 7.	To direct readers to country-specific requirements.
	In exclusion criterion #2, the HCV definition was updated, and HBV-DNA testing description was added.	See rationale Section 8.3.8.
	Clarified criterion #14 to indicate that this criterion applies to active or clinically significant infections.	Investigator/site feedback. Updated to ensure clarity.
	Expanded and moved testing guidance from criterion #15 to corresponding information in Section 8.3.6.	Updated for clarity in study entry and to allow for initial TB retesting of participants.

Section Number and Name	Description of Change	Brief Rationale
	Table 2; Country-specific reference was added.	To direct readers to country-specific requirements.
	Corrected reference to immunosuppressant criterion (#7) in criterion #21.	Corrected a protocol inconsistency.
	Clarified that for criterion #23, chronic infection is active.	To provide missing information.
	CCI [redacted]	
Section 6.5.1, Oral Corticosteroids	Non-responder definition was updated for consistency with statistical considerations in Section 9.	To harmonize with other sections of the protocol.
Section 8.3.2, Vital Signs	Added collection of vital signs timing exception.	Corrected a protocol inconsistency.
Section 8.3.6, TB Testing	Added TB testing guidance.	See rationale for Section 5.2 regarding TB testing.
Section 8.3.9, Photography	Initial SLE attributable alopecia events require photographs during the main study. All other photographs are recommended.	See rationale for Section 1.3.1 regarding photography.
Section 9.4.1, Efficacy Analysis Populations	The definition for ITT population was added.	Health authority feedback.
Section 9.5.1, Estimand(s)	Modified intercurrent event #2 to incorporate OCS use due to non SLE reason in the non-responder definition.	Updated for protocol consistency.
Section 9.5.2, Statistical Methods for Efficacy Analyses	Non-responder definition was harmonized with Section 6.5.1.	Updated for protocol consistency.
	The description of an additional sensitivity analysis using the ITT population was included.	See rationale for Section 9.4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 10.1.1, Code of Conduct for Interventional Clinical Trials	EU regulation number was added.	Added for completeness.
Section 10.1.3, Data Protection	Data protection guidelines have been updated.	To align with current regulatory guidance.
Section 10.2, Clinical Laboratory Tests	Note regarding direct Coomb's test not needing to be redrawn was added.	Note was added for flexibility and to ease participant burden.
	Reference to country-specific requirements was added.	To direct readers to country-specific requirements.
Section 10.4.1, Definitions	The definition for constituent part was added.	Added for completeness.
Section 10.7.2, China-specific Requirements	Country-specific SLE medications were added to the table of prohibited medications.	Corrected to align with country-specific list of approved medications.
	Lupus Autoantibody panel and Antiphospholipid panel can now be performed locally if needed.	To provide sites an alternative option to perform these tests.
Section 10.7.4, Japan-specific Requirements	Description of the HBV exclusion criterion was updated to match the global study protocol.	See rationale for Section 8.3.8.
	Section 10.4.1 Definitions were updated	To align with current country-specific guidance.
Section 10.7.5, France-Specific Requirements	Added text that General principles relating to research involving human beings (Art. L. 1121-6, Art L. 1121-8, Art. 1121-8-1) are to be followed.	Health authority feedback.
Section 10.13, TB Risk Factor Assessment Questionnaire	Appendix 13 added to assess TB risk.	See rationale for Section 5.2 regarding TB testing.
Throughout the document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MK-6194 in Adult Participants With Systemic Lupus Erythematosus

Short Title: MK-6194 in Adult Participants with Systemic Lupus Erythematosus

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In adult participants with moderate to severe SLE:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with SRI-4 response at Week 28. H1: At least 1 of the MK-6194 arms is superior to placebo in SRI-4 response at Week 28.	SRI-4 response
To evaluate the safety and tolerability of MK-6194.	-AEs -AEs leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with BICLA response at Week 28. H2: At least 1 of the MK-6194 arms is superior to placebo in BICLA response at Week 28.	BICLA response
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with SRI-4 response at Week 52.	SRI-4 response

To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with BICLA response at Week 52.	BICLA response
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with a CLASI activity score ≥8 at baseline achieving a CLASI-50 response at Weeks 28 and 52, respectively.	CLASI response, defined as a decrease of ≥50% from baseline CLASI activity score
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the change from baseline on 28 joint count in participants with ≥3 swollen joints at baseline, participants with ≥3 tender joints at baseline, and ≥3 tender and swollen joints at baseline at Weeks 28 and 52, respectively.	-Swollen joint count -Tender joint count -Tender and swollen joint count
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the change from baseline in corticosteroid dose at Weeks 28 and 52, respectively.	Corticosteroid dose reduction
To evaluate the efficacy of MK-6194 compared to placebo as assessed by cumulative oral corticosteroid use at Weeks 28 and 52, respectively.	Cumulative corticosteroid use
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants who achieve LLDAS at Week 28 and Week 52, respectively.	LLDAS

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Systemic lupus erythematosus
Population	Adult participants with moderate to severe SLE
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Sponsor
	Investigator
	Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3.5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. Participants will take part in the study for approximately 110 weeks. See Appendix 7 for country-specific requirements.

Number of Participants:

Approximately 270 participants will be randomized.

Intervention Groups and Duration:

Other current or former name or alias for the study intervention is as follows: PT101.

Total Number of Intervention Groups/Arms	3
Duration of Participation	After a Screening period of up to 6 weeks, each participant will receive study intervention for approximately 104 weeks (52 week double-blind Main study + 52 week double-blind Long-term Extension) followed by a safety follow-up telephone call approximately 28 days after the last study intervention is administered.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Disease Activity Adjudication Group	Yes

Study governance considerations are outlined in Appendix 1.

Study Accepts Healthy Participants:

No

A list of abbreviations is in Appendix 14.

1.2 Schema

The study design is depicted in Figure 1 and Figure 2.

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[redacted]

1.3 Schedule of Activities

1.3.1 Main Study Schedule of Activities – Week 0 to Week 52

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**													**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
Administrative procedures															
Informed consent	X														
Informed consent for FBR	X														FBR consent is optional. See Appendix 7 for country-specific requirements.
IRT visit registration	X	X		X	X		X	X		X	X	X		X	
Medical history	X														
Prior/concomitant medications	X	X		X	X	X	X	X		X	X	X	X	X	
Inclusion/exclusion criteria	X	X													
Participant identification card	X	X													Add Randomization number to card at Visit 2.
IRT randomization		X													Affirmation from DAAG required prior to Randomization. Sections 5.1 and 10.1.4.3.
Study intervention: dispense/return		X		X	X		X	X		X	X	X		X	Dispense at Wks 2 to 28, return at all visits. Assess compliance of returned syringe(s).

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**													**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
CCI [redacted]															
Participant Reminder Log: train/dispense		X		X	X		X	X		X	X	X		X	For recording study intervention administration, any complaints/illnesses, and new medications taken between visits
Participant Reminder Log: review/collect				X	X	X	X	X		X	X	X	X	X	Review for accuracy (verbal review at TCs)
Participant reminder telephone call						X							X		Additional dosing reminders as necessary per site.
Efficacy Procedures															Complete PROs in order listed before laboratory tests or other efficacy or safety procedures. Preferable for same rater to perform ClinROs per participant across visits.
CCI [redacted]															
Hybrid SLEDAI	X	X			X		X	X		X	X	X		X	

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**													**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
BILAG-2004	X	X			X		X	X		X	X	X		X	Collect historical BILAG-2004 at Screening
CCI															
PGA	X	X			X		X	X		X	X	X		X	May be amended once lab results from associated visit are available.
CLASI	X	X			X		X	X		X	X	X		X	
28 Joint Count	X	X			X		X	X		X	X	X		X	
CCI															
Safety Procedures															
Height	X														
Weight	X	X			X		X	X		X	X	X		X	
Vital signs (temperature, HR, and BP)	X*	X*		X	X		X	X		X	X	X		X*	Taken after completion of PROs and before blood samples collections *RR will also be collected at these visits
Full physical examination	X													X	
Directed physical examination		X		X	X		X	X		X	X	X			Per institutional standards
12-lead ECG	X													X	Locally read.
Chemistry	X	X			X		X	X		X	X	X		X	
Hematology	X	X		X	X		X	X		X	X	X		X	
Urinalysis (with microscopy)	X	X			X		X	X		X	X	X		X	
Urine protein/creatinine	X	X			X		X	X		X	X	X		X	

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**													**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
Direct Coomb's test	X	X			X		X	X		X	X	X		X	
Serum pregnancy test (hCG, POCBP only)	X														
FSH (PONCBP only)	X														To confirm postmenopausal state. See Section 10.5.1.
Local urine pregnancy test (POCBP only)		X			X		X	X		X	X	X		X	Performed pre-dose. If urine test cannot be confirmed as negative (eg, ambiguous result), serum test is required. See Appendix 7 for country-specific requirements.
HIV, HBV, and HCV testing	X														See Section 8.3.8 to determine if further testing is needed. See Appendix 7 for country-specific requirements.
HBV-DNA testing	X							X				X			Only for participants with positive HBcAb at Screening and for HBV-DNA <LLOQ.
TB testing	X														QFT or equivalent. See Section 8.3.6 and Section 5.2 (criterion #15).
Chest x-ray	X														Posterior-anterior chest x-ray. Locally read. See Appendix 7 for country-specific requirements.
AE/SAE review	X	X		X	X	X	X	X		X	X	X	X	X	

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**													**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
Photography	X	X						X						X	For SLE attributable rash and/or alopecia through resolution or timepoints noted; whichever occurs first. See recommendations/ requirements in Section 8.3.9.
Anti-dsDNA and complement panel (C3, C4)	X	X			X		X	X		X	X	X		X	
Lupus autoantibody panel and antiphospholipid panel	X														
PK/PD/Biomarkers (All Participants)															
Blood for serum ADA		X		X	X			X						X	Samples for ADA and PK should be drawn at the same time pre-dose.
Blood for serum PK		X	X	X	X			X	X					X	Samples for ADA and PK should be drawn at the same time pre-dose. Visit 3: 24h after Visit 2 dose (± 12h) Visit 8: 24h after Visit 7 dose (± 12h).
Blood for genetic analysis		X													Pre-dose from randomized participants only. See Section 8.8. See Appendix 7 for country-specific requirements.
Blood for DNA analysis		X			X			X						X	Leftover sample will be stored for FBR. See Section 8.9. See Appendix 7 for country-specific requirements.

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**													**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
Blood for immunophenotyping	X				X			X						X	For Subpopulation participants, samples must be shipped on same day of collection. See Section 8.7.2.
Blood for serum biomarkers analysis		X			X			X						X	Leftover sample will be stored for FBR. See Section 8.9. See Appendix 7 for country-specific requirements.
Blood for RNA analysis		X						X						X	Leftover sample will be stored for FBR. See Section 8.9. See Appendix 7 for country-specific requirements.

ADA=antidrug antibodies; AE= adverse event(s); BILAG= British Isles Lupus Assessment Group; BP= blood pressure; CLASI= Cutaneous Lupus Erythematosus Disease Area and Severity Index; ClinROs= clinician-reported outcomes; d= day(s); DAAG= Disease Activity Adjudication Group; Discon= discontinuation; DNA=deoxyribonucleic acid; dsDNA=double strand DNA; ECG= electrocardiogram; CCI [redacted] CCI [redacted] FBR= future biomedical research; FSH= follicle-stimulating hormone; HBcAb= hepatitis B core antibody; HBV= hepatitis B virus; hCG= human chorionic gonadotropin; HCV= hepatitis C virus; HIV= human immunodeficiency virus; HR= heart rate; IRT= interactive response technology; LLOQ= lower limit of quantitation; CCI [redacted]; PD= pharmacodynamics; PGA= physician's global assessment; PK= pharmacokinetics; POCBP= participant of childbearing potential; PONCBP= participant of not childbearing potential; PRO= patient-reported outcome; QFT= QuantiFERON®-TB Test; CCI [redacted]; Rand=randomization; RNA= ribonucleic acid; RR= respiratory rate; SAE= serious adverse event(s); SC= subcutaneous; SELENA= Safety of Estrogens in Lupus Erythematosus National Assessment; CCI [redacted]; SLE=systemic lupus erythematosus; SLEDAI= SLE Disease Activity Index; CCI [redacted]; TB= tuberculosis; TC= telephone call; Wk(s)= Week(s).

1.3.2 Main Study Schedule of Activities – Week 0 to Week 52 (continued)

Study Period:	**Main Study Double-blind Treatment Period**						**Discon**	**Notes**
Visit Number/Title:	**13**	**14**	**15**	**16**	**17**	**18[a]**		
Week	32	36	40	44	48	52		
Day	225	253	281	309	337	365		
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d		
Administrative procedures								
IRT visit registration	X	X	X	X	X		X	
Prior/concomitant medication review	X	X	X	X	X	X	X	
Study intervention: dispense/return	X	X	X	X	X	X	X	Dispense at Wks 32 to 48, return at all visits. Assess compliance of returned syringe(s).
Participant Reminder Log: train/dispense	X	X	X	X	X			For recording study intervention administration, any complaints/illnesses, and new medications taken between visits
Participant Reminder Log: review/collect	X	X	X	X	X	X	X	Review for accuracy
Efficacy Procedures								Complete PROs in order listed before lab tests or other efficacy or safety procedures. Preferable for same rater to perform ClinROs per participant across Visits.
CCI [redacted]								
Hybrid SLEDAI	X	X	X	X	X	X	X	
BILAG-2004	X	X	X	X	X	X	X	
CCI [redacted]								
PGA	X	X	X	X	X	X	X	May be amended once lab results from associated visit are available.
CLASI	X	X	X	X	X	X	X	
28 Joint Count	X	X	X	X	X	X	X	
CCI [redacted]								
Safety Procedures								
Weight	X	X	X	X	X	X	X	
Vital signs (temperature, HR, and BP)	X	X	X	X	X	X*	X	Taken after completion of PROs and before blood samples collections *RR will also be collected at this visit
Full physical examination						X	X	

Study Period:	**Main Study Double-blind Treatment Period**						**Discon**	**Notes**
Visit Number/Title:	**13**	**14**	**15**	**16**	**17**	**18[a]**		
Week	32	36	40	44	48	52		
Day	225	253	281	309	337	365		
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d		
Directed physical examination	X	X	X	X	X			Per institutional standards
12-lead ECG						X	X	Locally read.
Chemistry	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Direct Coomb's test	X	X	X	X	X	X	X	
Urinalysis (with microscopy)	X	X	X	X	X	X	X	
Urine protein/creatinine	X	X	X	X	X	X	X	
Local urine pregnancy test (POCBP only)	X	X	X	X	X		X	Performed pre-dose. If urine test cannot be confirmed as negative (eg, ambiguous result), serum test is required. See Appendix 7 for country-specific requirements.
HBV-DNA testing		X			X		X	Only for participants with positive HBcAb and HBV-DNA <LLOQ.
AE/SAE review	X	X	X	X	X	X	X	
Photography						X	X	
Anti-dsDNA and complement panel (C3, C4)	X	X	X	X	X	X	X	
PK/PD/Biomarkers (All Participants)								
Blood for serum ADA						X	X	Samples for ADA and PK should be drawn at the same time prior to dose intervention administration.
Blood for serum PK						X	X	
Blood for DNA analysis						X	X	Leftover sample will be stored for FBR (Section 8.9). See Appendix 7 for country-specific requirements.
Blood for immunophenotyping						X	X	For Subpopulation participants, samples must be shipped on same day of collection. See Section 8.7.2.
Blood for serum biomarkers analysis						X	X	Leftover sample will be stored for FBR (Section 8.9). See Appendix 7 for country-specific requirements.
Blood for RNA analysis						X	X	Leftover sample will be stored for FBR (Section 8.9). See Appendix 7 for country-specific requirements.

Study Period:	Main Study Double-blind Treatment Period						Discon	Notes
Visit Number/Title:	**13**	**14**	**15**	**16**	**17**	**18[a]**		
Week	32	36	40	44	48	52		
Day	225	253	281	309	337	365		
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d		

ADA= antidrug antibodies; AE= adverse event(s); BILAG= British Isles Lupus Assessment Group; BP= blood pressure; CLASI= Cutaneous Lupus Erythematosus Disease Area and Severity Index; d= day(s); ClinROs= clinician-reported outcomes; Discon= discontinuation; DNA=deoxyribonucleic acid; dsDNA=double strand DNA; CCI [redacted] FBR= future biomedical research; HBcAb= hepatitis B core antibody; HBV= hepatitis B virus; HR= heart rate; IRT= interactive response technology; LLOQ= lower limit of quantitation; CCI [redacted] PD= pharmacodynamics; PGA= physician's global assessment; PK= pharmacokinetics; POCBP= participant of childbearing potential; PRO= patient reported outcome; CCI [redacted] RNA= ribonucleic acid; RR= respiratory rate; SAE= serious adverse event(s); SC= subcutaneous; SELENA= Safety of Estrogens in Lupus Erythematosus National Assessment; CCI [redacted]; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index; CCI [redacted]; Wk(s)= Week(s).

(a) Procedures for the long-term extension portion of this visit are in Section 1.3.3.

1.3.3 Long-term Extension Schedule of Activities – Week 52 to Week 106

Study Period	**Double-blind Long-term Extension Treatment Period**									**Disc on**	**FU**	**Notes**
Visit Number/Title:	**18[a]**	**19**	**20**	**21**	**22**	**23**	**24**	**TC**	**25**		**TC**	
Week	52	54	56	60	64	76	90	102	104		106	
Day	365	379	393	421	449	533	631	715	729		743	
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±3d	±7d		+7d	
Administrative procedures												
Prior/concomitant medication review		X	X	X	X	X	X	X	X	X	X	
IRT visit registration	X	X	X	X	X	X	X		X	X		
IRT rerandomization	X											
Collect participant identification card from Main study period	X											
New participant identification card	X											Add new randomization number to card. See Section 8.1.3.
Study intervention: dispense/return	X	X	X	X	X	X	X		X	X		Dispense at Wks 52 to 90, return at all visits. Assess compliance of returned syringe(s).
Participant Reminder Log: train/dispense	X	X	X	X	X	X	X					For recording study intervention administration, any complaints/illnesses, and new medications taken between visits
Participant Reminder Log: review/collect		X	X	X	X	X	X	X	X	X		Review for accuracy (verbal review at TCs)
Dosing reminder telephone call								X				Last dose administered at Week 102. Additional reminders as necessary per site.
Efficacy Procedures												Complete PROs in order listed before lab tests or other efficacy or safety procedures. Preferable for same rater to perform ClinROs per participant across Visits.
CCI [redacted]												
Hybrid SLEDAI					X	X	X		X	X		
BILAG-2004					X	X	X		X	X		
CCI [redacted]												
PGA					X	X	X		X	X		May be amended once lab results from associated visit are available.
CLASI					X	X	X		X	X		

Study Period	Double-blind Long-term Extension Treatment Period									Disc on	FU	Notes
Visit Number/Title:	**18[a]**	**19**	**20**	**21**	**22**	**23**	**24**	**TC**	**25**		**TC**	
Week	52	54	56	60	64	76	90	102	104		106	
Day	365	379	393	421	449	533	631	715	729		743	
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±3d	±7d		+7d	
28 Joint Count					X	X	X		X	X		
CCI												
Safety Procedures												
Weight					X	X	X		X	X		
Vital signs (temperature, HR, and BP)		X	X	X	X	X	X		X	X		Taken after completion of PROs and before blood samples collection.
Full physical examination									X	X		
Directed physical examination		X	X	X	X	X	X					Per institutional standards
Chemistry			X	X	X	X	X		X	X		
Hematology		X	X	X	X	X	X		X	X		
Direct Coomb's test					X	X	X		X	X		
Urinalysis (with microscopy)			X		X	X	X		X	X		
Urine protein/creatinine					X	X	X		X	X		
TB testing	X											QFT or equivalent except for participants who tested positive at Screening
Local urine pregnancy test (POCBP only)	X		X	X	X	X	X		X	X		Performed pre-dose. If urine test cannot be confirmed as negative (eg, ambiguous result), serum test is required. See Appendix 7 for country-specific requirements.
HBV-DNA testing			X		X	X	X		X	X		Only for participants with positive HBcAb and HBV-DNA <LLOQ.
AE/SAE review		X	X	X	X	X	X	X	X	X	X	
Anti-dsDNA and complement panel (C3, C4)					X	X	X		X	X		
PK/PD/Biomarkers (All Participants)												
Blood for serum ADA									X	X		Samples for ADA and PK should be drawn at the same time pre-dose.
Blood for serum PK									X	X		
Blood serum for DNA analysis					X				X	X		Leftover sample will be stored for FBR. See Section 8.9. See Appendix 7 for country-specific requirements.
Blood serum for biomarker analysis					X				X	X		Leftover sample will be stored for FBR. See Section 8.9. See Appendix 7 for country-specific requirements.

Study Period	Double-blind Long-term Extension Treatment Period									Discon	FU	Notes
Visit Number/Title:	**18[a]**	**19**	**20**	**21**	**22**	**23**	**24**	**TC**	**25**		**TC**	
Week	52	54	56	60	64	76	90	102	104		106	
Day	365	379	393	421	449	533	631	715	729		743	
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±3d	±7d		+7d	
Blood serum for RNA analysis					X				X	X		Leftover sample will be stored for FBR. See Section 8.9. See Appendix 7 for country-specific requirements.

ADA= antidrug antibodies; AE= adverse event(s); BILAG= British Isles Lupus Assessment Group; BP= blood pressure; CLASI= Cutaneous Lupus Erythematosus Disease Area and Severity Index; ClinROs= clinician-reported outcomes; d= day(s); DAAG= Disease Activity Adjudication Group; Discon= discontinuation; DNA=deoxyribonucleic acid; dsDNA= double strand DNA; CCI CCI FBR= future biomedical research; FU= follow-up; HBcAb= hepatitis B core antibody; HBV= hepatitis B virus; HR= heart rate; IRT= interactive response technology; LLOQ= lower limit of quantitation; CCI ; PD= pharmacodynamics; PGA= physician's global assessment; PK= pharmacokinetics; POCBP= participant of childbearing potential; PRO= patient reported outcome; QFT= QuantiFERON-TB Test; CCI RNA= ribonucleic acid; SAE= serious adverse event(s); SC= subcutaneous; SELENA= Safety of Estrogens in Lupus Erythematosus National Assessment; CCI ; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR DI= Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; TB= tuberculosis; TC= telephone call; Wk= Week(s).

(a) Procedures for the Main study portion of this visit are in Section 1.3.2.

1.3.4 PK/PD/Biomarkers Subpopulation Schedule of Activities (for selected sites only)

Study Period:	**PK/PD/Biomarkers Subpopulation: Additional Samples[a]**								**Notes**
Visit Number/Title:	**1**	**2 Rand**	**3A**	**7**	**8A**	**11A**	**17A**	**Discon**	
		Wk 0	Day 8 Wk 1	Wk 12	Wk 13	Wk 25	Wk 49		
Day		1	8	85	92	176	344		
Scheduled Days		Day 1	7 days post Day 1 dose		7 days post Wk 12 dose	7 days post Wk 24 dose	7 days post Wk 48 dose		
Recommended Window:			±1d	±7d	±1d	±1d	±1d		
Informed Consent for additional PK/PD/Biomarker samples in Subpopulation	X								
WBC with differential			X		X	X	X		
Blood for serum PK		X*	X	X*	X	X	X		*Visit 2 or 7: 2h to 10h post dose. See Section 8.10.4.
Blood for immunophenotyping		X	X		X	X	X		Ship samples on the same day of collection.
Blood for DNA analysis			X		X	X	X		Leftover sample will be stored for FBR (Sec 8.9)
Blood for serum biomarkers analysis			X		X	X	X		Leftover sample will be stored for FBR (Sec 8.9)
Blood for RNA analysis			X		X	X	X		Leftover sample will be stored for FBR (Sec 8.9)
Blood for PBMC		X			X	X	X	X	Leftover sample will be stored for FBR (Sec 8.9).

d= day(s); Discon= discontinuation; DNA= deoxyribonucleic acid; FBR= future biomedical research; PBMC= peripheral blood mononuclear cells; PD= pharmacodynamics; PK= pharmacokinetics; Rand= randomization; RNA= ribonucleic acid; Sec= Section; SoA=schedule of activities; WBC= white blood cell; Wk= week.

(a) For participants at pre-selected sites (determined by operational feasibility of site for sample processing) who consent for additional PK/PD/Biomarker samples (ie, the Subpopulation) in **addition** to the activities listed in the Main study SoAs (Sections 1.3.1 and 1.3.2) for all study participants.

See Appendix 7 for country-specific requirements.

2 INTRODUCTION

2.1 Study Rationale

Human autoimmune disease results, in part, from dysfunctional or insufficient numbers of Tregs that are unable to properly restrict immune responses, resulting in inflammation and organ damage [Kolios, A. G. A., et al 2021]. MK-6194 is a novel IL-2 mutein that selectively expands regulatory T cells, without activating cytotoxic immune cell counterparts. This mechanism offers a unique opportunity to rebalance the dysregulated immune responses of patients with a wide range of autoimmune disease including SLE.

SLE is a progressive chronic autoimmune disease with highly heterogeneous manifestations and a large degree of variability in disease activity and organ system involvement. The peak age of onset is between 15 to 44 years of age. It affects both adults and children, yet it impacts women at higher ratios than men, and it is more common in people of African or Latin American ancestry [Fanouriakis, A., et al 2021] [Petri, M. 2002]. The disease can be mild and go undiagnosed or it can be severe and life-threatening. It can affect any part of the body, leading to pain, swelling, and irreversible organ damage. It is characterized by flares, spontaneous remission, and relapses. The pathophysiology of SLE is complex. It involves a range of genetic and environmental factors which can be influenced by hormonal milieu, the hypothalamic-pituitary-adrenal axis, and defective immune regulation [Mok, C. C. and Lau, C. S. 2003].

Effective treatments for SLE are difficult to achieve due to its complex underlying pathophysiology and the heterogeneous manifestations of the disease. Therapies include long-term use of corticosteroids and/or other immunosuppressive medications. The only FDA approved therapies for SLE since 1955 include belimumab (2011) and anifrolumab (2021), and off-label treatments are widely used. Additionally, belimumab (2020) and voclosporin (2021) were recently approved for lupus nephritis.

While the underlying pathophysiology driving SLE disease activity is complex and multifactorial, multiple lines of evidence indicate that Tregs in SLE are dysfunctional and inadequate to suppress ongoing inflammation. To counteract this dysfunction, expansion and activation of Tregs using repeated administration of low doses of IL-2 has shown preliminary evidence of clinical efficacy in open-label and proof-of-concept studies in SLE patients[He, J., et al 2016] [Rosenzwajg, M., et al 2019], in addition to a variety of other autoimmune diseases [Castela, E., et al 2014] [Koreth, J., et al 2011] [Saadoun, D., et al 2011] [Hartemann, A., et al 2013] [Rosenzwajg, M., et al 2015]. Two separate placebo-controlled studies in SLE patients demonstrated that a greater proportion of patients achieved SRI-4 responses after treatment with low-dose IL-2 resulting in Treg expansion, compared with placebo.

This study will include several tools to assess global and organ-specific disease activity, quality of life, and AEs, to holistically assess SLE disease activity and response to MK-6194 treatment. The primary objectives of this Phase 2a study are to evaluate the efficacy of MK-6194 CCI [redacted] compared to placebo as assessed by SRI-4 response in adult participants with moderate to severe SLE at Week 28 and to evaluate the safety and

tolerability of MK-6194. The key secondary objective is to evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with BICLA response at Week 28.

2.2 Background

Refer to the IB for detailed background information on MK-6194.

2.2.1 Pharmaceutical and Therapeutic Background

Autoimmune and inflammatory diseases result from disrupted immune homeostasis and inappropriate immune activity, often driven by activated immune cells. Tregs attenuate inflammatory processes by a variety of mechanisms that suppress the activity of activated immune cells [Klatzmann, D. and Abbas, A. K. 2015]. Expansion of Tregs using repeated administration of low doses of IL-2 has shown preliminary evidence of clinical efficacy in small proof-of-concept studies in participants with a variety of autoimmune diseases [Castela, E., et al 2014] [Hartemann, A., et al 2013] [He, J., et al 2016a] [Koreth, J., et al 2011] [Rosenzwajg, M., et al 2015] [Rosenzwajg, M., et al 2019] [Saadoun, D., et al 2011].

MK-6194 is a recombinant IL-2M fused at its CCI [redacted] IgG1 Fc domain. Compared with wild-type human IL-2, the modified IL-2M component of MK-6194 contains mutations that increase the binding affinity for the IL-2Rα subunit (CD25) and reduce the binding affinity for the IL-2Rβ subunit (CD122). Collectively, these mutations lead to MK-6194 selectively activating Tregs over other cell types, including CD4+ Tconv, CD8, and NK cells.

2.2.2 Preclinical and Completed Clinical Studies

After a single dose administration of MK-6194 to healthy adults, the geometric mean half-life of MK-6194 ranged from CCI [redacted]. MK-6194 exposure CCI [redacted]

After administration of a single dose of MK-6194 to healthy adults, CCI [redacted]

Refer to the IB for detailed preclinical and clinical information on MK-6194.

2.2.3 Ongoing Clinical Studies

The current ongoing clinical studies in the MK-6194 development program include 5 Phase 1 studies: CCI [redacted]

Preliminary blinded safety data from these studies indicate that MK-6194 has been generally well tolerated to date.

Refer to the IB for more information on MK-6194.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from study participation, as clinical studies are designed to provide information about the safety and efficacy of an investigational medicine.

MK-6194 administered subcutaneously appears to be generally well tolerated in the completed and ongoing Phase 1 clinical CCI [redacted] The number of participants exposed to multiple doses of MK-6194 over several weeks is continuously increasing due to the ongoing clinical development across several indications. The most frequently reported AEs are CCI [redacted]

The benefit/risk assessment for MK-6194 is considered favorable for its evaluation as a potential treatment of SLE.

Additional details are provided in the IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In adult participants with moderate to severe SLE:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with SRI-4 response at Week 28. H1: At least 1 of the MK-6194 arms is superior to placebo in SRI-4 response at Week 28.	SRI-4 response
To evaluate the safety and tolerability of MK-6194.	-AEs -AEs leading to discontinuation of study intervention
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with BICLA response at Week 28. H2: At least 1 of the MK-6194 arms is superior to placebo in BICLA response at Week 28.	BICLA response
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with SRI-4 response at Week 52.	SRI-4 response
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with BICLA response at Week 52.	BICLA response
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants with a CLASI activity score ≥8 at baseline achieving a CLASI-50 response at Weeks 28 and 52, respectively.	CLASI response, defined as a decrease of ≥50% from baseline CLASI activity score

To evaluate the efficacy of MK-6194 compared to placebo as assessed by the change from baseline on 28 joint count in participants with ≥3 swollen joints at baseline, participants with ≥3 tender joints at baseline, and ≥3 tender and swollen joints at baseline at Weeks 28 and 52, respectively.	-Swollen joint count -Tender joint count -Tender and swollen joint count
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the change from baseline in corticosteroid dose at Weeks 28 and 52, respectively.	Corticosteroid dose reduction
To evaluate the efficacy of MK-6194 compared to placebo as assessed by cumulative oral corticosteroid use at Weeks 28 and 52, respectively.	Cumulative corticosteroid use
To evaluate the efficacy of MK-6194 compared to placebo as assessed by the proportion of participants who achieve LLDAS at Week 28 and Week 52, respectively.	LLDAS
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

CCI [redacted]	
To evaluate the efficacy of MK-6194 compared to placebo upon immunologic parameters of disease activity change from baseline over time.	Anti-dsDNA, C3, and C4
To evaluate the PK of MK-6194 in participants with SLE.	MK-6194 serum PK: Cmax and Ctrough concentrations
To assess the ADA response to MK-6194 following multiple subcutaneous administrations of MK-6194.	ADA
To evaluate the PD of MK-6194 over time.	Assessment of Tregs and other peripheral immune cells.

To identify molecular biomarkers that may be indicative of clinical response, resistance, PD activity and/or the mechanism of action of MK-6194.	Blood derived biomarker parameters that may include but are not limited to DNA, RNA, and protein-based analyses.
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanism of disease. Variation across the human genome may be analyzed for association with clinical data collected.	Germline genetic variation and association to clinical data collected in this study.
CCI	[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, placebo-controlled, parallel-group, double-blind study of MK-6194 in adult participants with moderate to severe SLE. This study is designed to evaluate the efficacy and safety of CCI MK-6194 administered subcutaneously CCI with a primary efficacy endpoint of the proportion of participants who achieve an SRI-4 response at Week 28.

The study consists of a Screening period (up to 6 weeks), double-blind Main study (52 weeks), and double-blind Long-term Extension (52 weeks).

Screening

During the Screening period of up to 6 weeks, participants will be assessed for eligibility against the inclusion and exclusion criteria. Participants diagnosed with SLE at least 6 months prior to Screening (and confirmed at Screening per the EULAR/ACR 2019 classification) with active SLE involving skin and/or joints, and receiving at least 1 background therapy, are eligible to screen for the study. Participants must not be randomized until the CCI activity assessed by the investigator have satisfied the SLE entry criteria (Section 10.1.4.3) and there are no known clinical and/or administrative issues that would preclude participant randomization.

Main Study

Approximately 270 participants (90 per arm) will be randomized at Visit 2 to the Main study double-blind treatment period in a 1:1:1 ratio to receive CCI MK-6194 CCI CCI MK-6194 CCI or placebo in a double-dummy fashion. The study will be stratified by hybrid SLEDAI score at Screening, oral corticosteroid dose at Randomization, and geographic region (Section 6.3.2). Participants will take part in the Main study for approximately 52 weeks unless the participant withdraws from the study (Section 7.2). CCI

At Randomization (Visit 2), study sites will train participants/caregivers to self-administer/administer study intervention using a prefilled syringe (see Appendix 7 for country-specific requirements). CCI Telephone calls are required at approximately Week 6 and Week 26 to review concomitant medications, participant reminder logs, assess for AEs/SAEs, and to remind participants of at home dosing requirements. In addition, visits to collect only PK samples will occur the day after randomization and the day after the Week 12 visit.

During the Main study, participants on OCS will undergo periods of OCS stability and OCS taper with the goal to reduce the OCS dose to ≤7.5 mg/day by Week 20 (Section 6.5.1). After Randomization, the DAAG will review each participant's OCS dosing to affirm the protocol

required OCS taper is being considered and continue to review SLE disease activity scoring to affirm assessments performed by the investigator were consistently and appropriately conducted according to the protocol and established clinical measure guidance/instructions at individual visits and across visits. DAAG responsibilities are summarized in Section 10.1.4.3 and will be fully described in the DAAG charter.

eDMC and IA

An eDMC (Section 10.1.4.2) will be utilized during the study to periodically monitor unblinded safety data as well as to review results from a planned futility IA (Section 9.6). The IA will be performed when approximately 50% of randomized participants complete Week 28 or discontinue before Week 28. If futility criteria are met at the IA in both treatment arms, the study will stop early. If futility criteria are met for 1 treatment arm, further enrollment into this arm may be stopped provided enrollment is ongoing in the Main study. If the study is not stopped for futility, the study will continue until all participants complete the safety follow-up telephone call after the last dose of study intervention in the LTE or discontinue. A full description of the eDMC responsibilities will be provided in the eDMC Charter.

After the Week 28 primary endpoint assessment is complete, a study sub-team will be unblinded in order to perform and review the full analysis of data. A separate, blinded study sub-team (ie, blinded to participant-level intervention assignment) will then be assigned to continue the conduct of the study (Section 9.1).

Long-term Extension

Participants who complete the Main study on study intervention will enter the 52-week double-blind LTE. The LTE will begin at Week 52 and will last approximately 52 weeks unless the participant withdraws from the study (Section 7.2). Participants who were randomized to receive placebo during the Main study will be rerandomized in a 1:1 ratio to receive [redacted] MK-6194 [redacted] (Section 4.3) and will receive a new randomization number. Participants who were assigned [redacted] MK-6194 [redacted] during the Main study will also receive new randomization numbers but will continue the same regimen during the LTE. Study visits will take place every 2 to 4 weeks during the first 3 months, followed by study visits every 12 to 14 weeks until the end of the LTE.

If 1 treatment arm is determined to be futile at the IA, participants in that treatment arm completing the Main study will be switched to the non-futile arm for the LTE. When the Week 28 primary endpoint analysis is completed and reviewed, if a treatment arm is found to be sub-efficacious based on evaluation by the Sponsor, participants who are already part of the sub-efficacious arm may continue through the end of the treatment period, but there may be no new enrollment to the sub-efficacious arm in the LTE based upon recommendation from the Sponsor (Section 9.6). Participants who are still part of the sub-efficacious arm in the Main study will finish the Main study as randomized but may be part of the efficacious arm in the LTE.

Participants will receive the last dose of study intervention at approximately Week 102, followed by an on-site visit approximately 2 weeks later (Week 104 – no study intervention

administered) and a safety follow-up telephone contact at least 4 weeks after the last dose of study intervention, at approximately Week 106.

Throughout the Study (Main and LTE)

Physical examinations, vital signs measurements, clinical laboratory evaluations, PROs administration, and PK, PD, and biomarker sampling will be required for all participants at selected times during the Main study and LTE. Prior and concomitant therapy requirements are described in Sections 5.1, 5.2, 6.5, and Appendix 9. The Sponsor will provide continuous blinded medical monitoring of AEs, laboratory results, and adherence to the study protocol during the study.

Supplemental PK/PD/Biomarker sparse sampling will be collected in a subset of participants at pre-selected sites (approximately 15 participants per arm) to provide additional PK and PD measurements, allowing a more comprehensive characterization of the PK-PD relationship of MK-6194 (see Appendix 7 for country-specific requirements). Additional PD and biomarker samples will be collected to enable Treg and other biomarker assessments at more timepoints, to allow better understanding of PD and biomarker responses to MK-6194 in participants with SLE (Section 8.1.13).

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

Clinical site personnel and participants will remain blinded to study treatment until the LTE is complete.

4.2 Scientific Rationale for Study Design

This Phase 2a study will evaluate the efficacy, safety, and tolerability of MK-6194 in the treatment of SLE. The study will test the hypothesis that at least 1 of the MK-6194 arms is superior to placebo in the primary endpoint of percentage of participants with SRI-4 response at Week 28.

The study will use the double-blind, placebo-controlled, parallel-group design in the assessment of MK-6194 to minimize potential bias and improve reliability of the results. During the study, all participants will remain on any background therapy not prohibited in the study (Section 6.5, Appendix 9).

The primary efficacy endpoint was chosen to be at Week 28 to allow for sufficient duration to reliably assess the efficacy of MK-6194 in SLE. This duration is consistent with other recent studies in SLE. The Main study will continue to Week 52 to assess the durability of any treatment benefit. The 52-week LTE allows for collection of additional efficacy and safety data in the participants originally randomized to the placebo arm during the Main study period, as well as additional efficacy and safety data with longer treatment in the participants originally randomized to MK-6194.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Hybrid SLEDAI

The SELENA-SLEDAI tool is used to assess the current state of disease activity (within approximately the last 28 days) in patients with SLE and to determine global improvement (clinical and laboratory). This tool assigns weighted scores for 24 clinical and laboratory findings based upon their presence or absence. The hybrid SLEDAI is a modified version of the SELENA-SLEDAI tool which utilizes the proteinuria definition from the SLEDAI-2K tool. A patient's total score can be between 0 and 105, with the higher score representing a higher degree of disease activity.

Scoring:

- 0= No activity
- 1-5= mild activity
- 6-10= moderate activity
- 11-19= high activity
- ≥20= very high activity

BILAG-2004

The BILAG 2004 index is a tool for measuring SLE clinical disease activity based upon the principle of the physician's intention to treat [Isenberg, D. A., et al 2005]. It evaluates disease activity in the past 4 weeks compared to the previous 4 weeks for 9 individual organ systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological) by a graded score of severity and physician's perceived seriousness of disease manifestation [Ohmura, K. 2021].

Scoring:

- A= Very active disease
- B= Patient needs an increase in treatment
- C= Stable or mild disease requiring only symptomatic therapy
- D= Previous organ involvement but no current disease activity
- E= No current disease activity, system has never been involved

The BILAG index records each item as new, same, worse, or improving on each organ system as well as a global score helping to assess the efficacy of study intervention.

PGA

The PGA is a continuous visual analog scale (100 mm) which scores overall disease activity with anchors from 0 to 3 (0= none, 1= mild, 2=moderate, 3= severe) in approximately the last 28 days. Evaluations are performed by an attending physician and takes fatigue into account [Ohmura, K. 2021]. Since PGA scoring takes into account common clinical laboratory parameters necessary to rate specific organ disease activity (such as urinalysis, serum creatinine level, and blood cell count), it may be amended, if needed, after laboratory results are available.

SRI-4 Response

The SRI is a composite index used to assess clinical improvement in patients with SLE. SRI-4 is based on [Furie, R. A., et al 2009]:

- BILAG-2004: no new A (severe) or >1 new B (moderate) score from Baseline
- Hybrid SLEDAI: ≥4-point reduction from baseline
- PGA: no deterioration by ≥0.3 points from Baseline

By combining the BILAG-2004, hybrid SLEDAI, and PGA scores, the SRI-4 evaluates global improvement, any significant worsening in unaffected organ systems, and improvements in disease activity, without compromise to the patient's overall condition. Participants will be considered SRI-4 responders if they meet all 3 criteria mentioned above.

BICLA Score

The BICLA is a composite global measure of SLE disease activity [Ohmura, K. 2021]. It distinguishes between partial and complete improvement in all body systems. BICLA response is defined as:

- BILAG-2004: no new A (severe) or >1 new B (moderate) score from Baseline
- ≥1 gradation improvement in Baseline BILAG in all body systems with moderate or severe disease activity
- Hybrid SLEDAI: no worsening from Baseline
- PGA: no deterioration by ≥0.3 points from Baseline
- No use of restricted medications and no discontinuation of study intervention

CLASI Score

The CLASI score is a physician reported outcome measure used in patients with SLE who may also have cutaneous involvement. It produces 2 separate scores (not to be combined as a total score):

- **CLASI Activity Score:** Represents the overall CLE activity (erythema, scale, hypertrophy, mucous membrane involvement, recent hair loss, and non-scarring alopecia) as observed by the physician during examination.

- **CLASI Damage Score:** Represents the overall extent of CLE damage (dyspigmentation, scarring, atrophy, panniculitis, scarring alopecia) observed by the physician.

28 Joint Count Score

The joint count score is an evaluation of 28 joints (left and right shoulder, elbows, wrists, knees, MCP1, MCP2, MCP3, MCP4, MCP5, PIP1, PIP2, PIP3, PIP4, and PIP5) in which joints are assessed for presence or absence of swelling and presence or absence of tenderness. An active joint is defined as a joint that exhibits both swelling and tenderness on physical examination.

Glucocorticoid Use

Glucocorticoids are steroid hormones with rapidly acting anti-inflammatory properties used in the treatment of autoimmune diseases. They are associated with comorbidities as well as short- and long-term complications related to increased daily dose and cumulative use, such as increased risk of infection, osteoporosis and bone fracture, avascular necrosis, atherosclerosis, and organ damage. Oral corticosteroids are a systemic form of glucocorticoids available as different preparations with differing relative anti-inflammatory potencies, of which prednisone is one of the most commonly used. A comparison of relative potencies of commonly used oral corticosteroids is listed in Appendix 11.

LLDAS

LLDAS is a disease activity state associated with significant protection against flares and organ damage accrual. It includes both the measurement of disease activity and maintenance of immunosuppressive medications [Franklyn, K., et al 2016].

LLDAS is defined as:

- Disease activity
    - Hybrid SLEDAI ≤4, with no activity in major organ systems
    - No new features of SLE activity compared with the previous assessment
    - PGA ≤1.0
- Immunosuppressive medications
    - Current prednisolone (or equivalent) dose ≤7.5 mg daily
    - Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs

CCI

CCI

[redacted]

CCI

[redacted]

Other Exploratory Endpoints

- Immunologic parameters associated with SLE disease activity will be measured (ie, anti-dsDNA, C3, and C4).

4.2.1.2 Safety Endpoints

General safety and tolerability will be evaluated by clinical review of all relevant parameters, including AEs, vital signs, and laboratory safety tests (hematology, chemistry, and urinalysis), performed per the SoAs (Section 1.3). AEs will be evaluated and assessed according to the guidelines in Section 8.4. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

CCI

[redacted]

4.2.1.3 Pharmacokinetic Endpoints

PK samples will be collected from all participants at select visits as described in the SoAs (Section 1.3). On dosing days, PK samples will be collected before administration of study intervention. Additional PK samples will be collected in approximately 15 participants per treatment arm at selected sites (Section 1.3.4, and see Appendix 7 for country-specific requirements). PK samples will be used to evaluate MK-6194 serum concentrations and for exposure response models to evaluate PK/PD and PK/AE relationships, as appropriate. The pharmacometrics analyses will be reported separately.

4.2.1.4 Pharmacodynamic Endpoints

Whole blood samples will be collected from all participants for Treg assessment as described in the SoA (Section 1.3). At selected sites additional PK/PD/biomarker samples will be collected in approximately 15 participants per treatment arm allowing more frequent PD sample collection during the study (see Appendix 7 for country-specific requirements). Whole blood PD samples will be used for immunophenotypic analyses to evaluate MK-6194 pharmacodynamic effect under multiple dosing conditions.

4.2.1.5 Immunogenicity Endpoints

Immunogenicity to MK-6194 will be described as per the results of the ADA assay from samples taken during the treatment period as described in the SoA (Section 1.3). ADA samples will be collected from all participants prior to administration of study intervention at select visits. The incidence, magnitude (titer), and characterization of ADA positive participants and potential effects of ADA on PK, PD, and safety will be reported as appropriate.

4.2.1.6 Planned Exploratory Biomarker Research

The mechanism of action of many new therapeutics is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to the treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapies. To identify novel biomarkers, biospecimens (eg, blood components, tissue material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. See Appendix 7 for country-specific requirements. Investigations may include, but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. Genome and exome wide approaches may be used for this effort. In addition, epigenetic characterization techniques (ie, DNA methylation status, histone profiling) may also be explored. If genetic and/or epigenetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population.

Blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in blood may be performed to define gene signatures that correlate to clinical response to treatment with therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Blood protein biomarker analyses

Blood samples from this study may undergo protein-based biomarker analyses using a variety of platforms that could include, but are not limited to; immunoassays (eg, ELISA) liquid chromatography/mass spectrometry, cytometry, and immunohistochemistry. These approaches may be used to quantify soluble, cell-based analytes to further elucidate therapy mechanism of action and/or assess disease-related parameters. For immunohistochemical

analyses information on spatial context and cellular distribution may also be included. Correlation of protein expression to response to therapy may be performed to identify novel predictive biomarkers that could aid in patient selection for therapy. This research would serve to develop such assays for future clinical use.

4.2.1.6.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

See Appendix 7 for country-specific requirements.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6. See Appendix 7 for country-specific requirements.

4.2.2 Rationale for the Use of Placebo

This study will be placebo-controlled in order to avoid bias in the collection and evaluation of efficacy and safety data during the Main study period, and to assess whether any observed effects are treatment-related or an effect of study participation. Participants will be required to be on background standard of care (Section 6.5) and may discontinue the study

intervention at any time. Given that there are limited approved treatments for SLE, the use of a placebo is justified.

4.3 Justification for Dose

CCI [redacted]

Published clinical studies have examined the impact of low-dose IL-2 on Treg expansion in a range of autoimmune diseases. These studies have shown that the greatest likelihood of clinical efficacy is associated with peak Treg expansion of ≥2-fold above baseline across differing autoimmune diseases [Rosenzwajg, M., et al 2019] [Allegretti, J., et al 2021] [Fanton, C., et al 2020]. CCI [redacted]

CCI [redacted]

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

See Appendix 7 for country-specific requirements.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

Additionally, if futility criteria are met at the IA, the study will stop early (Section 9.6).

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

At Screening Visit

1. Has a diagnosis of SLE ≥6 months prior to Screening and is confirmed at Screening with a score ≥10 per EULAR/ACR 2019 classification (https://pubmed.ncbi.nlm.nih.gov/31385462/#&gid=article-figures&pid=figure-2-uid-1).
2. Has +ANA (titer ≥1:80) or positive anti-dsDNA antibody or positive anti-Sm antibody, or positive anti-SSA/Ro antibody at Screening.
3. Has the presence of at least one of the following manifestations of SLE at Screening:
   - Active lupus rash with CLASI-A erythema and scale/hypertrophy combined score >2
   - >2 tender and swollen joints in wrists, MCPs, or PIPs
4. Has a hybrid SLEDAI total score of ≥6 and clinical hybrid SLEDAI score of ≥4 at Screening.
   - The clinical SLEDAI score excludes all urine and blood laboratory results including immunologic measures.
   - Organic brain syndrome, lupus headache, mucosal ulcers, and fever must be recorded on the hybrid SLEDAI but are not counted toward the total or "clinical" scores for eligibility, and
   - Alopecia must be recorded on the hybrid SLEDAI but will count toward the total or "clinical" scores for eligibility only if there is also a CLASI-A alopecia score of 2 or 3 associated with erythema or scale of the scalp.

At Randomization Visit

5. Has the presence of at least one of the following manifestations of SLE on the day of Randomization:
   - Active lupus rash with CLASI-A erythema and scale/hypertrophy combined score >2
   - >2 tender and swollen joints in wrists, MCPs, or PIPs
6. Has active SLE disease features on the day of Randomization contributing toward a "clinical" hybrid SLEDAI score of ≥4 points.
   - The clinical SLEDAI score excludes all urine and blood laboratory results including immunologic measures.
   - Organic brain syndrome, lupus headache, mucosal ulcers, and fever must be recorded on the hybrid SLEDAI but are not counted toward the total or "clinical" scores for eligibility, and
   - Alopecia must be recorded on the hybrid SLEDAI but will count toward the total or "clinical" scores for eligibility only if there is also a CLASI-A alopecia score of 2 or 3 associated with erythema or scale of the scalp.
7. Is taking at least 1 background therapy (1 immunosuppressant or dapsone and/or 1 antimalarial and/or oral corticosteroids) for SLE as follows:
   1. Non-biologic standard of care therapy (1 immunosuppressant or dapsone and/or 1 antimalarial) for SLE must have been initiated >12 weeks prior to Randomization and a stable dose must be maintained for at least 4 weeks prior to Randomization and is expected to be stable throughout the duration of the trial, at doses up to the prescribed maximum listed in Table 1.

Table 1 Allowed Background Therapies

Antimalarials	• hydroxychloroquine 400 mg/day • quinacrine 100 mg/day • chloroquine 250 mg/day
Immunosuppressants	• azathioprine 200 mg/day • methotrexate 25 mg/week • leflunomide 20 mg/day • mycophenolate mofetil 3 g/day • mycophenolic acid 2.16 g/day • tacrolimus 0.2 mg/kg/day • cyclosporine 5 mg/kg/day • voclosporin 23.7 mg twice a day
Other	• dapsone 150 mg/day

Note: Other therapy not included in Table 1 may be considered acceptable background medication for entry only after Sponsor consultation and approval by Clinical Director. If a

participant is taking a permitted concomitant therapy but will discontinue prior to participating in the study, the washout period is 4 weeks prior to Randomization. Allowed background therapies should follow local regulations.

2. Oral corticosteroids are permitted if they were not increased by >5 mg/day of prednisone (or equivalent) within 4 weeks prior to Randomization and must be maintained at a stable dose of prednisone ≤20 mg/day (or equivalent) for at least 2 weeks prior to Randomization.

8. Has received via IRT, affirmation from the DAAG that SLE diagnosis and disease activity assessed by the investigator has satisfied SLE entry criteria and there are no known clinical and/or administrative issues that would preclude participant randomization.

Demographics

9. Is an individual of any sex/gender, from 18 years to 75 years of age inclusive, at the time of providing the informed consent.

Female Participants

10. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP
  OR
- Is a POCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 28 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. 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. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
  - Abstains from breastfeeding during the study intervention period and for at least 28 days after study intervention MK-6194 is last administered.

- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

11. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR. See Appendix 7 for country-specific requirements.

Additional Categories

12. Is willing and considered able by the investigator to comply with study procedures, including adherence with study intervention, visit schedule, and completion of PROs. Participant must be able to read, understand, and complete the PROs.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

(See Appendix 7 for country-specific requirements).

Medical Conditions

1. Has a history of or current inflammatory condition other than SLE that, in the opinion of the investigator, could interfere with disease activity assessments or corticosteroid taper, including inflammatory joint or skin disease and overlap syndromes such as rheumatoid arthritis, mixed connective tissue disease, scleroderma, inflammatory myopathies, primary vasculitis, or steroid-dependent asthma. Secondary Sjogren's syndrome and clinically stable celiac disease and autoimmune thyroid disease are not excluded.
2. Is known to be infected with HBV, HCV, or HIV.
   - Participants with positive HbsAg are excluded from the study. Participants with negative HbsAg and positive HbcAb must have further testing for HBV DNA. Participants with HBV DNA ≥LLOQ are not eligible for the study. Participants with HBV DNA <LLOQ are eligible and the participant should have HBV-DNA testing performed approximately every 12 weeks (in correlation with a scheduled visit). For country-specific requirements, refer to Appendix 7.
   - Participants with positive HCV antibody at Screening must have further testing for HCV RNA. Participants with HCV RNA detectable are not eligible for the study. Participants with positive HCV antibodies but HCV RNA not detectable and successfully treated HCV with no recurrence for ≥1 year are eligible.
   - Participants with a history of HIV infection or have a positive antibody test are not eligible for the study.

3. Has a concurrent clinically significant disease or clinically relevant laboratory abnormalities, or a history of any illness or medical condition that, in the opinion of the investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.
4. Has symptomatic heart failure (New York Heart Association class III or IV) or myocardial infarction or unstable angina pectoris within 6 months prior to Screening.
5. Has a severe chronic pulmonary disease requiring oxygen therapy.
6. Has a transplanted organ which requires continued immunosuppression.
7. Has a known systemic hypersensitivity to IL-2, or modified IL-2 including MK-6194, or its inactive ingredients (Note: refer to the IB for details regarding excipients for MK-6194).
8. Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
9. Has drug-induced CLE and/or drug-induced SLE in the setting of continued treatment with a causative agent.
10. Has active severe lupus nephritis (including but not limited to Class III or Class IV nephritis) as defined by urine protein to creatinine ratio >3.0 or eGFR <30 mL/min/1.73 m^2, for which treatment with high-dose corticosteroids combined with immunosuppressive, biologic, and/or cytotoxic therapy was initiated within 6 months prior to Screening or may be required.
11. Has active or unstable neuropsychiatric lupus including but not limited to the following: seizure, new or worsening impaired level of consciousness, psychosis, delirium or confused state, aseptic meningitis, cranial neuropathy, cerebrovascular accident, ascending or transverse myelitis, chorea, cerebellar ataxia, mononeuritis multiplex, or demyelinating syndromes.
12. Has a diagnosis of Antiphospholipid Syndrome with history of vascular thrombosis, catastrophic APS, or pregnancy morbidity within 6 months prior to Screening (see Appendix 8 for the APS criteria). Participants with one first trimester loss within 6 months prior to Screening with no other history of clinical criteria for APS may be eligible to participate.
13. Has a history of any malignancy, except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix.
14. Has an active or clinically significant infection requiring hospitalization or treatment with IV anti-infectives up to 4 weeks prior to Randomization or oral/intramuscular anti-infective therapy up to 2 weeks prior to Randomization.
15. Has evidence of active TB, latent TB, or inadequately treated TB (for participants with history of TB) as evidenced by 1 of the following:
    - Positive QuantiFERON-TB test or equivalent test; see Section 8.3.6 for TB testing guidance.
    - Positive findings of active TB on CXR (or CT scan if locally required)
      Note: CXR is not required if the participant had a previous normal CXR per local standard of care or chest CT within 90 days prior to Screening, provided all source

documentation is available and nothing has changed in the participant's medical history to warrant a repeat test.
Note: For participants with history of active or latent TB, documentation of treatment must be provided to the investigative site. Participants who are fully treated per local standard of care are eligible for the study. These participants do not require QFT testing. CXR is still required at Screening; normal CXR or CT within 90 days prior to Screening is acceptable.

16. Has confirmed or suspected COVID-19 infection.
    Note: Participants with recent confirmed or suspected COVID-19 infection may participate under the following conditions:
    - Participants with COVID-19 infection, confirmed by a PCR or an antigen test:
      For asymptomatic participants, Randomization must be at least 10 days after the positive COVID-19 test.

      For symptomatic participants, Randomization must be at least 10 days after onset of symptoms and at least 3 days after resolution of fever without the use of fever-reducing medications, and the participant must have clinically meaningful improvement in symptoms.
    - Participants with suspected COVID-19 infection:
      For participants with signs/symptoms suggestive of COVID-19 infection, a molecular (ie, PCR) test must be performed to rule out COVID-19 infection prior to Randomization;
      Or
      Randomization must be at least 10 days after onset of symptoms and at least 3 days after resolution of fever without the use of fever-reducing medications, and the participant must have clinically meaningful improvement in symptoms.
17. CCI [redacted]
18. Has history of drug or alcohol abuse within 6 months prior to Screening (can be participant-reported).
19. Has had major surgery within 3 months prior to Screening or has a major surgery planned during the study.

Prior/Concomitant Therapy

20. Has received prohibited medications within the specified timeframes prior to Randomization (Table 2) These medications are also prohibited during the study.

Table 2 Prohibited Medications

Medication Category	Prohibited Period Prior to Randomization
Biologics and Targeted Immunosuppressive Therapies	
• Recombinant IL-2 • IL-2 muteins/analogs • Immune checkpoint inhibitors (ie, PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, etc.). Note: Abatacept is not a CTLA-4 inhibitor. See Appendix 9.	Any time
• T cell depleting therapies (eg, alemtuzumab, antithymocyte globulin)	12 months
• B cell depleting therapies (eg, rituximab, ocrelizumab, obinutuzumab)	6 months
• Biologics with immunosuppressive potential See Appendix 9 for examples of biologics Note: Non-immunosuppressive biologics may be used after discussion with the study Clinical Director	3 months or 5 half-lives (whichever is longer)
• JAK inhibitors • PDE4 inhibitors • S1P modulators • TYK2 inhibitors See Appendix 9 for examples of these medications	4 weeks
Medications Used to Treat SLE[a]	
• Belimumab	3 months
• Anifrolumab	3 months
• High potency topical corticosteroid and/or topical immunosuppressant agents for skin lesions	7 days
• Sulfasalazine	4 weeks
• Intralesional corticosteroid	8 weeks
• Thalidomide or lenalidomide	4 weeks
• Danazol	4 weeks
• IM, intraarticular, intrabursal corticosteroids	8 weeks
• IV corticosteroids	8 weeks
• Plasmapheresis or IV or SC immunoglobulin	3 months
• Cyclophosphamide	6 months
Other Therapies	
• Any investigational drugs	4 weeks or 5 half-lives of the investigational drug (whichever is longer)
• Live vaccines Note: JYNNEOS for prevention of smallpox and mpox (also referred to as monkeypox disease) is allowed. JYNNEOS is a live, non-replicating vaccine See Appendix 9 for examples of live and non-live vaccines	4 weeks or longer if required locally
• Medications associated with high risk of QT prolongation (Appendix 12)	5 half-lives
• Traditional Chinese medicine or herbal supplement used to treat SLE	4 weeks

CTLA-4=cytotoxic T-lymphocyte-associated protein 4; JAK= Janus kinase; IA=intraarticular; IL-2= interleukin 2; IM= intramuscular; IV= intravenous; PD-1= programmed cell death protein 1; PDE4= phosphodiesterase-4; PD-L 1= programmed cell death ligand 1; S1P= sphingosine 1 phosphate; SC= subcutaneous; SLE= systemic lupus erythematosus; TYK2= tyrosine kinase 2.
[a] See Appendix 7 for country-specific requirements.

21. Is taking more than 1 immunosuppressant.
    Note: See inclusion criterion 7 for a list of permitted immunosuppressants.
22. Is taking more than 1 oral NSAID (excluding low-dose aspirin [<350 mg/day]) or is taking daily oral NSAID at greater than the maximum recommended dosage.
23. Is currently on any chronic systemic (oral or IV) anti-infective therapy for chronic active infection (such as pneumocystis, cytomegalovirus, herpes zoster, or atypical mycobacteria).

Prior/Concurrent Clinical Study Experience

24. Has participated in another investigational study within 4 weeks (see Table 2) prior to Randomization.

Diagnostic Assessments

25. Has Screening laboratory test results within the following parameters:

- Hemoglobin <8.5 g/dL
- WBC <2.5 x 10^3/µL
- Absolute neutrophil count <1.5 x 10^3/µL
- Absolute lymphocyte count <0.5 x 10^3/µL
- Platelets <75 x 10^3/µL
- >2.0 x ULN of any of the following: ALT, AST, ALP; or >ULN total bilirubin (>1.5 x ULN total bilirubin if known Gilbert's syndrome)
- eGFR ≤30 mL/min/1.73 m^2 based on the MDRD equation
- CCI [redacted]

Note: For any of the above listed laboratory assessments, 1 repeat measurement will be allowed at the investigator's discretion before being considered a screen-failure.

26. CCI [redacted]

Other Exclusions

27. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

Sun or Light Exposure

Study participants should be instructed on standard UV light avoidance measures, such as:

- Use of broad-spectrum sunscreen blocking both UVA and UVB rays (minimum SPF of 15 and containing inorganic ingredients such as zinc oxide and titanium oxide)
- Wearing sun protective clothing and hats
- Avoidance of sun exposure during peak mid-day hours or other UV light sources (eg, tanning booths, sunlamps)

Blood Donation

Study participants should be instructed not to donate blood or blood products during the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Rescreening is allowed once per participant (Section 8.1.6 and Section 8.10.1).

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies study intervention(s) provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 3.

Country-specific requirements are noted in Appendix 7.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
MK-6194 CCI	Experimental	MK-6194	Biological/Vaccine	Injection, Solution	CCI		SC	Main study + LTE	Test Product	IMP	Provided centrally by the Sponsor
MK-6194 CCI	Experimental	MK-6194	Biological/Vaccine	Injection, Solution			SC	Main study + LTE	Test Product	IMP	Provided centrally by the Sponsor
MK-6194 CCI	Experimental	Placebo	Biological/Vaccine	Injection, Solution			SC	Main study + LTE	Placebo	IMP	Provided centrally by the Sponsor
Placebo CCI	Placebo Comparator	Placebo	Biological/Vaccine	Injection, Solution			SC	Main study only	Placebo	IMP	Provided centrally by the Sponsor

EEA=European Economic Area; IMP=investigational medicinal product; LTE= long-term extension; NIMP/AxMP=noninvestigational/auxiliary medicinal product; CCI CCI SC= subcutaneous.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: All participants will receive study intervention CCI For country-specific requirements, see Appendix 7.

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.1.1 Drug-Device Combination Products/Combination Medicinal Product

The investigational drug-device combination product/combination medicinal product provided for use in this study is MK-6194. Refer to Section 8.4.8 and Appendix 4 for reporting events.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 3 study intervention arms. Participants will be assigned randomly in a 1:1:1 ratio to placebo, CCI MK-6194 CCI or CCI MK-6194 CCI during the Main study period.

During the LTE period, participants who were assigned to the placebo arm during the Main study period will be rerandomized 1:1 to CCI using an IRT system and will be given new randomization numbers. Participants who were assigned to either of the MK-6194 arms during the Main study will continue to receive CCI ; however, will be assigned new randomization numbers in order to maintain the study blind during the LTE.

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If an arm is found to be sub-efficacious after the Week 28 primary endpoint analysis, participants in the LTE who are already part of the sub-efficacious arm may continue on that arm, however there will be no new enrollment to the sub-efficacious arm (Section 9.6). Participants who are still part of the sub-efficacious arm in the Main study will finish the Main study as randomized but may be part of the efficacious arm in the LTE.

6.3.2 Stratification

Intervention randomization for the Main study and the LTE will be stratified according to the following factors:

1. Hybrid SLEDAI score (<10 vs. ≥10) at Screening

2. Oral corticosteroid dose at Randomization (prednisone <10 mg/day vs ≥10 mg/day [or equivalent])

3. Geographic region ([1] Eastern Europe and Latin America, [2] rest of the world)

The above stratification factors are chosen as they may impact the efficacy endpoints. Baseline disease severity as measured by the hybrid SLEDAI may influence the likelihood of

achieving the primary endpoint. Baseline oral corticosteroid use will impact daily dose and cumulative dose endpoints. Standard of care treatments, including oral corticosteroids, may vary according to geographic regions and may influence placebo responses.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-6194 and placebo will be packaged identically so that blind is maintained.

Clinical site personnel, participants, and most Sponsor personnel will remain blinded until the LTE is complete. Selected Sponsor personnel involved in performing and reviewing the results of the Week 28 and the Week 52 analyses will be unblinded at the time of the respective database locks. Participants and all field and study site personnel will remain blinded through the study. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

See Section 8.1.11 for the description of unblinding if a medical emergency occurs during the study.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for ≥2 consecutive injections require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants self-administer study intervention at the site (witnessed doses per SoA), compliance with study intervention will be assessed by site personnel observation. Alternatively, participants may receive study intervention directly from the investigator or designee. The date and time of each dose administered in the clinic will be recorded in the source documents, the CRF and the Participant Reminder Log.

When participants self-administer study intervention away from the clinic, compliance with study intervention will be assessed at the following site visit. Participants will record the date and time of the administered dose in the Participant Reminder Log. Compliance will be assessed by direct questioning during review of the Participant Reminder Log and visual inspection of the returned study intervention syringe(s) (used and unused, when applicable) and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the source documents and the CRF.

If a discrepancy is noted when comparing entries in the Participant Reminder Log with the amounts of returned study intervention, the investigator or qualified designee must discuss the discrepancy with the participant and the explanation must be documented. Only the participant is allowed to make any changes to the log entries. The investigator or qualified designee will be responsible for transferring the appropriate information from the log into the appropriate CRF.

A record of the number of prefilled syringes dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention administration dates will also be recorded in the CRF. For country-specific requirements, see Appendix 7.

6.5 Concomitant Therapy

Participants will continue their existing SLE treatment(s) during the study provided the treatment complies with the eligibility criteria (Section 5.1 and Section 5.2).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study OR during time periods specified by this protocol for that medication. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator may discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, route, and frequency

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

Note: It is the responsibility of the investigator to ensure participants with concomitant medical conditions are treated according to local guidelines/standard of care.

Permitted Concomitant Medications

Immunosuppressants and Antimalarials

Participants must be on at least 1 background therapy for SLE (immunosuppressant or dapsone and/or antimalarial and/or oral corticosteroid). The standard of care treatments for SLE listed in Table 1 are allowed, providing the participant has been initiated >12 weeks prior to Randomization and a stable dose has been maintained for at least 4 weeks prior to Randomization. Doses are NOT permitted to change during the study treatment period up to Week 52, with the following exception for dose modification:

Doses of immunosuppressants and antimalarials may be decreased for toxicity reasons or in the context of an AE such as infection. Such instances must be documented as an AE. The

dose can be returned to the Day 1 level if the toxicity/event resolves and if clinically indicated.

Participants may not be taking more than 1 immunosuppressant during the study.

NSAIDs and Analgesics

- Participants taking daily doses of NSAIDs (eg, ibuprofen, naproxen) for SLE symptoms prior to the Screening Visit must be on a stable dose 2 weeks prior to Randomization and through Week 28, may not be taking in combination with other oral NSAIDs except for low-dose aspirin, and must be taking doses equal to or less than the maximum recommended dosage. NSAIDs may be taken as needed on an intermittent basis for non-SLE-related reasons provided it does not exceed the maximum recommended dose.
- Low-dose aspirin (<350 mg/day) at stable doses for cardiovascular prophylaxis is permitted.
- Topical NSAIDs for SLE symptoms are permitted provided they are on a stable regimen starting 2 weeks prior to Randomization and through Week 28.
- Acetaminophen (paracetamol) ≤3 g/day may be initiated for pain control during the study and should be titrated down as tolerated.
- Other pain medications, including opiates or other narcotics, are permitted provided the dose has been stable for ≥4 weeks, the dose is anticipated to remain stable throughout the study period, and in the opinion of the investigator is not anticipated to impact the protocol-specific efficacy and safety assessments.
- Participants should refrain from taking NSAIDs, opiates, or other narcotics past midnight on the day of a scheduled study visit but may resume after all assessments are complete.

Topical Corticosteroids

The use of low or lower-mid-potency topical steroids is allowed during the study, although throughout the study it is recommended that participants avoid use of topical corticosteroids on the day of study site visits prior to CLASI assessments but may resume after the visit. Table 4 provides examples of low or lower-mid-potency topical corticosteroid use. Use of high potency topical corticosteroids are prohibited.

Table 4 Examples of Low or Lower-Mid-Potency Topical Corticosteroids

Lower-Mid-Potency	Low Potency
Betamethasone valerate 0.05% cream Desonide 0.05% ointment Fluocinolone acetonide 0.025% cream Hydrocortisone butyrate 0.1% cream, ointment Hydrocortisone valerate 0.2% cream Triamcinolone acetonide 0.025% ointment Prednicarbate 0.1% cream Dexamethasone 0.1% cream	Fluocinolone acetonide 0.01% cream Triamcinolone acetonide 0.025% cream Alclomethasone dipropionate 0.05% cream, ointment Desonide 0.05% cream, lotion Hydrocortisone 0.5-2% cream, ointment Hydrocortisone acetate 1-2.5% cream, lotion

Use of a topical corticosteroid not included in Table 4 may be acceptable only after Sponsor consultation and approval by Clinical Director.

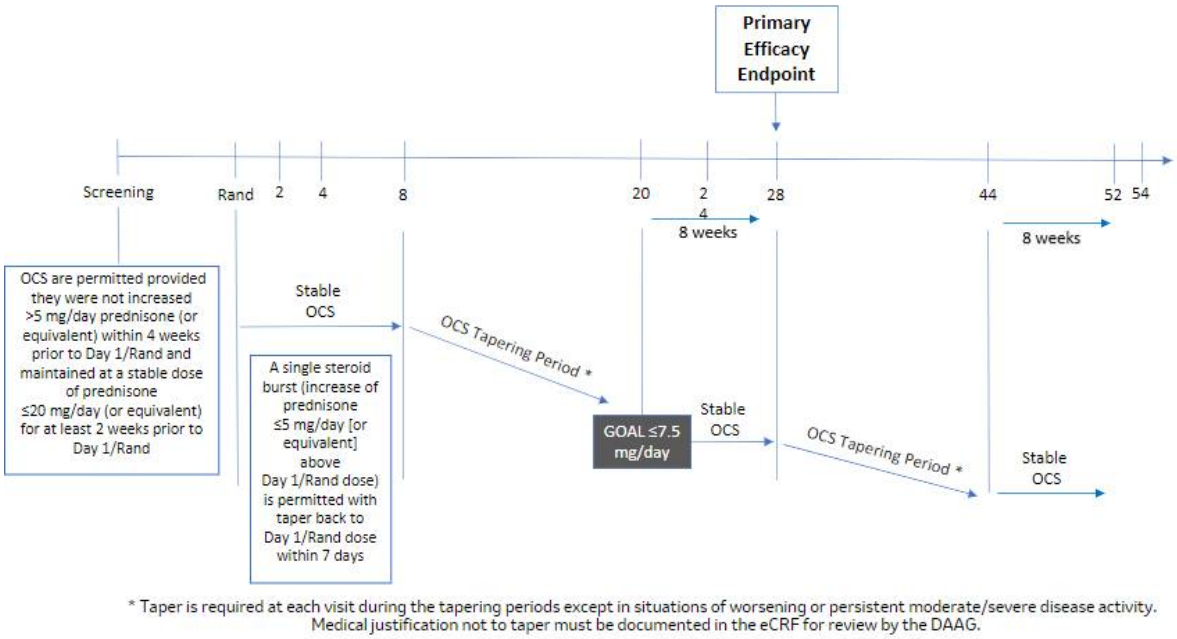
Prohibited Concomitant Medications

Prohibited medications or vaccinations specifically prohibited in the exclusion criteria are also prohibited during the study. See Table 2 (Section 5.2) and Appendix 9 for medications prohibited during the study until the last dose of study intervention. Live vaccines, except for JYNNEOS, are prohibited during the study until 6 weeks after the last dose of study intervention. A comprehensive list of allowed and prohibited medications and vaccinations is in Appendix 9.

6.5.1 Oral Corticosteroids

Participants taking OCS are eligible for Randomization if OCS were not increased by >5 mg/day of prednisone (or equivalent) within 4 weeks prior to Randomization and were maintained at a stable OCS dose of prednisone ≤20 mg/day (or equivalent) for at least 2 weeks prior to Randomization. After Randomization participants will undergo periods of OCS stability and OCS taper as described below and shown in Figure 3. Participant's OCS dosing will be reviewed by the CCI [redacted] as outlined in Section 10.1.4.3.

Figure 3 Main Study Steroid Taper



OCS= oral corticosteroids; Rand= randomization

During periods of taper, the OCS dose MUST be tapered for each participant at each visit, EXCEPT in situations of increasing or persistent moderately-severe or severe disease activity. Tapering may be started on the scheduled study visit day based on clinical presentation and the laboratory values from the previous visit or within approximately 7 days after the study visit once current laboratory values are received. If a decision is made to taper the OCS dose at a given visit based on clinical presentation and previous visit laboratory results, and the laboratory results performed at the current visit show worsening SLE disease activity, the decision to taper may be reversed.

If the decision by the investigator is NOT to taper the OCS dose, the medical justification must be documented in the source documents and eCRF for the associated visit and will be reviewed by the DAAG.

Reasons assessed by the investigator to not taper the OCS may include but is not limited to a participant experiencing increasing or persistent moderately-severe or severe SLE disease activity.

Randomization to Week 8 (Stable OCS period)

Participants should remain on a stable dose of prednisone ≤20 mg/day (or equivalent) between Randomization and Week 8; the OCS dose must not be increased or decreased except in situations of increasing or persistent moderately-severe or severe disease activity. A single steroid burst (increase of prednisone ≤5 mg/day [or equivalent] above the Randomization OCS dose) is allowed between Randomization and Week 8 but is strongly

recommended to be avoided within 1 week of a planned study visit and should be tapered to the Day 1 OCS dose within 7 days.

Week 8 to Week 20 (OCS Tapering period)

After all study visit assessments have been completed and study intervention has been administered, the OCS dose MUST be tapered for each participant at the Week 8, Week 12 and Week 16 visits, EXCEPT in situations of increasing or persistent moderately-severe or severe disease activity with the goal to reduce the OCS dose to ≤7.5 mg/day by Week 20.

A recommended OCS taper schedule based upon starting prednisone dose is detailed in Table 5.

Table 5 Recommended OCS Taper Schedule

	Starting prednisone dose	20 mg	17.5 mg	15 mg	12.5 mg	10 mg	7.5 mg	5 mg	2.5 mg to 5 mg
Taper Period	Week 8	15 mg	12.5 mg	10 mg	10 mg	7.5 mg	5 mg	5 mg	2.5 mg
	Week 12	12.5 mg	10 mg	7.5 mg	7.5 mg	5 mg	5 mg	2.5 mg	0 to 2.5 mg
	Week 16	10 mg	7.5 mg	7.5 mg	5 mg	2.5 to 5 mg	2.5 mg	2.5 mg	0 to 2.5 mg
Stable Period	Week 20 (Target dose)	7.5 mg	5 to 7.5 mg[a]	5 to 7.5 mg[a]	5 mg	2.5 to 5 mg[a]	2.5 mg	0 to 2.5 mg[a]	0 to 2.5 mg[a]
	Week 24								
	Week 28 (Primary Efficacy)								

OCS=oral corticosteroids
a. Participant should receive the same dose between Week 20 and Week 28.

Between Week 8 and Week 20, a participant experiencing an increase in SLE disease activity secondary to OCS tapering may increase the dose to the previous dose for up to 1 week before resuming the tapering schedule, without the participant being considered a non-responder for subsequent assessment of disease activity.

If the decision by the investigator is NOT to taper the OCS dose, medical justification must be documented in the source documents and eCRF.

Participants starting at a baseline prednisone dose of >7.5 mg/day (or equivalent) who are unable to taper their dose to ≤7.5 mg/day (or equivalent) by Week 20 will be considered non-responders.

Week 20 to Week 28 (Stable OCS Period)

Participants should remain on a stable dose of prednisone ≤20 mg/day (or equivalent) between Week 20 and Week 28 (Primary Endpoint measurement); the OCS dose must not be increased or decreased except in situations of worsening or persistent moderate/severe disease activity.

Week 28 to Week 44 (OCS Tapering Period)

After all assessments have been completed and study intervention has been administered, the OCS dose MUST be tapered for each participant at the Week 28, Week 32, Week 36, and Week 40 visits except in situations of increasing or persistent moderately-severe or severe disease activity. The tapering schedule may be at the investigator's discretion. Between Week 28 and Week 44, a participant experiencing an increase in SLE disease activity secondary to OCS tapering may increase the dose to the previous dose for up to 1 week before resuming the tapering schedule, without the participant being considered a non-responder for subsequent assessment of disease activity.

Week 44 to Week 52 (Stable OCS Period)

Participants should remain on a stable dose of prednisone ≤20 mg/day (or equivalent) between Week 44 and Week 52; the OCS dose must not be increased or decreased except in situations of worsening or persistent moderate/severe disease activity.

LTE: Week 52 to Week 104 (OCS Tapering Period)

After all assessments have been completed and study intervention has been administered, the OCS dose should be tapered for participants receiving prednisone >7.5 mg/day (or equivalent) or as clinically appropriate at the Week 52, Week 64, Week 76, and Week 90 visits, except in situations of worsening or persistent moderate/severe disease activity.

Increases in the OCS dose

Outside of the permitted single steroid boost between Randomization and Week 8 or the temporary permitted taper reversals, if a participant has an increase in the OCS dose for SLE-related reasons at any time in the study, the participant will be considered a non-responder (refer to Section 9.5 for more details).

After the Week 8 Visit, participants who have an increase in their daily OCS dose by >5 mg/day for ≥1 week for non-SLE reasons may continue in the study but may be considered non-responders for subsequent assessment of disease activity (details are defined in the SAP). The timing, dose, and duration of the OCS increase will be reviewed to determine potential impact on efficacy assessments.

6.5.2 Rescue Medications and Supportive Care

Supportive care to mitigate local effects that have occurred at the administration site (eg, injection site reactions) of study treatment are allowed, in addition to applying ice packs to

the site. These may include topical or systemic antihistamines, acetaminophen, NSAIDs, or low-potency topical corticosteroids. Any medications used should be recorded in the eCRF.

Treatment for severe manifestations of SLE leading to discontinuation of study treatment (Section 7.1) should be administered according to local standard of care. Any medications used should be recorded in the eCRF.

6.6 Dose Modification

There are no dose modifications in this study.

6.6.1 Management of Serious Adverse Event of Infection

Interrupt study intervention if a participant develops an SAE of infection. Study intervention may be restarted once the infection has been successfully treated, per investigator discretion.

6.6.2 Management of COVID-19 Infection

Interrupt study intervention if a participant has a confirmed diagnosis of COVID-19 infection. Study intervention may be restarted once the infection or symptom is resolved, per investigator discretion.

6.6.3 CCI

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[redacted]

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.10.5 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

  See Appendix 7 for country-specific requirements.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- CCI
- The participant develops active or latent TB.
- The participant is diagnosed with HBV, HCV, or HIV infection.
- The participant has an SAE of infection (eg, sepsis) which cannot be adequately controlled by anti-infective treatment.

- The participant has any malignancy, except for surgically removed and cured localized non-melanoma skin cancer or carcinoma in-situ of the cervix.

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- The participant develops severe SLE manifestations that in the opinion of the investigator requires treatment with therapies such as cyclophosphamide, high dose steroids, plasmapheresis, and intravenous immunoglobulin that are prohibited in the study.

For participants who are discontinued from study intervention but continue to be monitored in the study, selected visits and procedures, as outlined in the SoA and Section 8.10.5, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

A participant who consented for the Subpopulation procedures, or participant's legally acceptable representative, may withdraw consent for the additional PK/PD/Biomarker sample collections. Specific details regarding activities to be performed at the time of withdrawal from the Subpopulation procedures are outlined in Section 8.1.10.2. Withdrawal from the Subpopulation does not represent withdrawal from the study. See Appendix 7 for country-specific requirements.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- 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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in the Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

Informed consent given by the participant (or their legally acceptable representative) must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion. A copy of the signed and dated ICF should be given to the participant (or their legally acceptable representative) before participation in the study.

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

See Appendix 7 for country-specific requirements.

8.1.1.1 General Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

See Appendix 7 for country-specific requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

See Appendix 7 for country-specific requirements.

8.1.1.3 Consent for PK/PD/Biomarker Subpopulation

The investigator or medically qualified designee will explain the consent for additional PK/PD/biomarker sample collection to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to the PK/PD/biomarker Subpopulation. A copy of the informed consent will be given to the participant before performing any procedure related to the PK/PD/biomarker Subpopulation. See Appendix 7 for country-specific requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at the Screening and Randomization Visits as outlined in the SoA (Section 1.3) by the investigator or sub-investigator delegate, who is a qualified physician, to ensure that the participant qualifies for the study.

Participants must **not** be randomized into the study until affirmation from the DAAG is received via IRT confirming that SLE diagnosis and disease activity assessed by the investigator has satisfied SLE entry criteria (Section 10.1.4.3).

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

During the LTE, participants who complete the Main study on study intervention will receive a new participant identification card at Visit 18; the new randomization number will be added to the new participant identification card. The participant identification card from the Main study should be collected at this time.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at the Screening Visit. Participants will be asked to provide any background or concomitant conditions, drug allergies, and surgeries. Additionally, a complete SLE medical history will be collected.

Clinically significant findings in physical examination, laboratory tests, ECGs, and other physical evaluations during Screening are to be noted in the medical history. Clinically significant changes from the screening evaluation during the study should be captured as AEs.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements (Table 2, Section 6.5, and Appendix 9), and record prior medication taken by the participant within 10 weeks before the first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Prohibited concomitant medications, therapies, and products outlined in

Section 5.2 (Table 2), Section 6.5, and Appendix 9, should not be administered from the indicated period before Randomization to the last dose of study intervention administration.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

During the LTE (Visit 18), participants who were randomized to receive placebo during the Main study will be rerandomized in a 1:1 ratio to receive [redacted] MK-6194 [redacted] (Section 4.3) using an IRT system and will be given new randomization numbers. Participants who were assigned [redacted] MK-6194 [redacted] during the Main study and in order to maintain the blind will also receive new randomization numbers but will continue the same regimen during the LTE.

8.1.8 IRT Visit Registration, IRT Randomization, and Study Intervention Dispensing

The investigator (or designee) will register the participant in IRT at the visits specified in the SoA. Participants who satisfy all entry criteria, including SLE diagnosis and disease activity criteria as assessed by the investigator [redacted], will be assigned a randomization number via IRT at Visit 2 (Day 1). Participants who complete the Main study on study intervention and continue to the LTE will at Visit 18 be assigned a new randomization number via IRT (Sections 1.3.3 and 8.1.7). IRT will manage participant's stratification as outlined in Section 6.3.2 and the LTE rerandomization of the placebo arm as outlined in Section 6.3.1.

Participants who do not meet eligibility criteria will be entered into IRT as screen failures. IRT will also be used to identify the study intervention supplies that will be dispensed to participants at the visits specified in the SoA. Details about the IRT system will be provided in a separate manual.

IRT will be contacted for participant closeout purposes at the Discontinuation Visit or the Week 104 Visit.

8.1.9 Study Intervention Administration

Self-administration of study intervention is recommended, however, administration of study intervention by site personnel or a caregiver/home health aide/family member is permitted (see Appendix 7 for country specific requirements). Self-administration should be in one of the approved injection areas/sites as outlined in the "MK-6194 Instructions for Use" provided to the participant. All participants will be instructed NOT to inject in an inflamed area. Participants will be trained on the proper technique of self-administration and be advised to review the "MK-6194 Instructions for Use" before their first injection. Retraining should occur as necessary at subsequent visits.

Details on appropriate handling, storage, and accountability of study intervention are provided in Section 6.2.2.

8.1.9.1 Timing of Dose Administration

When a study site visit is scheduled, self-administration of study intervention should take place at the study site *after* all required procedures have been performed. A witnessed dose is not required unless specified in the SoA (Section 1.3). CCI [redacted] Participants will be instructed to review the "MK-6194 Instructions for Use" when administering injections of study intervention at home.

The Sponsor should be contacted if the participant misses ≥2 consecutive injections (Section 6.4).

8.1.9.2 Study Intervention Dispense or Return

Study intervention prefilled syringe(s) will be provided to each participant at the times outlined in the SoA. All used (and unused, as applicable) study intervention prefilled syringes must be returned at the end of each study Visit as outlined in the SoA. Study sites will keep track of returned syringes to assess study intervention administration compliance.

8.1.9.3 Train or Retrain Participant on Self-administration of Study Intervention

All participants and/or caregivers/home health aide/family members will be trained by the appropriate study staff on the proper administration of study intervention technique before the participant's first injection (see Appendix 7 for country specific requirements). Training or retraining on self-administration of study intervention will take place during the study visits marked in the SoA and at other visits on an as-needed basis (see Section 8.1.9). Participants will receive written instructions and will be directed to review the "MK-6194 Instructions for Use" prior to self-administration of study intervention.

Individuals responsible for administering study intervention will be instructed NOT to inject into an inflamed area.

8.1.9.4 Witnessed Dose

Study intervention administration should be witnessed and documented by the investigator or study staff during the specific visits outlined in the SoA. Self-administration of study intervention by the participant or administration by a caregiver/home health aide/family member should occur *after* completion of all study procedures, including collection of all blood samples except for PK sample collections on Visits 3 and 8 (see Appendix 7 for country specific requirements). Participants will document dosing in the Participant Reminder Log. The study site staff will ensure proper self-administration technique.

Additionally, on study visit days when the dose is not required to be witnessed by the investigator and/or study staff, administration at the study site (whether by participant or caregiver/family member/site staff) is preferred, but not required (see Appendix 7 for country specific requirements).

8.1.9.5 Dosing Reminder

Participant Reminder Log

A paper 'Participant Reminder Log' will be provided to each randomized participant for documentation of study intervention administration (each dose administered), any complaints/illnesses, and any new medications taken between study visits. Participants will be trained on how to use and complete the Participant Reminder Log at the Visits outlined in the SoA.

Participants should be instructed to bring their completed 'Participant Reminder Log' to each study visit. The investigator and/or designee will review the 'Participant Reminder Log' with the participant at the next visit for accuracy, and any errors/discrepancies should be corrected by the participant per GCP (one line cross out with initials/date of change). The investigator and/or designee will then collect the 'Participant Reminder Log' from participants at the visits described in the SoA. The information recorded in the 'Participant Reminder Log' will be used to assist the investigator (and/or designee) in assessing study intervention compliance, identifying potential AEs, and determining whether any concomitant medications were taken; applicable study data will be recorded on the appropriate eCRF.

Participant Reminder Telephone Call

Telephone contacts will be made to assess compliance of study intervention administration away from the clinic at specific visits outlined in the SoA (Section 1.3). During the telephone call, AE and concomitant medication information will also be reviewed. Additional reminder telephone calls are recommended if a participant has not been compliant with administration of study intervention or when deemed necessary by the study site.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period will have a Discontinuation Visit and should be encouraged to continue to be followed for all remaining study visits until the end of the study period in which they discontinued as outlined in the SoA and Section 8.10.5.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Discontinuation Visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

See Appendix 7 for country-specific requirements.

8.1.10.2 Withdrawal From Additional PK, PD, Biomarker Samples Subpopulation

Participants may withdraw consent for the Subpopulation procedures at any time by contacting the study investigator. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received. Specific details regarding activities to be performed at the time of withdrawal from the Subpopulation procedures are outlined in Section 8.10.5. See Appendix 7 for country-specific requirements.

8.1.11 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.13 PK/PD Biomarker Subpopulation

At selected sites, additional PK/PD/biomarker samples will be collected from approximately 15 participants per treatment arm as outlined in the SoA, in addition to the samples listed in the Main study and LTE SoAs (Section 1.3).

The purpose of the Subpopulation is to provide additional PK and PD measurements, allowing a more comprehensive characterization of the PK-PD relationship of MK-6194.The additional PD and biomarker sample collection is to enable Treg and other biomarker assessments at more timepoints, to allow better understanding of PD and biomarker responses to MK-6194 in participants with SLE. See Appendix 7 for country-specific requirements.

8.2 Efficacy Assessments

8.2.1 PROs

CCI

8.2.1.1 CCI

CCI

8.2.1.2 CCI

CCI

8.2.1.3 CCI

CCI

8.2.1.4 CCI

CCI

8.2.2 ClinROs

ClinRO assessments are to be completed by the investigator or medically qualified designee at visits outlined in the SoA (Section 1.3). In an effort to maintain consistency, it is preferable, but not required, that the same rater perform these assessments across visits for individual participants.

During the Screening Visit, ClinROs need to be completed before DAAG affirmation.

The following ClinROs are to be completed at the visits outlined in the SoA:

- Hybrid SLEDAI
- BILAG 2004
- CCI
- PGA
- CLASI
- 28 Joint Count
- CCI

Additional information is provided in a separate manual and in Section 4.2.1.1.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study

(from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A full physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the visits listed in the SoA.

The full examination should be based on the following body systems: general appearance, head (oral inspection, ears, eyes, nose, and throat), respiratory (auscultation/stethoscopy examination of the lungs), heart (auscultation/stethoscopy examination of the heart), abdomen, musculoskeletal, neurological, lymph nodes, and skin including scalp (alopecia, rash, injection site). Other body systems may be examined at the discretion of the investigator.

Height and body weight will be measured and recorded per the SoA and will be obtained with the participant's shoes off and jacket or coat removed.

Physical findings at Screening will be recorded as medical history. Abnormal findings that are worsening of a baseline finding or any new abnormal findings from other visits will be recorded as an AE.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at the visits listed in the SoA.

A physical examination (full or limited, based on investigator judgment) can be performed at any unscheduled visit if deemed necessary by the investigator. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

- Temperature, HR, and BP will be assessed at all Visits outlined in the SoA. Additionally, RR will be collected at specific Visits outlined in the SoA. The same method should be used for all measurements for each individual participating.
- BP and HR measurements will be assessed in a sitting position and should be preceded by a few minutes of rest.
- Vital signs are to be taken ***after*** completion of PROs and ***before*** blood collection for laboratory tests, except for Visit 2 (Randomization) where vital signs are collected before PROs as part of confirmation of eligibility.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. ECGs may be over-read by the investigator or medically qualified designee if artifact is suspected. ECGs should be performed after the participant has rested quietly for at least 5 minutes. Refer to Appendix 10.3.2 for evaluation of potentially significant findings.

The correction formula to be used for QTc is Fridericia ($QT / RR^{1/3}$).

If a participant demonstrates an increase in QTc interval >500 msec or prolongation >60 msec compared with the baseline assessment, the ECG should be repeated 2 more times at least 1 minute apart at the clinic visit. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the prolongation of the QTc interval meets the criteria for participant discontinuation (see Section 7.1), the participant should be discontinued from study intervention, referred to the appropriate medical professional for management, and should be reported as an AE.

The investigator is responsible for retaining all copies of the ECG reports.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Pregnancy Testing

- Pregnancy testing:

  Pregnancy testing requirements for study inclusion are described in Section 5.1.

  Pregnancy testing (urine and/or serum) should be conducted as per SoA at the specified visits during intervention. A negative pregnancy test should be confirmed prior to administration of study intervention.

  Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

See Appendix 7 for country specific requirements.

8.3.6 TB Testing

Participants will be screened for TB using the QFT test or equivalent as outlined in the TB screening eligibility criterion #15 (Section 5.2). The QFT test, or equivalent, must be performed and read by trained and licensed personnel. If this testing was performed at any site other than the investigator's facility, the results must be made available in written form as source documentation.

All participants must be evaluated for TB at Screening. The results of the TB screening must be interpreted in the context of the participant's epidemiology, history, examination findings, etc, and it is the responsibility of the investigator to determine if a participant has previous, active, or latent TB.

TB Testing:

- The QFT should be performed at Screening on all participants unless the participant is considered to be TB test positive prior to Screening. The purified protein derivative (PPD) skin test (also known as TB Skin Test or Mantoux Test) should be utilized when the QFT is not possible or if both tests are required per local guidelines. If local requirements dictate a local PPD be performed, this should be in addition to the QFT.
- Participants with documentation of prior positive results of QFT, PPD skin test, and/or history of latent or active TB are not required to repeat a TB test at Screening or during the study and should be considered TB test positive.
- If either PPD or QFT is positive, the TB test is considered positive.
- If the QFT or PPD skin test are performed within 90 days prior to Screening and source documentation is available these tests do not need to be performed at Screening provided nothing has changed in the participant's medical history to warrant a repeat test.
- If performed, the PPD should be read by a licensed healthcare professional between 48 and 72 hours after administration. A participant who does not return within 72 hours will need to be rescheduled for another skin test. The PPD skin test reaction will be measured in millimeters (mm) of induration and induration ≥5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."

- Participants who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed, and the TB Skin Test should be considered positive.
- If the QFT is indeterminate, the site should perform a local QFT (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the participant is considered to be positive for the purpose of this study. If the testing result is negative, then the participant is considered to be negative.
- If TB testing is done at Screening in participants considered at low risk for TB as described below and a positive result is reported, the procedure for "Interpretation of a positive TB test in low-risk participants" should be followed OR a prior treatment for latent TB is required.

  Interpretation of a positive TB test in low-risk participants: In cases where the QFT by the central laboratory is positive and the investigator considers the participant at low risk for TB (ie, no risk factors identified on TB risk assessment questionnaire see Appendix 13) and has no clinical suspicion of TB, the investigator may perform a local QFT (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing is positive or indeterminate, the test is considered positive.

- An equivalent interferon Gamma Release Assay such as T-SPOT TB test) may be substituted for the QFT.
- TB test results will be retained at the site as the original source documentation.

Refer to the Laboratory Manual for any additional processing information and shipping instructions.

Participants with history of TB at screening do not need to repeat TB testing during the LTE.

8.3.7 Chest X-ray

If permitted by the local health authority and IRB/EC, a chest x-ray will be obtained as outlined in the SoA to screen for TB (see exclusion criterion in Section 5.2). The chest x-ray must be focused on identifying abnormalities suggestive of TB. Posterior-anterior chest x-ray is recommended, however local guidelines should be followed (see Appendix 7 for country-specific requirements).

The chest x-rays must be read and assessed by a medically qualified designee. Results must be within normal limits or not clinically significant for enrollment in the study. The investigator is responsible for retaining all source documentation.

8.3.8 HBV, HCV, and HIV Testing

Participants will be screened for HBV, HCV, and HIV as outlined in the SoA. See the HBV/HCV/HIV screening eligibility criterion (Section 5.2) to determine if further testing is

needed or if the participant is eligible for the study. See Appendix 7 for country specific requirements.

Hepatitis B

All participants will be tested for the presence of HBV at Screening using the following tests:

- HBsAg (hepatitis B surface antigen)
- HBcAb/anti-HBc (hepatitis B core antibody)

HBV serologic test results will be interpreted and managed as shown in Figure 4.

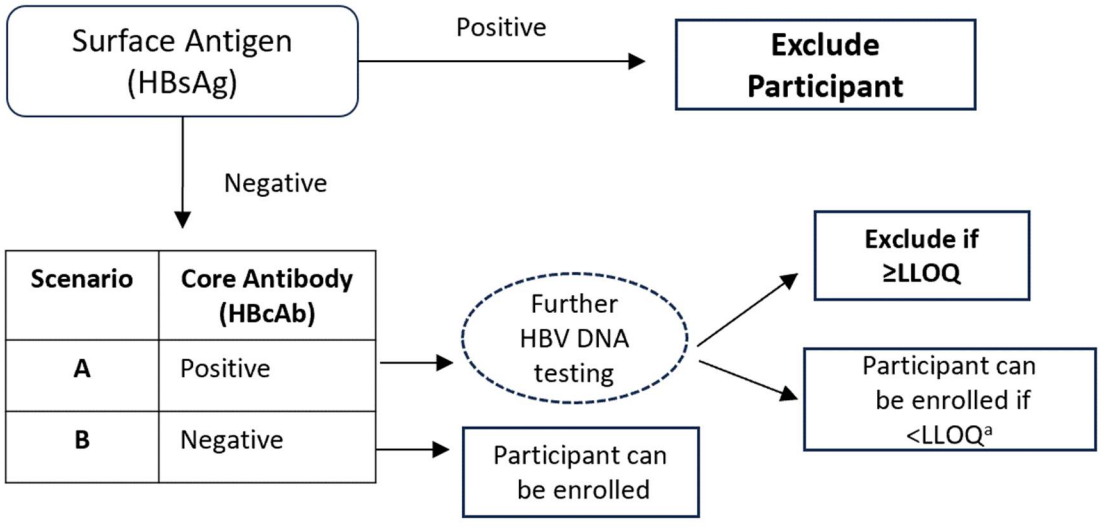
A positive result for HBsAg will be exclusionary.

A negative test result for HBcAb does not require HBV DNA PCR qualitative testing and the participant may be enrolled (Scenario B).

A positive test result for HBcAb requires HBV DNA PCR testing (automatic reflex testing) (Scenario A):

- HBV DNA ≥LLOQ will be exclusionary
- A participant with HBV DNA <LLOQ may be enrolled and the participant should have HBV-DNA testing performed approximately every 12 weeks (in correlation with a scheduled visit). If HBV-DNA is ≥LLOQ, the participant will require discontinuation of study intervention (Section 7.1).

Figure 4 Interpretation and Management of HBV Serologic Test Results



DNA=deoxyribonucleic acid, HBcAb=hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, LLOQ=lower limit of quantification.

[a] These participants should have HBV-DNA testing performed approximately every 12 weeks (in correlation with a scheduled visit). If HBV-DNA is ≥LLOQ, the participant will require discontinuation of study intervention (Section 7.1).

See Appendix 7 for country specific requirements.

8.3.9 Photography

Photography of rash and/or alopecia suspected to be attributable to participant's SLE will only be taken during the Main study using the provided electronic tablet. Initial photographs are required during the Main study if alopecia and/or rash is present at Screening or with new onset after Screening. Additional follow-up photographs are recommended during the Main study at timepoints outlined in the SoA through resolution. Photographs are recommended at the time of event resolution if resolution occurs during the Main study and may be taken at an unscheduled visit during the Main study if resolution occurs prior to a timepoint outlined in the SoA. Photographs are not to be taken at timepoints in the Main study after resolution photographs have been taken unless there is reoccurrence at which point photographs will again be required at initial re-occurrence and recommended at follow-up timepoints in the Main study as outlined in the SoA through resolution. Photographs are not required in the LTE with new onset or if an event which began during the Main study has not resolved.

Photographs will be anonymized to the extent possible in order to protect participant's identity. Additional instructions are provided in a separate manual.

Photographs taken during the Main study may be reviewed by the DAAG for purposes described in Section 10.1.4.3 or included in the CSR or other publications but will not be used for formal assessments of efficacy.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events 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 as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through 28 days after cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events 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 the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 6.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 6 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE 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.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born

with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.7 Events of Clinical Interest

CCI

8.4.8 Drug-device Combination Products/Combination Medicinal Products – Complaints, PQCs and Malfunctions

The method of documenting and reporting complaints, PQCs, and malfunctions will occur as below and in Appendix 4. Refer to Appendix 7 for country-specific information and definitions.

To fulfill regulatory reporting obligations worldwide, medical device information associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines.

All SAEs due to malfunction will be followed until resolution, stabilization, until the event is otherwise explained, or the participant or associated person is lost to follow-up.

PQCs/malfunctions, including those that involve a participant or any user/associated person, must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to the drug-device combination products/combination medicinal products being used in clinical studies.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the AE and the device constituent of combination product.

8.5 Treatment of Overdose

CCI [redacted]

[redacted] must be performed prior to the next dose of study intervention. If the overdose is associated with an AE, the participant should have the CBC with differential performed as soon as possible.

8.6 Pharmacokinetics

The decision as to which serum samples collected will be measured for evaluation of PK will be collaboratively determined by the Sponsor. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for additional PD markers. Blood samples collected may be stored and further analysis may be performed, if required.

Samples for PK and ADA should be drawn at the same time prior to study intervention administration.

CCI [redacted]

8.6.1 Blood Collection for Serum MK-6194

Sample collection, storage, and shipment instructions for serum samples are provided in the Laboratory Manual.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples are provided in the Laboratory Manual. Blood samples collected may be stored and further analysis may be performed, if required. See Appendix 7 for country-specific requirements.

8.7.1 Immunogenicity Assessments

Samples for ADA analysis will be collected prior to study intervention administration at the timepoints specified in the SoA. Samples for ADA and PK should be drawn at the same time. Confirmed ADA samples will be assayed for titer. Other assays for neutralizing antibodies, ADA domain mapping and cross-reactivity to WT-IL-2 may be performed. Sample collection, storage, and shipment instructions for serum samples are provided in the Laboratory Manual.

8.7.2 Immunophenotyping

Blood for immunophenotyping will be collected for all participants as outlined in the SoAs. Additional samples will be collected from participants that are part of the PK/PD/Biomarker Subpopulation as outlined in Section 1.3.4.

Blood collected for immunophenotyping will be assessed using the Treg immunophenotyping assay and TBNK-Treg assay. For all participants, blood will be collected for use in the TBNK-Treg. For participants in the Subpopulation, blood will be collected to use in both Treg-immunophenotyping and TBNK-Treg assays. For participants taking part in the PK/PD/Biomarker Subpopulation, samples must be shipped on the same day of collection. See Appendix 7 for country-specific requirements.

8.8 Biomarkers

The following samples for biomarker research will be collected from participants prior to study intervention administration as specified in the SoA:

- Blood for planned genetic analysis
- Blood for PBMC biomarkers
- Blood for serum biomarkers analysis
- Blood for DNA biomarkers analysis
- Blood for RNA biomarkers analysis

Sample collection, storage, and shipment instructions for biomarker samples are provided in the Laboratory Manual. See Appendix 7 for country-specific requirements.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

See Appendix 7 for country-specific requirements.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover samples listed in Section 8.8

See Appendix 7 for country-specific requirements.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

Scheduling Visits

A visit should occur within the recommended scheduling window shown in the SoA. Study visits that include study intervention dispensation (Section 1.3) should be scheduled at least 10 days apart to avoid overdose (Section 8.5).

Unscheduled Visits are allowed whenever necessary.

8.10.1 Screening/Rescreening Visits

Screening

Up to 6 weeks before intervention randomization, potential participants will be evaluated to determine whether they fulfill the entry requirements as set forth in Section 5. During Screening, the DAAG will review the SLE diagnosis (per EULAR/ACR 2019 classification) and disease activity scoring to affirm the assessments performed by the investigator were consistently and appropriately conducted according to the protocol and established clinical measure guidance/instructions.

Rescreening

Participants are allowed to rescreen 1 time. Participants who are rescreened will retain the original screening number assigned at the initial Screening Visit (Section 8.1.6). Once a participant has started the rescreening process, a new screening period will begin (ie, an additional 6 week window) during which time screening procedures will be repeated. If the participant's original screening laboratory results and procedures were not exclusionary and samples were taken and/or procedures were completed ≤6 weeks prior to the randomization

date, the original screening laboratory assessments and procedures do not need to be repeated.

If the informed consent has been updated, participants must be reconsented before rescreening. If no updates have been made, the informed consent from the original screening period should be reviewed with the participant and a verbal reconsent to continue in the study should be documented.

8.10.2 Main Study Treatment Period

Each visit should be performed as specified in the SoA.

Randomization Visit

A participant must not be randomized until the DAAG has, via IRT, affirmed the SLE diagnosis and SLE disease activity per associated entry criteria and that there are no clinical and/or administrative issues that would preclude participant randomization. (Section 10.1.4.3).

Main Study Double-blind Treatment Visits

Participants who satisfy all entry criteria will be randomized (via IRT) to the Main study at Visit 2 (Day 1).

Participants/caregivers will be educated by a trained member of the site staff on appropriate administration of study intervention (Section 8.1.9.3 and for country specific requirements, see Appendix 7) and use of the electronic tablet (Section 8.2.1). The first dose of study intervention will be witnessed by a member of the site staff in the clinic *after* completion of all other study procedures (Section 8.1.9.4). Witnessed dosing will occur at visits outlined in the SoA.

At **Visit 3** (1 day after Randomization) and **Visit 8** (1 day after the Week 12 visit), all participants will come to the study site for blood collection (24 hours [±12 hours] after study intervention administration), as outlined in the SoA. These samples are allowed to be collected by home health aides when permitted by local regulations.

Week 52 (Visit 18)

At Visit 18 (Week 52), all procedures for the Main study (Section 1.3.1, 1.3.2) need to be completed BEFORE the Week 52 dose intervention administration as the Week 52 dosing is part of the LTE.

8.10.3 Long-term Extension Period

Study procedures for the LTE are outlined in the SoA (Section 1.3). Participants who have completed the Main study on study intervention will continue in the LTE. Participants who were assigned to the placebo arm during the Main study period will be rerandomized to an

active arm in the LTE as outlined in Section 6.3.1. Participants who were assigned to an active MK-6194 arm during the Main study period will continue in the LTE in the same arm.

Participants who permanently discontinued study intervention will continue to be monitored in the study until the end of the study period in which they discontinued according to the parameters outlined in Section 8.10.5.

8.10.4 PK/PD/Biomarker Subpopulation Visits

At selected sites, additional PK/PD/biomarker samples will be collected from participants who consent as outlined in the SoA (Section 1.3.4) in addition to the activities listed in the Main study and LTE SoAs (Sections 1.3.1, 1.3.2, and 1.3.3).

During Visit 2, an additional PK sample will be collected 2 to 10 hours after study intervention administration. Participants will need to remain at, or come back to, the site to have this sample collected. If the PK sample is not able to be collected at Visit 2, then the sample will be collected 2 to 10 hours after study intervention administration at Visit 7.

Sample collections by home health aides are allowed for Visits 3A, 8A, 11A, and 17A when permitted by local regulations.

Participants who discontinue study intervention will no longer be part of this Subpopulation. See Appendix 7 for country-specific requirements.

8.10.5 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Any participant who prematurely discontinues study intervention will have a Discontinuation Visit as outlined in the SoA (Section 1.3). Participants will be encouraged to continue their participation in the study off study intervention until the end of the study period in which they discontinued and be followed for all remaining study visits for that period (Section 7.1) as outlined in the SoA with the following exceptions, which are not applicable after study intervention is discontinued:

- Efficacy procedures (ClinROs and PROs)
- Photography
- PK, PD, biomarker sample collection
- Study intervention dispense/return
- Witnessed dose
- Train/retrain participant on self-administration
- Dosing reminder telephone call

Discontinuation Visit assessments should be performed at the time of discontinuation. Any AEs present at the time of discontinuation should be followed in accordance with the safety requirements outlined in Section 8.4.

Concomitant therapies specifically prohibited (see Section 6.5 and Appendix 9) while the participant was on study intervention are no longer prohibited after discontinuation of study intervention except for live vaccines.

Note: At the discontinuation visit, IRT will be contacted for close out purposes.

8.10.6 Follow-up Telephone Call

Participants will be contacted at least 28 days (+7 days) after the last administration of study intervention to determine if any AEs have occurred since discontinuing study intervention. During this telephone call, AEs and concomitant medications information will be collected.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, there are changes made to the primary hypothesis, or the statistical methods related, then the protocol will be amended (consistent with ICH Guidance for Industry E9). Changes to non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding will be documented in a Statistical Analysis Plan and referenced in the CSR for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the SAP) will be developed to detail other planned analyses including those specific to the analysis of PK data.

9.1 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Sponsor. This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database of the main study will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

After the Week 28 primary efficacy endpoint assessment is complete, a study sub-team will be unblinded in order to perform and review the final analysis of results. A separate, blinded study sub-team (ie, blinded to participant-level intervention assignment) will then be assigned to continue the conduct of the long term extension study. The unblinded sub-team will notify the blinded study team of any sub-efficacious arm. Once the blinded team is notified of the sub-efficacious arm, the blinded study team may stop enrolling participants in the LTE in that particular arm. All personnel in the unblinded sub-team will be excluded from any future data review at the individual participant level.

The Biostatistics and Research Decision Sciences department will generate the randomized allocation schedule(s) for study intervention assignment.

Unblinding for Interim Analysis

A planned IA is described in Section 9.6. Study enrollment is likely to be ongoing at the time of the IA. Blinding to intervention assignment will be maintained at all investigational sites. The results of the IA will not be shared with the investigators prior to the completion of the study.

Results of the IA will be provided by the external unblinded statistician to the eDMC. The eDMC will serve as the primary reviewer of the IA results and will make recommendations for discontinuation of the study or modification to the MSD Executive Oversight Committee. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, limited Sponsor personnel may be unblinded to the treatment-level results in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of the IA will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC charter.

If futility criteria are met at the IA in both treatment arms, the study will stop early. If futility criteria are met for 1 treatment arm, further enrollment into this arm may be stopped provided enrollment is still ongoing in the Main study. If the study is not stopped for futility, the study will continue until all participants complete the safety follow-up telephone call after the last dose of study intervention in the LTE or discontinue. A full description of the eDMC responsibilities will be provided in the eDMC Charter.

The external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IA.

Long-term Extension

After the Main study, participants will enter a 52-week double-blind LTE. Participants who were assigned placebo during the Main study will be re-randomized in a 1:1 ratio to receive treatment of CCI MK-6194 CCI. Participants who were assigned to CCI MK-6194 CCI during the Main study will continue treatment on the same regimen during the LTE (Section 4.1).

If 1 treatment arm is determined to be futile at the IA, participants in that treatment arm completing the double-blind Main study will be switched to the non-futile arm for the LTE. When the Week 28 primary endpoint analysis is completed and reviewed, if a treatment arm is found to be sub-efficacious based on evaluation by the Sponsor, participants who are already part of the sub-efficacious arm may continue through the end of the treatment period, but there may be no new enrollment to the sub-efficacious arm in the LTE based upon recommendation from the Sponsor. Participants who are still part of the sub-efficacious arm in the Main study will finish the Main study as randomized but may be switched to the efficacious arm in the LTE.

9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.3.1 Efficacy Endpoints

Primary Efficacy Endpoint

- SRI-4 response at Week 28

Key Secondary Efficacy Endpoint

- BICLA response at Week 28

Other secondary efficacy endpoints are stated in Section 3.

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are stated in Section 3.

Derivation of efficacy endpoints will be provided in Section 4.2.1.1.

9.3.2 Safety Endpoints

Safety endpoints are stated in Section 3.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test results, and vital signs.

9.4 Analysis Populations

9.4.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the efficacy data analysis. The FAS population consists of all randomized participants who received at least one injection of study intervention. Participants will be analyzed by the treatment group assigned at Randomization.

The modified FAS CLASI population consists of all randomized participants with CLASI activity score ≥8 at baseline, who received at least one injection of study intervention. Participants will be analyzed by the treatment group assigned at randomization.

The modified FAS 28 Joint Count population consists of all randomized with 28 joint count score in participants with ≥3 swollen joints, ≥3 tender joints and ≥3 tender and swollen joints at baseline, who received at least one injection of study intervention. Participants will be analyzed by the treatment group assigned at randomization.

The ITT population will serve as an additional population for primary endpoint SRI-4 at Week 28 and secondary endpoint BICLA at Week 28. ITT population consists of all randomized participants. Participants will be analyzed by the treatment group assigned at randomization.

9.4.2 Pharmacokinetic Analysis Population

The population for PK data analysis will include all participants with at least 1 measurable PK sample after treatment with MK-6194.

9.4.3 Pharmacodynamic Analysis Population

The population for the PD endpoints will be the FAS population. All randomized participants who have at least 1 injection (including only partial) of study intervention and have at least 1 assessment for those analyses for which this is required will be included in this population.

9.4.4 Immunogenicity Analysis Population

The population for immunogenicity analysis will include all participants with at least 1 ADA assay result after treatment with MK-6194.

9.4.5 Safety Analysis Populations

The APaT population will be used for the safety data analysis. The APaT population consists of all randomized participants who received at least one injection of study intervention. Participants will be analyzed by the treatment actually received.

9.5 Statistical Methods

Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.7.

9.5.1 Estimand(s)

CCI

CCI

[redacted]

9.5.2 Statistical Methods for Efficacy Analyses

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

9.5.3.1 Overall Safety Assessment

The overall safety evaluation will include a summary (ie, frequency and percentage) by treatment group of the number of participants with at least 1 AEs, drug-related AEs, serious AEs, serious and drug-related AEs, discontinuation from study intervention due to an AE, and AE resulting in death.

Point estimates and 95% CIs of the differences between treatment groups in the percentages of participants will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. Figures and/or plots will be provided as needed.

For continuous safety measures, such as change from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment.

Table 8 summarizes analysis strategy for safety endpoints in this study.

Table 8 Analysis Strategy for Safety Variables

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between group CI[a]	Graphical Display
Overall Safety Assessment	Any AE Any serious AE Any drug-related AE Any serious drug-related AE Discontinued study treatment due to AE AE that resulted in Death	X X X X X X	X X X X X	
	Specific AEs, SOCs, or PDLCs (percentage ≥4 participants in any treatment groups)	X	X[a]	X[a]
	Change from Baseline Results (Labs, Vital Signs)	X		

AE=adverse event; CI=Confidence Interval; SOC=System Organ Class.
a. Threshold for incidence will be applied for CI and Graphical Display.

9.6 Interim Analyses

One planned IA will be conducted for futility when approximately CCI [redacted]
Results will be reviewed and presented to the eDMC where a recommendation based on the futility analysis will be communicated to the MSD Executive Oversight Committee. Details will be provided in the SAP.

The eDMC will perform periodic interim safety reviews and details will be specified in the eDMC charter.

9.7 Multiplicity

Multiplicity adjustment will be made for testing 2 dose regimens on the primary endpoints and the 2 dose regimens for the key secondary endpoint for the analysis, ie, for testing a family of the following hypotheses:

H_{11}: MK-6194 CCI [redacted] is superior to Placebo in SRI-4 response at Week 28

H_{12}: MK-6194 [redacted] is superior to Placebo in SRI-4 response at Week 28

H_{21}: MK-6194 [redacted] is superior to Placebo in BICLA response at Week 28

H_{22}: MK-6194 [redacted] is superior to Placebo in BICLA response at Week 28

The family-wise Type I error rate over the 2 dose regimens of the primary and secondary hypotheses mentioned above will be strongly controlled using a parallel gatekeeping method. The first family F1 will consist of H_{11} and H_{12} and the second family F2 will consist of H_{21}, H_{22}. Additional details will be provided in the SAP.

9.8 Sample Size and Power Calculations

The study will randomize 90 participants per arm in a 1:1:1 allocati

on ratio to receive CCI [redacted] and placebo in a double-blinded fashion. There is more than 80% power to demonstrate the superiority of at least 1 MK-6194 dose regimen over placebo at an overall 2-sided 5% alpha-level if the underlying treatment difference between the placebo rate and active rate is 20 percentage points. The rate of dropout and intercurrent events has been accounted for in the active and placebo rate assumptions. The placebo rate and active rate are assumed to be 40% and 60% respectively. The power and the sample size are calculated assuming one IA for futility. An arm is considered futile if the conditional power is less than 20%. The multiplicity was controlled using a Hochberg's test with the 2 arms.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and

healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Pursuant to Union law (Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation 536/2014), the Investigator is responsible for pseudonymizing and assigning a key-code/patient ID to each study subject. In addition, the Investigator is required by Union law to store the Key (linking the Patient ID to the full name of the study subject) at the site in the EU/EEA throughout the course of the study and for a designated period of time thereafter. Finally, the study site is only permitted to share pseudonymized study subject personal data with the Sponsor.

The European Data Protection Board, in its Recommendations 01/2020 on measures that supplement transfer tools to ensure compliance with the EU level of protection of personal data ("Recommendations"), states in Paragraph 85 that pseudonymization (of study subject) personal data under the conditions described above constitutes an effective supplemental measure.

Organizational measures are contractually imposed on third party vendors wherever possible, to ensure that Personal Data are protected by industry-best practices against accidental destruction or loss (physical/logical) which include regular backup procedures, Firewalls, and disaster recovery plans.

In support of Corporate Policy 1 Information Risk Management, on a Sponsor-wide basis all supplier relationships, both IT and non-IT related, are strongly encouraged to meet the Sponsor's Supplier Information Risk Management Standard. To protect the confidentiality, availability and integrity of Sponsor information, conformity to information risk requirements by supplier personnel, hardware and software may be measured, analyzed and appropriate corrective/preventive actions taken as necessary. Based on the supplier criticality, additional activities (e.g., on-site reviews, integrated business continuity exercises) may be required to ensure the cyber-resiliency of the supplier on an on-going basis.

The Sponsor has implemented (Corporate Policy 13.1 Information Security Standards Handbook) an organization-wide process to assign user access rights based on the whether the employee/contractor has a legitimate need to utilize a database in order to carry out his/her job; manager approval is required when granting user access rights (beyond those sites or databases intended for all employees/contractors); and a process is in place for an annual review by each manager of the user access rights currently in place. Organizational measures, also contractually imposed on third party vendors, to prevent data processing systems from being used by unauthorized persons include i) user identification and authentication procedures (e.g., special characters, minimum length, regular change of password), and ii) automatic blocking (e.g., password or timeout).

The Sponsor utilizes a database called "InForm", operated by Oracle, for the storage of its study subject clinical trial data. InForm is a role-based system and only authorized users can see the data. Sites may only see the data they have entered. Access by Sponsor users is restricted to only those associated with a specific clinical trial.

Study sites are provided with a password to access the database. Access to InForm requires https (Secure Socket Layer) with a FIPS 140-2 compliant algorithm to connect to the application via the study site's web browser. Once logged into the system, the connection between the database, located in Ashburn, Virginia, USA, and the site, is encrypted. The Sponsor also stores the name and access credentials of the Investigators and other site staff (Study Coordinators) who record patient data into InForm. Such study staff personal data is not pseudonymized. Note, such encryption during transmission may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Data, whether concerning a study subject or site staff, stored in the InForm database is encrypted. Note, such encryption may not meet all conditions imposed by the EDPB in its Recommendations for this encryption, on its own, to constitute an effective supplemental measure.

Whenever possible, organization wide measures are imposed on third party vendors to prevent unauthorized persons from gaining access to the data processing systems available on premises and in facilities (including databases, application servers and related hardware), where Personal Data are processed, include i) Access control system (ID reader, chip), ii) key management, card-keys procedures, and iii) on-site security personnel and alarm system.

InForm is a HIPAA Part 11 capable system. Any data entered/changed or deleted will be associated with a viewable audit trail.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20). Pursuant to organization-wide requirements, the Sponsor periodically conducts audits of the vendors providing IT services, including Oracle, the vendor supporting the InForm database. The most recent audit of Oracle and its operations of InForm occurred in May 2020. Finally, Oracle has obtained ISO 27001 certification for the various databases it offers to third parties as a service, including the InForm database.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on

various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.6) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Disease Activity Adjudication Group

With the objective to ensure enrollment of a patient population in line with entry criteria and to protect the integrity of trial results, a DAAG, composed of site-independent medically qualified physicians, will:

1. During the Screening period, review each participant's SLE diagnosis (per EULAR/ACR 2019 classification) and disease activity scoring to affirm the assessments performed by the investigator were consistently and appropriately conducted according to the protocol and established clinical measure guidance/instructions. The site independent reviewers will, via IRT, affirm SLE diagnosis and disease activity scoring per associated entry criteria and that there are no known clinical and/or administrative issues that would preclude participant randomization.

2. After Randomization, review each participant's OCS dosing to affirm the protocol required OCS taper is being followed and continue to review SLE disease activity scoring to affirm assessments performed by the investigator were consistently and appropriately conducted according to the protocol and established clinical measure guidance/instructions at individual visits and across visits.

During both Screening and after Randomization, the DAAG will query scoring as deemed necessary according to measure guidance/instructions until resolution of inconsistencies and clinical questions.

The DAAG charter will describe fully the responsibilities of the DAAG.

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.4.4 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the eDMC regarding the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and

all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required at a scheduled visit, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH % Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	nonfasting Glucose	Calcium	Alkaline phosphatase	
Urine analysis	• Creatinine • Protein			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for POCBP)			
Other Screening Tests	• FSH (as needed in PONCBP only) • Serology (HIV antibody, HBsAg, HBcAb, HCV antibody)[a] • QuantiFERON-TB test • PCR test (only required for participants exhibiting COVID-19 symptoms) • Lupus Autoantibody Panel and Antiphospholipid Panel (see Appendix 7 for country-specific requirements)			

Laboratory Assessments	**Parameters**
Other Tests	• Direct Coomb's Test to assess activity on BILAG-2004 (performed locally if necessary). **Note: I**f sample is unable to be processed due to stability or other issues in sample processing, a redraw will NOT be required unless needed for the workup of anemia. • Anti-dsDNA and complement (C3, C4) to assess activity on hybrid SLEDAI

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; COVID-19= coronavirus infection disease 2019; DNA= deoxyribonucleic acid; dsDNA=double strand DNA; FSH=follicle-stimulating hormone; HBcAb= hepatitis B core antibody; HBsAb= hepatitis B surface antibody; HBV= hepatitis B virus; hCG=human chorionic gonadotropin; HCV= hepatitis C virus; HIV= human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PCR= polymerase chain reaction; POCBP=participant of childbearing potential; PONCBP=participant of nonchildbearing potential; RBC=red blood cell; RNA= ribonucleic acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; ULN=upper limit of normal; WBC= white blood cells.

a. Further testing will be needed for:

- Participants with positive HBcAb and negative HBsAg must have further testing for HBV-DNA.
- Participants with positive HCV Ab must have further testing for HCV-RNA.

Note: All Study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy tests and COVID-19 PCR test.

See Appendix 7 for additional country specific requirements.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or 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.
- Exacerbation of a chronic or intermittent preexisting 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.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT 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).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 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.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- 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.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) 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 (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - 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 used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

  Exposure: Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  Time Course: Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

Dechallenge: Was the study intervention discontinued or dose/exposure/frequency reduced?

- If yes, did the AE resolve or improve?
- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)

Rechallenge: Was the participant reexposed to the study intervention in this study?

- If yes, did the AE recur or worsen?
- If yes, this is a positive rechallenge.
- If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).

  Yes, there is a reasonable possibility of study intervention relationship:

  - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

  No, there is not a reasonable possibility of study intervention relationship:

  - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the 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 the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.

  Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

  If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

  Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Drug–Device Combination Products/Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

The recording and follow-up procedures described in this protocol apply to drug-device combination products/combination medicinal products. For purposes of this section, medical devices in scope for device information collection include drug-device combination products/combination medicinal products listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

See Appendix 7 for country-specific requirements.

10.4.1 Definitions

Combination Product – A product composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.

Complaint – Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part – A drug, device, or biological product that is part of a combination product.

Malfunction – The failure of a device including the device component of a combination product to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the medical device/device constituent part. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Medical Device – Any instrument, apparatus, appliance, implement, machine, contrivance, implant, in-vitro reagent or other similar or related article, including a component part, or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

PQC – Any communication (written or oral) that describes a potential defect related to the identity, strength, quality, purity, or performance of a product identified by external customers. This includes potential device or device component malfunctions.

Serious Deterioration of Health/Serious Injury/Serious Illness – This includes:

1. Life-threatening illness, even if temporary in nature,

2. Results in permanent impairment of a body function or permanent damage to a body structure, or

3. A condition necessitating medical or surgical intervention, including hospitalization or prolonged hospitalization to preclude permanent impairment of a body function or permanent damage to a body structure.

4. Cases that are considered medically significant,

5. Fetal distress, fetal death, or any congenital abnormality or birth defects.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

Japan specific definitions and documenting/reporting requirements can be found in Section 10.7.

10.4.2 Recording, Assessing Causality, and Follow-up of Complaints, PQCs/Malfunctions

Recording

When a complaint, including PQC/malfunction occurs it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

Adverse Events occurring during the study will be recorded in the participant's medical records (or equivalent), in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines (or equivalent). Device constituent part of drug-device combination product/combination medicinal product information (regardless of participant or associated person) will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor. It is important that the investigator provides an assessment of causality (relationship to the medical device) at the time of the initial report.

Assessing Causality

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

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 should be considered and investigated.

Follow-up

The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

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

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[b,d] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception [b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception [b,c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. 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.
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [b] Penile/external condoms must be used in addition to the POCBP's hormonal contraception. [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin-releasing IUD. Note: • Tubal occlusion includes tubal ligation

CTFG= Clinical Trial Facilitation Group; IUD= intrauterine device; IUS= intrauterine hormone-releasing system; POCBP= participant of childbearing potential.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

See Appendix 7 for country-specific requirements.

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed

from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

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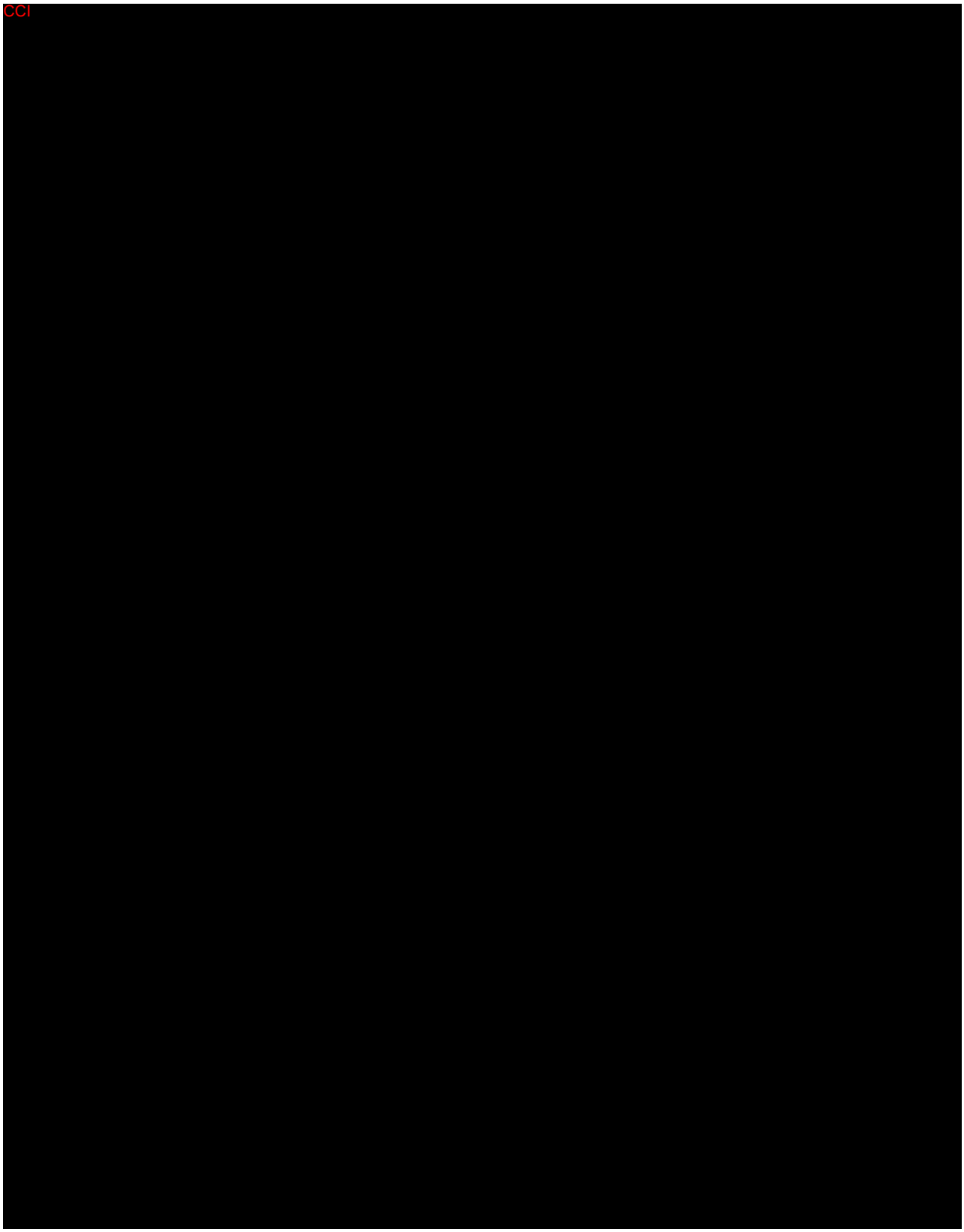

Section 1.3.1 Main Study Schedule of Activities – Week 0 to Week 52

Study Period:	**Screen**	**Main Study Double-blind Treatment Period**												**Notes**
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**10**	**11**	**TC**	**12**	
Scheduled Days	Wk -6 to Day -1	Day 1	Day 2 (24h post Day 1 dose)						24h post Wk 12 dose						
Week		0	0	2	4	6	8	12	12 +1d	16	20	24	26	28	
Day		1	2	15	29	43	57	85	86	113	141	169	183	197	
Recommended Window:			±12 h	±3d	±3d	±3d	±7d	±7d	±12 h	±7d	±7d	±7d	±3d	±7d	
Safety Procedures															
HBV-DNA testing	X							X				X			Only for participants with positive HBcAb and/or positive HBsAb and HBV-DNA <LLOQ at Screening.

Section 1.3.2 Main Study Schedule of Activities – Week 0 to Week 52 (continued)

Study Period:	**Main Study Double-blind Treatment Period**						**Discon**	**Notes**
Visit Number/Title:	**13**	**14**	**15**	**16**	**17**	**18[a]**		
Week	32	36	40	44	48	52		
Day	225	253	281	309	337	365		
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d		
Safety Procedures								
HBV-DNA testing		X			X		X	Only for participants with positive HBcAb and/or positive HBsAb and HBV-DNA <LLOQ at Screening.

Section 1.3.3 Long-term Extension Schedule of Activities – Week 52 to Week 106

Study Period	**Double-blind Long-term Extension Treatment Period**									**Disc on**	**FU**	**Notes**
Visit Number/Title:	**18[a]**	**19**	**20**	**21**	**22**	**23**	**24**	**TC**	**25**		**TC**	
Week	52	54	56	60	64	76	90	102	104		106	
Day	365	379	393	421	449	533	631	715	729		743	
Recommended Window:	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±3d	±7d		+7d	
Safety Procedures												
HBV-DNA testing			X		X	X	X		X	X		Only for participants with positive HBcAb and/or positive HBsAb and HBV-DNA <LLOQ at Screening.

Section 10.4 Appendix 4: Drug-Device Combination Products/Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Section 10.4.1 Definitions

Medical Device - Devices, etc. (other than regenerative medicine products) intended for use in the diagnosis, treatment, or prevention of disease in humans or animals, or intended to affect the structure or functions of the body of humans or animals.

Combination Medicinal Product - The products to be manufactured and marketed as a single drug, medical device, or regenerative medical product by combining two or more different type of drugs, medical devices or processed cells that are presumed to fall under the category of drugs, medical devices, or regenerative medical products if it is distributed alone.

Malfunction - When the device constituent part of a combination medicinal product, as described in the protocol, has quality, safety, or performance issue, such as damage or failure in operation, regardless of the stage of design, delivery, storage, or use.

Serious Adverse Event due to Malfunction - An SAE occurring in participant and/or the associated person in clinical trial caused by, or suspected to be caused by, the use of the device constituent part of the combination medicinal product, as described in the protocol.

Malfunction That may Lead to Serious Adverse Events - Any malfunction of a device constituent part of a combination medicinal product, as described in the protocol, which might have led to the death of a participant (and/or the associated person), or to a serious deterioration in their state of health. “Which might have led to” means there is the possibility death, or a serious deterioration might have occurred in a participant (and/or the associated person), although no event has occurred.

Section 10.4.2 Recording, Assessing Causality, and Follow-up of Complaints, PQCs/Malfunctions

Malfunction which may lead to SAEs will be reported to the Sponsor within 5 calendar days of learning of the information via a paper reporting form.

10.7.5 France-Specific Requirements

Section 5.2: Exclusion Criteria

In addition to all exclusion criteria listed in Section 5.2, the General principles relating to research involving human beings (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1) are to be followed.

Adults protected by laws, persons deprived of their liberty by a judicial or administrative decision, those hospitalized without consent in accordance with local law as further defined in the informed consent form, persons admitted to a health or social institution for purposes

other than research, and adults who are subject to a legal protection measure or who are unable to express their consent are not eligible to participate.

10.8 Appendix 8: Classification Criteria for Antiphospholipid Syndrome

Antiphospholipid syndrome is present if at least 1 of the clinical criteria and 1 of the laboratory criteria that follow are met:
Clinical Criteria
1. *Vascular thrombosis* One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. *Pregnancy morbidity* a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10-week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b. One or more premature births of a morphologically normal neonate before the 34-week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency; or c. Three or more unexplained consecutive spontaneous abortions before the 10-week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of participants who have more than 1 type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of participants according to a, b, or c above.
Laboratory Criteria
1. LA present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or >the 99th percentile), on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

3. Anti-beta2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on 2 or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

10.9 Appendix 9: Examples of Commonly Used Medications and Vaccines

Biologic Therapies

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are not allowed at any time prior to Randomization and throughout the study until the last dose of study intervention. Examples of immune checkpoint inhibitors include, but are not limited to, the medications in Table 10.

Table 10 Commonly Used Immune Checkpoint Inhibitors

PD-1 Inhibitors	PD-L1 Inhibitors	CTLA-4 Inhibitors
Cemiplimab Nivolumab Pembrolizumab	Atezolizumab Avelumab Durvalumab	Ipilimumab Tremelimumab
CTLA-4= cytotoxic T-lymphocyte-associated protein 4; PD-1=programmed cell death protein 1; PD-L1= programmed cell death ligand 1.		

Biologic Therapies with Immunosuppressive Potential

Biologic therapies with immunosuppressive potential are prohibited within 3 months or 5 half-lives (whichever is longer) prior to Randomization and throughout the study until the last dose of study intervention. Examples of prohibited biologics include, but are not limited to, the medications in Table 11.

Table 11 Commonly Used Biologic Therapies

Name of Medication		
Abatacept	Golimumab	Reslizumab
Adalimumab	Infliximab	Risankizumab
Anakinra	Ixekizumab	Secukinumab
Anifrolumab-fnia	Lebrikizumab	Tocilizumab
Belimumab	Mepolizumab	Tralokinumab
Certolizumab	Natalizumab	Ustekinumab
Dupilumab	Nemolizumab	Vedolizumab
Etanercept		
Guselkumab		

Non-immunosuppressive biologic therapies may be used; the Sponsor Clinical Director must be consulted before use.

Advanced Immunosuppressive Small Molecule Medications

JAK inhibitors, PDE4 inhibitors, S1P modulators, and TYK2 inhibitors are prohibited within 4 weeks prior to Randomization and throughout the study until the last dose of study intervention. Examples of these medications include, but are not limited to, those in Table 12.

Table 12 Commonly Used Advanced Immunosuppressive Small Molecule Medications

JAK Inhibitors[a]		PDE4 Inhibitors	S1P Modulators	TYK2 Inhibitors
Abrocitinib	Pacritinib	Apremilast	Fingolimod	Deucravacitinib
Baricitinib	Peficitinib	Cilomilast	Ozanimod	
Delgocitinib	Ritlecitinib	Crisaborole	Ponesimod	
Fedratinib	Ruxolitinib	Ibudilast	Siponimod	
Filgotinib	Tofacitinib	Roflumilast		
Oclacitinib	Upadacitinib			

JAK = Janus kinase; PDE4 = phosphodiesterase 4; S1P = sphingosine 1-phosphate; TYK2 = tyrosine kinase 2.
[a] JAK1, JAK2, and/or JAK3 isoforms.

Vaccines

It is recommended that participants be brought up to date with immunizations prior to Screening, in line with current local immunization guidelines.

Inactive (Non-live) Vaccines

Administration of inactive (non-live) vaccines is permitted prior to and during the study according to local practice. Examples of common non-live vaccines include, but are not limited to, the following:

- Injectable influenza vaccine
- Pneumococcal vaccine
- Shingrix (herpes zoster; recombinant, adjuvanted) vaccine
- Pertussis (Tdap) vaccine
- SARS-CoV-2 vaccine (inactivated, mRNA, RNA)

Live Vaccines

Administration of JYNNEOS (smallpox/mpox [also referred to as monkeypox] vaccine, live, non-replicating) is permitted.

Except for JYNNEOS, other live vaccines are prohibited within 4 weeks (or longer if required locally) prior to Randomization and during the study until 6 weeks after the last dose of study intervention. Examples of prohibited live vaccines include, but are not limited to, the following:

- Bacille Calmette-Guerin vaccine
- Measles-mumps-rubella or measles-mumps-rubella-varicella vaccine
- Monovalent live influenza A (H1N1) vaccine (intranasal)
- Oral polio vaccine
- Rotavirus vaccine
- Seasonal trivalent live influenza vaccine (intranasal)
- Smallpox vaccine
- Typhoid vaccine (oral)
- Varicella (chicken pox) vaccine
- Yellow fever vaccine
- Zostavax (herpes zoster, live attenuated) vaccine

10.10 Appendix 10: Hypereosinophilic Syndrome or Eosinophil-Associated Organ Injury

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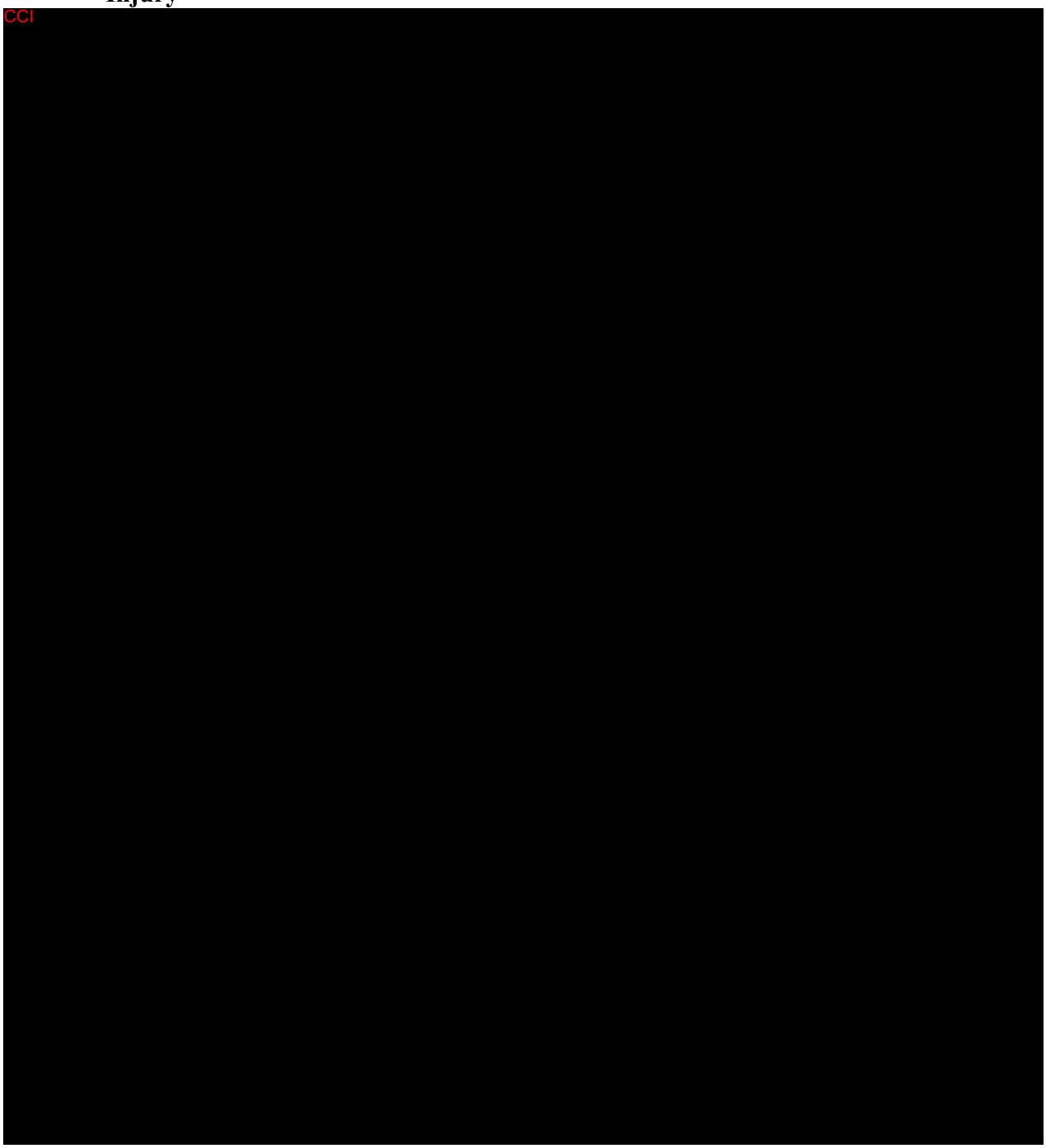

10.11 Appendix 11: Oral Corticosteroids

Table 14 outlines oral OCS equivalents.

Table 14 Oral Corticosteroid Dose Equivalents

Oral Corticosteroid	**Dose Equivalent to Prednisone**						
Prednisone	**2.5 mg**	**5 mg**	**7.5 mg**	**10 mg**	**12.5 mg**	**15 mg**	**20 mg**
Cortisone	12.5 mg	25 mg	37.5 mg	50 mg	62.5 mg	75 mg	100 mg
Hydrocortisone	10 mg	20 mg	30 mg	40 mg	50 mg	60 mg	80 mg
Prednisolone	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20 mg
Methylprednisolone	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg	16 mg
Triamcinolone	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg	16 mg
Budesonide	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	8 mg
Dexamethasone	0.375 mg	0.75 mg	1.125 mg	1.5 mg	1.875 mg	2.25 mg	3 mg

Adapted from Uptodate.com

10.12 Appendix 12: Prohibited Medications Associated With High Risk of QT Prolongation

Table 15 outlines medications associated with high risk of QT prolongation.

Table 15 List of Medications with High Risk of QT Prolongation

Adagrasib	Cisaparide	Lenvatinib	Selpercatinib
Ajmaline	Delamanid	Levoketoconazole	Sertindole
Amiodarone	Disopyramide	Methadone	Sotalol
Arsenic trioxide	Dofetilide	Mobocertinib	Terfenadine
Astemizole	Dronedarone	Papaverine (intracoronary)	Vandetanib
Bedaquiline	Haloperidol (IV)	Procainamide	Vernakalant
Bepridil	Ibutilide	Quinidine	Ziprasidone
Chlorpromazine	Ivosidenib	Quinine	

Source: UpToDate.com; Acquired long QT syndrome: Definitions, pathophysiology, and causes.

10.13 Appendix 13: TB Risk Factor Assessment Questionnaire

For screening TB risk assessment, ask Part I and Part II questions.

For annual TB risk assessment, only ask the Part I questions.

Part I:

1. Has an immediate family member or other close contact been newly diagnosed with or treated for active or latent tuberculosis during the last 3 months?
2. Within the past year, have you or an immediate family member, had any of the following problems lasting for 3 weeks or longer which remained unexplained:

- Chronic cough
- Production of sputum
- Blood-streaked sputum
- Weight loss
- Fever
- Fatigue/tiredness
- Night sweats
- Shortness of breath

Part II:

1. Have you ever been diagnosed or treated for active or latent tuberculosis?
2. Have you lived in or had prolonged (>30 days) travels to any of the following high burden TB endemic regions?

- Angola
- Bangladesh
- Brazil
- Cambodia
- Central African Republic
- China
- Congo
- Democratic People's Republic of Korea
- Democratic Republic of the Congo
- Ethiopia
- Gabon
- India
- Indonesia
- Kenya
- Lesotho
- Liberia
- Mongolia
- Mozambique
- Myanmar
- Namibia
- Nigeria
- Pakistan
- Papua New Guinea
- Philippines
- Russian Federation
- Sierra Leone
- South Africa
- Thailand
- Uganda
- United Republic of Tanzania
- Viet Nam
- Zambia
- Zimbabwe

3. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?

https://www.cdc.gove/tb/topic/testing/diagnosingltbi.htm
Global tuberculosis report 2023 (who.int)

10.14 Appendix 14: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
CCI	[redacted]
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANCOVA	analysis of covariance
APaT	All-Participants-as-Treated
APS	antiphospholipid syndrome
AST	aspartate aminotransferase
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BP	blood pressure
CBC	complete blood count
CD	cluster of differentiation
CFR	code of federal regulations
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	cutaneous lupus erythematosus
ClinRO	clinician-reported outcomes
Cmax	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus infection disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
Ctrough	trough concentration
CXR	chest x-ray

Abbreviation	Expanded Term
DAAG	Disease Activity Adjudication Group
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
dsDNA	double strand DNA
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
CCI [redacted]	[redacted]
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
CCI [redacted]	[redacted]
FAS	Full Analysis Set
FBR	future biomedical research
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen

Abbreviation	Expanded Term
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
CCI [redacted]	[redacted]
HIV	human immunodeficiency virus
HR	heart rate
HRQL	health-related quality of life
HRT	hormone replacement therapy
HTA	health technology assessment
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2	interleukin-2
IL-2R	IL-2 receptor
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JAK	Janus kinase
JRCT	Japan Registry of Clinical Trials

Abbreviation	Expanded Term
LDA	longitudinal data analysis
LLDAS	low level of disease activity
LLOQ	lower limit of quantitation
LTE	long-term extension
MAD	multiple ascending dose
MCP	metacarpophalangeal
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MLE	maximum likelihood estimate
MOD	modeling
mRNA	messenger RNA
M&N	Miettinen and Nurminen
NK	natural killer
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug(s)
OCS	oral corticosteroids
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PDE4	phosphodiesterase-4
PDLC	predefined limit of change
PGA	physician's global assessment
PIP	proximal interphalangeal
PK	pharmacokinetic
POCBP	participant of childbearing potential
PONCBP	participant of not childbearing potential
PPD	purified protein derivation
PQC	product quality complaint
PRO	patient-reported outcome
CCI	[redacted]

Abbreviation	Expanded Term
CCI [redacted]	[redacted]
QFT	QuantiFERON-TB Test
CCI [redacted]	[redacted]
RNA	ribonucleic acid
RR	respiratory rate
S1P	sphingosine -1-phosphate
SAC	Scientific Advisory Committee
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SELENA	Safety Estrogen in Lupus Erythematosus National Assessment
CCI [redacted]	
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLAB	supplemental laboratory test(s)
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
CCI [redacted]	[redacted]
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
SPF	sun protection factor
SRI-4	systemic lupus erythematosus responder index
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBNK	T cells, B cells, and NK cells

Abbreviation	Expanded Term
Tmax	time to maximum concentration
Treg	regulatory T cells
TYK2	tyrosine kinase 2
UC	ulcerative colitis
ULN	upper limit of normal
UTN	Universal Trial Number
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VAS	visual analog scale
WBC	white blood cell

11 REFERENCES

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