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 Non-Segmental Vitiligo
NCT number:	NCT06113328
Document Date:	09-April-2024

TITLE PAGE

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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 Non-Segmental Vitiligo

Protocol Number: 007-02

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	06113328
EU CT	2023-503502-37-00
EudraCT	Not applicable
JRCT	JRCT2031230622
WHO	Not applicable
UTN	U1111-1287-4329
IND	165557

Approval Date: 09 April 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	09-APR-2024	This amendment was created to enhance requirements for HBV safety monitoring.
Amendment 01	08-DEC-2023	This amendment was created to fulfill a request by the health authority in France.
Original Protocol	27-JUL-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

This amendment was created to enhance requirements for 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 requirements for 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 of day/week for scheduling purposes.
Section 1.3.1, Double-Blind Treatment Period	Verbal review at TC was added to the Participant Reminder Log: review/collect row.	Clarification of expectations during TC visits.
	Reference to Section 8.3.8 was added to the HIV, HBV, and HCV testing row.	Refer to rationale for change in Section 8.3.8.
	A separate row for HBV-DNA testing was added.	Refer to rationale for change in 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.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3.2, Blinded Extension Period	Removed Week 54 scheduled time for conducting the Follow-up TC and added +7-day window.	Follow-up TC should be conducted 28 days after last dose of study intervention.
	Verbal review at TC was added to the Participant Reminder Log: review/collect row.	Refer to rationale for change in Section 1.3.1.
	A row for HBV-DNA testing was added.	Refer to rationale for change in Section 8.3.8.
Section 2.1, Study Rationale	Description of vitiligo disease activity was expanded.	Clarified definition of disease activity.
Section 4.1, Overall Design	Clarified that participants will stay in the study unless consent is withdrawn.	Updated for protocol consistency.
	Modified text to indicate that participants will alternate between placebo and MK-6194.	Placebo and MK-6194 are both considered study interventions.
	Modified the text to indicate that enrollment for the PK/PD/Biomarker sampling will be at least 15 participants per arm.	To avoid misunderstanding the number of subpopulation participants.
	Added definition of follow-up safety TC.	Refer to rationale for change in Section 1.3.2 regarding follow-up TC.
Section 4.2.1.3, Pharmacokinetic Endpoints	Modified the text to indicate that enrollment for the PK/PD/Biomarker sampling will be at least 15 participants per arm.	Refer to rationale for change in Section 4.1.
Section 4.2.1.4, Pharmacodynamic Endpoints	Modified the text to indicate that enrollment for the PK/PD/Biomarker sampling will be at least 15 participants per arm.	Refer to rationale for change in Section 4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 4.2.1.6, Planned Exploratory Biomarker Research	Removed microbiome analysis.	Not applicable to this study.
Section 5.2, Exclusion Criteria	In exclusion criterion #12, HBV-DNA testing description was added, and the HCV definition was updated.	Refer to rationale for change in Section 8.3.8.
	Moved QuantiFERON-TB Gold testing guidance from criterion #13 to corresponding Section 8.3.6.	To clarify study entry guidance and initial TB retesting.
	In exclusion criterion #19, Table 1 Prohibited Medications, the 5-drug half-lives period of phototherapy was deleted.	Phototherapy does not have a half-life.
	A footnote was added to Table 1 Prohibited Medications to indicate that medications are prohibited until the last dose of study intervention is administered.	Updated to align with Sections 6.5 and 8.1.5.2.
Section 6.3.1, Intervention Assignment	Modified text to indicate that participants will alternate between placebo and MK-6194.	Refer to Section 4.1 rationale regarding study intervention.
Section 6.3.2, Stratification	Descriptions of stratification factors were expanded.	Updated to address investigator/site feedback.
Section 7.1, Discontinuation of Study Intervention	Added criterion for discontinuation if HBV-DNA is ≥LLOQ.	Refer to rationale for change in Section 8.3.8.
Section 8.1.1.3, Consent for PK/PD/Biomarker Subpopulation	Text added to indicate PK/PD/Biomarker consent will be collected at selected sites.	PK/PD/Biomarker testing is limited to selected sites.
Section 8.1.11, Participant Blinding/Unblinding	Added treatment unblinding guidance.	Inadvertently omitted during original protocol creation.
Section 8.1.13, PK/PD/Biomarker Subpopulation	Modified the text to indicate that enrollment for the PK/PD/Biomarker sampling will be at least 15 participants per arm.	Refer to rationale for change in Section 4.1.

Section Number and Name	Description of Change	Brief Rationale
Section 8.2.1, PROs	Added PROs timing and training information.	To harmonize with other sections of the protocol.
Section 8.3.2, Vital signs	HR and BP will be assessed similarly.	Corrected to avoid confusion.
	Added collection of vital signs timing exception.	Corrected a protocol inconsistency.
Section 8.3.6, TB Testing	Added TB testing guidance.	Refer for change in Section 5.2 regarding TB testing.
Section 8.3.7, Chest X-ray	Added the focus of chest x-rays is to identify TB.	Added as additional investigator guidance.
Section 8.10.2, Double-Blind Treatment Period	Added clarification regarding PROs administration.	Refer to rationale for change in Section 8.2.1.
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	Added local TB testing to the footnote in the Protocol-required Safety Laboratory Assessments table.	TB testing will be conducted locally, as applicable.
Section 10.3.2, Definition of AE	New or progression of existing cancer was added to the list of events meeting the AE definition.	Refer to rationale for change in Section 8.1.11.
Section 10.7.4, Country-specific Requirements for Japan	HBV description was updated to match the global study protocol.	Refer to rationale for change in Section 8.3.8.
	HBV-DNA testing was removed from Visit 2.	To eliminate redundancy.
	Section 10.4.1 definitions were updated.	To align with current country-specific guidance.
Section 10.10, TB Risk Factor Assessment Questionnaire	Appendix 10 was added to help assess TB risk outlined in Section 8.3.6.	Refer to rationale for change in 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 Non-Segmental Vitiligo

Short Title: MK-6194 in Adult Participants with Non-Segmental Vitiligo

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

In adult participants with non-segmented vitiligo:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of MK-6194 on the percent change from baseline in Facial Vitiligo Area Scoring Index (F-VASI) at Week 24 H1: At least 1 MK-6194 dose is superior to placebo on percent change from baseline in Facial Vitiligo Area Scoring Index (F-VASI) at Week 24	F-VASI
To evaluate the safety and tolerability of MK-6194	AEs Discontinuation due to AEs
Secondary Objective	**Secondary Endpoint**
To evaluate the efficacy of MK-6194 on the percent change from baseline in Total Vitiligo Area Scoring Index (T-VASI) at Week 24	T-VASI

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Vitiligo
Population	Adult participants with non-segmental vitiligo
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 28 months 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 58 weeks. See Appendix 7 for country-specific requirements.

Number of Participants:

Approximately 165 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
MK-6194 Q2W	MK-6194	3 mg	3 mg	SC	Double-Blind Treatment and Blinded Extension Periods	Test Product
MK-6194 Q4W	MK-6194	3 mg	3 mg	SC	Double-Blind Treatment and Blinded Extension Periods	Test Product
MK-6194 Q4W	Placebo	0 mg	0 mg	SC	Double-Blind Treatment and Blinded Extension Periods	Placebo
Placebo Q2W	Placebo	0 mg	0 mg	SC	Double-Blind Treatment Period	Placebo

SC=subcutaneous; Q2W=every 2 weeks, Q4W=every 4 weeks
Note: To maintain the blind for MK-6194 Q4W, alternating placebo will be administered between the MK-6194 doses. Participants randomized to the placebo arm Q2W during the Double-Blind Treatment Period will be rerandomized to MK-6194 Q2W or MK-6194 Q4W during the Blinded Extension Period.

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 4 weeks, each participant will receive study intervention for approximately 52 weeks (24 weeks Double-Blind Treatment Period + 28 weeks Blinded Extension Period), followed by a safety follow-up telephone call 28 days after last study intervention is administered.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

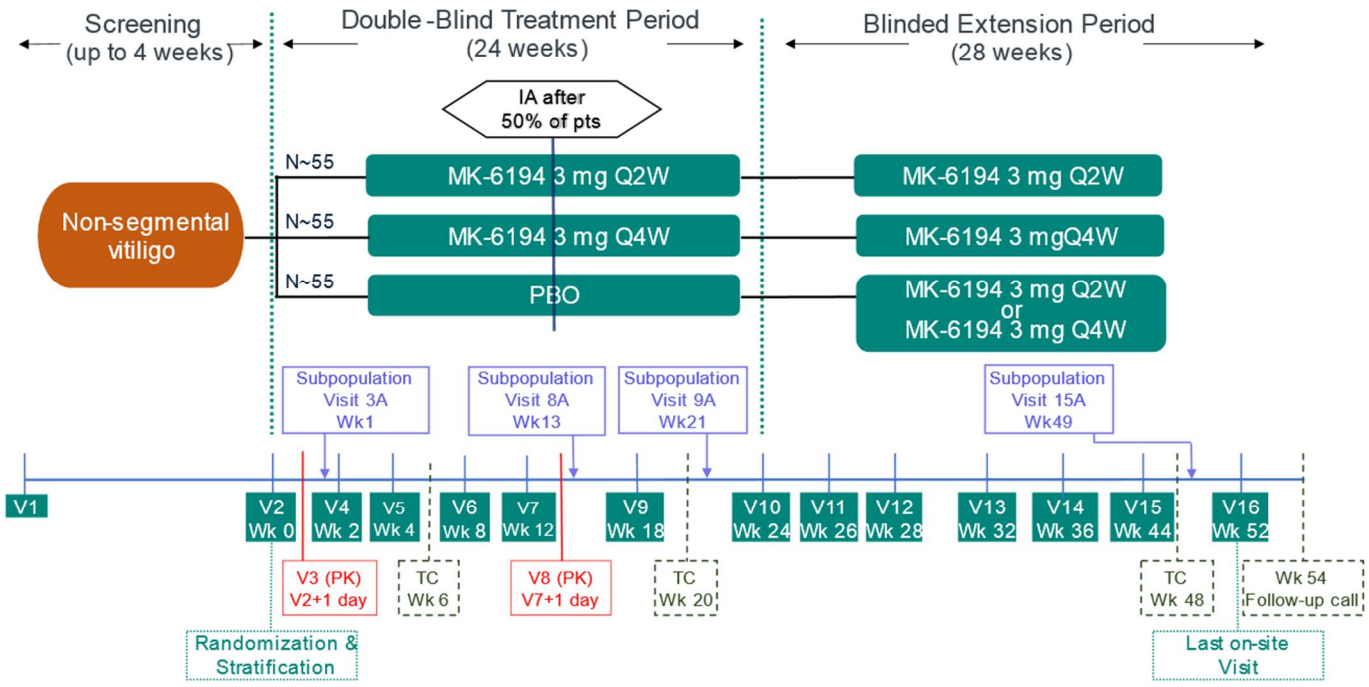
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



IA= interim analysis; PBO= placebo; PK= pharmacokinetics; pts= participants; Q2W= every 2 weeks; Q4W= every 4 weeks; TC= telephone call; V= visit; Wk(s)= week(s)

1.3 Schedule of Activities

1.3.1 Double-Blind Treatment Period

	Screen	Double-Blind Treatment Period												Notes
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week:	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86	127	141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Administrative Procedures														
Informed consent	X													
Informed consent for FBR	X													FBR consent is optional
IRT visit registration	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	
Inclusion/exclusion criteria	X	X												
Participant identification card	X	X												Add Randomization number to card at Visit 2.
IRT randomization		X												
Study intervention dispense/return		X		X	X		X	X		X		X	X	Dispense at Wks 2-18; return at all visits. Assess compliance of returned syringe(s).
SC injection: train/retrain participant on self-administration		X		X										Self-administration is preferrable. Retrain as necessary. See Section 8.1.9.3.
SC injection: witnessed dose		X		X				X						Study staff to ensure proper self-administration. technique. See Section 8.1.9.4.

	Screen	Double-Blind Treatment Period											Notes
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week:	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86	127	141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Participant Reminder Log: train/dispense		X		X	X		X	X		X				For recording study intervention administration, any complaints/illnesses, and any new medications taken between study visits.
Participant Reminder Log: review/collect				X	X	X	X	X		X	X	X	X	To be reviewed for accuracy. Verbal review at TC. See Section 8.1.9.5.
Dosing reminder telephone call						X					X			Additional reminders as necessary per site
Efficacy Procedures														PROs to be completed in order listed, before laboratory tests or other safety or efficacy procedures
VitiQoL Instrument		X						X				X	X	
VNS								X				X	X	
Patient Global Impression of Severity		X						X				X	X	
Patient Global Impression of Change/Meaningfulness								X				X	X	
Clinical Global Impression of Severity		X						X				X	X	
Clinical Global Impression of Change								X				X	X	
F-VASI	X	X		X	X		X	X		X		X	X	
T-VASI	X	X			X			X		X		X	X	
CCI														

	Screen	Double-Blind Treatment Period											Notes
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week:	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86	127	141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Other Procedures														
Photography (face)	X	X					X	X				X	X	If baseline photographs are sufficient, photographs at Randomization are not required. See Section 8.2.3.
Photography (total body)	X	X						X				X	X	If baseline photographs are sufficient, photographs at Randomization are not required. See Section 8.2.3.
CCI														
Safety Procedures														
Height	X													
Weight	X											X	X	
Vital signs	X	X		X	X		X	X		X		X	X	Taken after completion of PROs and before blood samples collection
Full physical examination	X											X	X	
Directed physical examination		X		X	X		X	X		X				Per institutional standards, consistent with local requirements
12-lead ECG	X													Locally read
Chemistry	X				X		X	X		X		X	X	
Hematology	X			X	X		X	X		X		X	X	

	Screen	Double-Blind Treatment Period												Notes
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week:	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86	127	141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Urinalysis (with microscopy)	X											X	X	To be performed at additional visits if clinical symptoms suggestive of UTI
Serum pregnancy test (hCG; POCBP only)	X													
FSH- (PONCBP only)	X													To confirm postmenopausal status. See Section 10.5.1.
Local urine pregnancy test (POCBP only)		X			X		X	X		X		X		Administered predose. If a urine test cannot be confirmed as negative (eg, an ambiguous result), serum test is required. See Appendix 7 for country-specific requirements.
TSH	X													
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	X	Only for participants with positive HBcAb and HBV-DNA <LLOQ at Screening.
TB testing	X													QFT TB Gold test or equivalent. See Section 8.3.6 and Section 5.2 (exclusion criterion #13).

	Screen	Double-Blind Treatment Period												Notes
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week:	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86	127	141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Chest X-ray	X													Posterior-anterior chest x-ray. Locally read. See Section 8.3.7.
AE/SAE review	X	X		X	X	X	X	X		X	X	X	X	
PK/PD/Biomarkers (All participants)														
Blood for serum ADA		X		X	X			X				X	X	Samples for ADA and PK should be drawn at the same time predose
Blood for serum PK		X	X	X	X			X	X			X	X	CCI [redacted]
Blood for genetic analysis		X												Predose from randomized participants only, See Section 8.8.1.
Blood for DNA analysis		X			X			X				X	X	Leftover sample will be stored for FBR. See Section 8.9.
Blood for immunophenotyping	X	X			X			X				X	X	See Section 8.7.2

	Screen	Double-Blind Treatment Period											Notes
Visit Number/Title:	**1** Screen	**2** Rand	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week:	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86	127	141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Blood for serum biomarkers analysis		X			X			X				X	X	Leftover sample will be stored for FBR. See Section 8.9.
Blood for RNA analysis		X						X				X	X	Leftover sample will be stored for FBR. See Section 8.9.

ADA= antidrug antibodies; AE= adverse event(s); d= day; Discon= discontinuation; DNA= deoxyribonucleic acid; EC=Ethics Committee; ECG= electrocardiogram; FBR= Future Biomedical Research; FSH= follicle-stimulating hormone; F-VASI= Facial Vitiligo Area Scoring Index; h= hour; HBcAb= hepatitis B core antibody; HBV= hepatitis B virus; HCV= hepatitis C virus; hCG= human chorionic gonadotropin; HIV= human immunodeficiency virus; IRB= Institutional Review Board; IRT= interactive response technology; LLOQ= lowest limit of quantitation; PD= pharmacodynamics; PK= pharmacokinetics; POCBP= Participant of childbearing potential; PONCBP= Participant of nonchildbearing potential; PROs=participant reported outcomes; Q2W= every 2 weeks; QFT= QuantiFERON; QoL= quality of life; Rand= randomization; RNA= ribonucleic acid; SAE= serious adverse event(s); SC= subcutaneous; TB= tuberculosis; TC= telephone call; TSH= thyroid-stimulating hormone; T-VASI= Total Vitiligo Area Scoring Index; UTI= urinary tract infection; V=visit; CCI [redacted]; VitiQoL= Vitiligo Quality of Life Instrument; VNS= Vitiligo Noticeability Scale; Wk(s)= Week(s).

(a) Procedures for the Blinded Extension portion of this visit are in Section 1.3.2.

1.3.2 Blinded Extension Period

Study Period:	**Blinded Extension Period**										**Notes**
Visit Number/Title:	**10[a]**	**11**	**12**	**13**	**14**	**15**	**TC**	**16**	**Discon**	**F/U TC**	
Scheduled Day/Week	Wk 24	Wk 26	Wk 28	Wk 32	Wk 36	Wk 44	Wk 48	Wk 52		28 Days After Last Dose	
Day	169	183	197	225	253	309	337	365			
Recommended Window:	±7d	±3d	±3d	±7d	±7d	±7d	±3d	±7d		+7d	
Administrative Procedures											
Prior/concomitant medication		X	X	X	X	X	X	X	X	X	
IRT visit registration	X	X	X	X	X	X		X	X		
IRT rerandomization	X										
Collect participant identification card from the Double-Blind Treatment Period	X										
New participant identification card	X										Add rerandomization number to card at Visit 10. See Section 8.1.3.
Study intervention dispense/return	X	X	X	X	X	X		X	X		Assess compliance of returned syringe(s). Dispense at Wks 24 to 44; return at all visits.
Participant Reminder Log: train/dispense	X	X	X	X	X	X					For recording study intervention administration, any complaints/illnesses, and any new medications taken between study visits
Participant Reminder Log: review/collect		X	X	X	X	X	X	X	X		To be reviewed for accuracy. Verbal review at TC. See Section 8.1.9.5.
Dosing reminder telephone call							X				Last dose to be administered at Wk 50. Additional reminders as necessary per site.
Efficacy Procedures											PROs to be completed in order listed, before laboratory tests or other safety or efficacy procedures
VitiQoL Instrument					X			X	X		
VNS					X			X	X		
Patient Global Impression of Severity					X			X	X		
Patient Global Impression of Change/Meaningfulness					X			X	X		
Clinical Global Impression of Severity					X			X	X		
Clinical Global Impression of Change					X			X	X		

Study Period:	**Blinded Extension Period**										**Notes**
Visit Number/Title:	**10[a]**	**11**	**12**	**13**	**14**	**15**	**TC**	**16**	**Discon**	**F/U TC**	
Scheduled Day/Week	Wk 24	Wk 26	Wk 28	Wk 32	Wk 36	Wk 44	Wk 48	Wk 52		28 Days After Last Dose	
Day	169	183	197	225	253	309	337	365			
Recommended Window:	±7d	±3d	±3d	±7d	±7d	±7d	±3d	±7d		+7d	
F-VASI			X	X	X	X		X	X		
T-VASI					X			X	X		
CCI											
Other Procedures											
Photography (face)					X			X	X		
Photography (total body)					X			X	X		
CCI											
Safety Procedures											
Weight								X	X		
Vital signs		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					Per institutional standards, consistent with local requirements.
Chemistry			X	X	X	X		X	X		
Hematology		X	X	X	X	X		X	X		
Urinalysis (with microscopy)								X	X		To be performed at additional visits if clinical symptoms suggestive of UTI.
Local urine pregnancy test (POCBP only)			X	X	X	X		X	X		Administered predose. If urine test not 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 at Screening.
AE/SAE review		X	X	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 same time predose
Blood for serum PK								X	X		Samples for ADA and PK should be drawn at same time predose
Blood for DNA analysis								X	X		Leftover sample will be stored for FBR. See Section 8.9.

Study Period:	**Blinded Extension Period**										**Notes**
Visit Number/Title:	**10[a]**	**11**	**12**	**13**	**14**	**15**	**TC**	**16**	**Discon**	**F/U TC**	
Scheduled Day/Week	Wk 24	Wk 26	Wk 28	Wk 32	Wk 36	Wk 44	Wk 48	Wk 52		28 Days After Last Dose	
Day	169	183	197	225	253	309	337	365			
Recommended Window:	±7d	±3d	±3d	±7d	±7d	±7d	±3d	±7d		+7d	
Blood for immunophenotyping								X	X		See Section 8.7.2
Blood for serum biomarkers analysis								X	X		Leftover sample will be stored for FBR. See Section 8.9.
Blood for RNA analysis								X	X		Leftover sample will be stored for FBR. See Section 8.9.

ADA= antidrug antibodies; AE= adverse event(s); d= day; Discon= discontinuation; DNA= deoxyribonucleic acid; FBR= future biomedical research; F/U= follow-up; F-VASI= Facial Vitiligo Area Scoring Index; HBcAb= hepatitis B core antibody; HBV= hepatitis B virus; IRT= interactive response technology; LLOQ= lower limit of quantitation; PD= pharmacodynamics; PK= pharmacokinetics; POCBP= Participant of childbearing potential; Q2W= every 2 weeks; QoL= quality of life; RNA= ribonucleic acid; SAE= serious adverse event(s); SC= subcutaneous; TC= telephone call; TSH= thyroid-stimulating hormone; T-VASI= Total Vitiligo Area Scoring Index; UTI= urinary tract infection; CCI [redacted] VitiQoL= Vitiligo Quality of Life Instrument; VNS= Vitiligo Noticeability Scale; Wk= Week.
(a) Procedures for the Double-Blind portion of this visit are in Section 1.3.1 and should be completed before Blinded Extension procedures

1.3.3 PK/PD/Biomarker Subpopulation

Study Period:	**PK/PD/Biomarker Additional Samples[a,]**											**Notes**
Visit Number/Title:	**1**	**2 Rand**	**3A**	**5**	**7**	**8A**	**9A**	**10**	**15A**	**16**	**Discon**	
Scheduled Day/Week:		Day 1 Wk0	Day 8 Wk 1	Wk 4	Wk 12	Wk 13	Wk 21	Wk 24	Wk 49	Wk 52		
			7 Days post Day 1 dose			7 Days post Wk 12 dose	7 Days post Wk 20 dose		7 Days post Wk 48 dose			
Day		1	8	29	85	92	148	169	344	365		
Recommended Window:			±1d			±1d	±1d		±1d			
Informed consent for additional PK/PD/Biomarker samples in Subpopulation	X											
Hematology			X			X	X		X			
Blood for PBMC		X				X	X		X			Leftover sample will be stored for FBR. See Section 8.9
Blood for serum PK		X*	X		X*	X	X		X			*Visit 2 or 7: 2h to 10h post dose. See Section 8.10.4 for details
Blood for DNA analysis			X			X	X		X			Leftover sample will be stored for FBR. See Section 8.9.
Blood for immunophenotyping	X	X	X	X	X	X	X	X	X	X		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
Blood for RNA analysis			X			X	X		X			Leftover sample will be stored for FBR. See Section 8.9

d= day; Discon= discontinuation; DNA= deoxyribonucleic acid; FBR= future biomedical research; PBMC= peripheral blood mononuclear cells; PD= pharmacodynamics; PK= pharmacokinetics; Rand= randomization; RNA= ribonucleic acid; Wk= Week.
[a] For participants at preselected 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 Treatment and Extension Period Schedule of Activities (Sections 1.3.1 and 1.3.2) for all study participants.

2 INTRODUCTION

2.1 Study Rationale

Human autoimmune disease results, in part, from dysfunctional or insufficient numbers of Tregs that cause organ damage by not properly restricting immune responses [Kolios, A. G. A., et al 2021]. MK-6194 is a novel IL-2M 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.

Vitiligo is an acquired chronic inflammatory skin depigmenting disorder resulting from selective destruction of melanocytes. This destruction leads to the development of typical vitiligo lesions defined as milky white, nonscaly macules with distinct margins. Progressive patchy loss of pigmentation from skin, overlying hair, and sometimes mucosa remains the basis of a diagnosis of vitiligo [Ezzedine, K., et al 2015].

Vitiligo is a common disease with a worldwide reported prevalence of 0.5 to 1 % overall, but with rates eg, as high as 8.8% in India. The difference of prevalence is not fully understood and might in part be due to differences in reporting frequency. It is by far the most common depigmenting disease. Adults and children of both sexes are equally affected, although women and girls often present for treatment more frequently [Ezzedine, K., et al 2015].

Vitiligo can be classified into 2 major forms, segmental and non-segmental vitiligo. The non-segmental form is the most common and will be studied in this trial. Non-segmental vitiligo develops at all ages, approximately 50% of patients present before the age of 20 and almost 70 to 80% before the age of 30, although it can also develop beyond the age of 40. Childhood-onset vitiligo (before age 12 years) is reported to be common and can affect more than 30% of patients. The course of the disease is unpredictable and phases of almost no progression can be followed by more active phases. In addition to new or extending lesions, other indicators of areas of higher disease activity are clinically assessable and include Koebner's phenomenon, trichrome lesions, confetti lesions, and inflammatory vitiligo lesions. The treatment trajectory depending on the activity status a patient is in might change the outcome, so it is important to assess and distinguish [Ezzedine, K., et al 2015].

While vitiligo has no impact on life expectancy, due to the nature of the color dissimilarity it has a great impact on the psychosocial aspect of affected patients' life and mental well-being. The unpredictability of the disease in the form of sudden new and enlarged lesions creates additional stress from this disease to the patient [Ezzedine, K., et al 2015].

The associated stigma results in a higher rate of psychiatric comorbidities[Ezzedine, K., et al 2015].

Currently there is only one FDA-approved treatment available, which is a topical JAKi, and it showed significant repigmentation when applied twice daily to up to 10% of the body surface [Rosmarin, D., et al 2022]. Other treatments include steroids, systemic and topical as well as calcineurin inhibitors, and phototherapy [Ezzedine, K., et al 2015]. All available

treatment options come either with a serious warning in their label, including a black box warning in the US for JAKi and/or a high patient burden so there remains a high unmet need for safe and tolerable treatment options [U.S. Prescribing Information 2023].

The pathophysiology of vitiligo is complex, but has not yet been fully understood and it involves multiple factors [Ezzedine, K., et al 2015].

Various theories have been suggested for the cause of melanocyte loss in vitiligo, with the autoimmune hypothesis having the strongest evidence. This includes the clinical association of vitiligo with other autoimmune disorders, such as autoimmune thyroid disease, type 1 diabetes, pernicious anemia, rheumatoid arthritis, systemic lupus erythematosus, and Addison disease as well as atopic background. These findings are consistently reported although the frequency varies[Alkhateeb, A., et al 2003].

A shared underlying genetic susceptibility to autoimmune diseases has been suggested as an increased frequency of autoimmune diseases have been reported in relatives of vitiligo patients.

Several studies in animals support the role of the innate immune response. An overactive so-called danger signaling cascade in vitiligo lesions has been shown and melanocytes from patients with vitiligo have proved more susceptible to oxidative stress than those from unaffected individuals and more difficult to culture ex vivo than those from healthy controls. In response to stressors, reactive oxygen species are released from melanocytes. This ultimately leads to the activation of innate immune cells (eg, natural killer cells and inflammatory dendritic cells). Reactive oxygen species can also initiate a signaling cascade through unfolded protein response activation. Induction of the unfolded protein response can result in the direct release of proinflammatory cytokines (interleukins 6 and 8) from melanocytes, which can antagonize the suppressor function of regulatory T cells [Ezzedine, K., et al 2015] [Seneschal, J., et al 2021].

The role of CD4+ T cells in the pathogenesis of the disease is still unclear, a possible role of dysregulated regulatory T cells has been suggested [Lili, Y., et al 2012] [Zhou, L., et al 2012]. GWAS identified a polymorphism of FOXP3, the master transcription factor of Tregs, in vitiliginous skin [Shen, C., et al 2016] as well as involvement of genes encoding IL2RA [Jin, Y., et al 2010] [Shen, C., et al 2016]. Additional data from skin lesions is suggesting an increased skin expression of CCL22 responsible for inducing the migration of Tregs into the skin. [Eby, J. M., et al 2015] Selective mouse models of depigmentation further suggests a role of regulatory Tregs by demonstrating FOXP3+CD3+cells were 2.6-fold more frequent in repigmented than depigmented areas [Eby, J. M., et al 2014].

The selective activation of Tregs is therefore a potential approach for improving vitiligo.

The primary objective of this study is to characterize the efficacy and safety of MK-6194 among participants with non-segmental vitiligo.

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 Teff. Tregs attenuate inflammatory processes by a variety of mechanisms that suppress the activity of Teff [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 2016] [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 C-terminus to the N-terminus of an effector function ablated human 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 Tconv 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 20.4 to 28.3 hours, and the geometric mean T_{max} was 10.5 to 13.5 hours. MK-6194 exposure was generally dose-proportional. There was no evidence of induction of pharmacologically or clinically relevant ADA to MK-6194 after a single administration.

CCI

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, a MAD study in participants with ulcerative colitis (P002), a MAD study in healthy participants (P003), a single-dose study in healthy Japanese participants (P004), a MAD trial in participants with atopic dermatitis (P008), and a study to evaluate the impact of injection site on PK and relative bioavailability in healthy participants (P013).

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 studies at single doses 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 cutaneous AEs, including injection-site reactions, and elevated absolute eosinophil count. The cutaneous AEs were generally mild or moderate in intensity, self-limited, and did not require medical therapy. Transient mild to moderate increased absolute eosinophil counts have been observed in some participants who received MK-6194, which returned to normal range or were trending toward normal by the end of the treatment. There have been no events of eosinophil-associated organ injury. Injection-site reactions and increased eosinophil counts have been previously reported in patients receiving recombinant IL-2, including low-dose IL-2, for the treatment of autoimmune diseases [Fanton, C., et al 2020] [Van Gool, F., et al 2014] [Rosenzwajg, M., et al 2019].

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

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In adult participants with non-segmented vitiligo:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of MK-6194 on the percent change from baseline in Facial Vitiligo Area Scoring Index (F-VASI) at Week 24 H1: At least 1 MK-6194 dose is superior to placebo on percent change from baseline in Facial Vitiligo Area Scoring Index (F-VASI) at Week 24	F-VASI
To evaluate the safety and tolerability of MK-6194	AEs Discontinuation due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of MK-6194 on the percent change from baseline in Total Vitiligo Area Scoring Index (T-VASI) at Week 24	T-VASI
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the efficacy of MK-6194 on the proportion of participants achieving 50%, 75%, and 90% improvement in F-VASI response at Week 24	F-VASI-50, F-VASI-75, F-VASI-90
To evaluate the efficacy of MK-6194 on the proportion of participants achieving 50%, 75%, and 90% improvement in T-VASI response at Week 24	T-VASI-50, T-VASI-75, T-VASI-90
To evaluate the efficacy of MK-6194 on the F-VASI score at all timepoints assessed and the proportion of participants achieving 25%, 50%, 75%, 90% improvement in F-VASI response at all timepoints assessed	F-VASI F-VASI-25/50/75/90
To evaluate the efficacy of MK-6194 on the T-VASI score at all timepoints assessed and the proportion of participants achieving 25%, 50%, 75%, 90% improvement in T-VASI response at all timepoints assessed	T-VASI T-VASI-25/50/75/90

To evaluate the efficacy of MK-6194 on investigator's assessment of severity and change in vitiligo at all timepoints assessed	CGI-S CGI-C
CCI [redacted]	
To evaluate the effect of MK-6194 on participant's quality of life and noticeability of vitiligo at all timepoints assessed	VitiQoL VNS
To evaluate the efficacy of MK-6194 on participant's assessment of severity and change in vitiligo at all timepoints assessed	PGI-S PGIC/M
To evaluate the PK of MK-6194 at 1 day post first dose and Week 12 dose (C_{max}) and at Weeks 2, 4, 12, 24, and end of study (C_{trough})	MK-6194 serum PK
To evaluate the PK of MK-6194 at 7 days post Weeks 0, 12, 20 and 48 in a subset of study participants	MK-6194 serum PK
To evaluate the immunogenicity of MK-6194 at predose and Weeks 2, 4, 12, 24, and end of study	ADA in serum (incidence and magnitude)
To evaluate the effect of MK-6194 on Tregs	Immunophenotyping 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 treatments administered, and mechanism of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study	Germline genetic variation and association to clinical data collected in this study

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 non-segmental vitiligo. This study is designed to evaluate the efficacy and safety of MK-6194 3 mg administered subcutaneously Q2W and 3 mg administered subcutaneously Q4W.

This study has 3 periods, Screening, Double-Blind Treatment, and Blinded Extension. During the screening period of up to 4 weeks, participants will be assessed for eligibility against the inclusion and exclusion criteria (see Section 8).

As it is unknown whether exposure to JAK inhibitors may affect response to an IL-2M, up to approximately 50% of participants study wide with prior JAKi exposure (topical and/or systemic) may be randomized after the appropriate washout period if either of the following criteria are met:

- Response to previous treatment with a JAKi after an appropriate treatment duration (ie, ≥12 weeks)
- History of previous JAKi use for <12 weeks regardless of response status

Note: Response is defined by the investigator, or assessed in a previous interaction with a qualified physician/ dermatologist; participants in which previous exposure to JAKi for ≥12 weeks resulted in treatment failure will be excluded.

The study will also be stratified by whether participants have a history of previous JAKi use (yes, no) regardless of response and according to stable vs. active non-segmental vitiligo at Randomization (Section 6.3.2).

During the Double-Blind Treatment Period (starting at Visit 2), approximately 165 participants will be randomized in a 1:1:1 ratio and stratified (Section 6.3.2) to receive either MK-6194 3 mg Q2W, 3 mg Q4W, or placebo 2QW. Participants will take part in the Double-Blind Treatment Period of the study for approximately 24 weeks unless the participant withdraws from the study (Section 7.2). To maintain the blind, all participants will self-administer study intervention Q2W. Participants in the MK-6194 3-mg Q4W group will alternate between placebo and MK-6194 Q2W in a blinded manner (Section 8.1.9.1).

Those participants who complete 24 weeks of treatment in the Double-Blind Treatment Period on study intervention will then enter the Blinded Extension Period. Participants randomized to receive MK-6194 in the Double-Blind Treatment Period will continue on the same MK-6194 regimen in the Blinded Extension Period. Participants randomized to receive placebo in the Double-Blind Treatment Period will be rerandomized to receive either MK-6194 3 mg Q2W or 3 mg Q4W in the Blinded Extension Period.

The Blinded Extension Period will begin at Week 24 and will last approximately 28 weeks unless the participant withdraws from the study (Section 7.2). Participants will receive either

MK-6194 3 mg Q2W or MK-6194 3 mg Q4W during the Blinded Extension Period. Participants will receive the last dose of study intervention at ~Week 50, followed by an on-site visit at approximately 2 weeks later (Week 52 – no study intervention administered), and a follow-up safety phone call at approximately 28 days after the last dose of study intervention.

At Visit 2, study sites will train participants/caregivers to subcutaneously self-administer study intervention using a prefilled syringe (see Appendix 7 for country-specific requirements). Study site visits will take place every 2 weeks (±3 days) for the first month of the Double-Blind and Blinded Extension Periods, followed by visits every 4 to 8 weeks (±7 days) until the end of the period. In addition, a visit to collect PK samples the day after Randomization and the day after the Week 12 study site visit will occur. When a study site visit is scheduled, self-administration of study intervention should take place at the study site if possible. Participants will subcutaneously self-administer study intervention away from the clinic between study visits (Section 8.1.9).

An eDMC (Section 10.1.4.2) will be used during the study to periodically monitor unblinded safety data as well as to review results from a planned futility IA (Section 9.6) and the Week 24 primary endpoint analysis. The IA will be performed when approximately 50% of randomized participants complete Week 24 or discontinue before Week 24. If futility criteria are met at the IA in both treatment arms, the study will stop early. If futility criteria are met for one treatment arm, participants who complete the double-blind portion of the study, but have not started the Blinded Extension, will be switched to the nonfutile arm for the extension period. 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 Blinded Extension or discontinue. The interim analysis for futility may not take place if the timing of the IA falls too close to the Final Analysis of the primary endpoint. A full description of the eDMC responsibilities will be provided in the eDMC Charter.

PK and PD sampling will be taken for all participants during the study. The Sponsor will provide continuous medical monitoring of AEs, laboratory results, and adherence to the study protocol during the study.

Concomitant therapy is described in Section 6.5 and Section 5.2 (Table 1).

Supplemental PK/PD/Biomarker sparse sampling will be collected in a subset of participants at preselected sites (>15 participants per arm) to provide additional PK and PD measurements, allowing a more comprehensive characterization of the PK-PD relationship of MK-6194 (Sections 4.2.1.3 and 4.2.1.4). 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 vitiligo.

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.

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 non-segmental vitiligo. The study will test the hypothesis that at least one dose of MK-6194 is superior to placebo in the primary endpoint of percent change from baseline in F-VASI score at Week 24.

This study will use a double-blind, placebo-controlled, parallel-group design in the assessment of MK-6194 to minimize potential bias and improve reliability of the results. Eligibility criteria for this study will support enrollment of participants with a clinical diagnosis of non-segmental vitiligo with disease duration of at least 6 months before screening.

The primary efficacy endpoint will be assessed at Week 24 to allow for a reasonably sufficient duration to reliably assess the efficacy and safety of MK-6194 3 mg administered Q2W and Q4W. This duration is considered appropriate to capture the primary endpoint, F-VASI. A Blinded Extension Period is included to allow for collection of additional efficacy and safety data in the participants originally randomized to the placebo group during the Double-Blind Treatment Period, as well as additional efficacy and safety data with longer treatment in the participants originally randomized to MK-6194. The study duration is consistent with other recent treatment studies in vitiligo.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy/QoL Endpoints

F-VASI and T-VASI

The VASI is a validated scoring method that assesses the extent and severity of areas of vitiligo depigmentation [Hamzavi, I., et al 2004]. Two VASI scores will be calculated; the F-VASI to indicate facial lesions, and the T-VASI to indicate vitiligo affecting the total body, including the face. The primary efficacy endpoint for this study is based on the F-VASI given the importance of the face to patients' well-being. The F-VASI will also be used to measure several exploratory endpoints for various levels of improvement in vitiligo lesions on the face.

Changes in T-VASI will comprise a key secondary endpoint as well as several exploratory endpoints measuring for various levels of improvement in vitiligo lesions on the body.

ClinROs

Clinical Global Impression of Change and Clinical Global Impression of Severity

The following global assessments will be performed in this study to assess impact of treatment intervention from the investigator's perspective: 1) Clinical Global Impression of Change (CGI-C), and 2) Clinical Global Impression of Severity (CGI-S). Both of these assessments range from "none" to "very severe" for severity and "much better" to "much

worse" for change. The assessment of severity and change in vitiligo at several timepoints are exploratory endpoints.

CCI

[redacted]

PROs

VitiQoL Instrument

The VitiQoL is a 16-item validated, disease-specific instrument that measures the impact of vitiligo on patients' social, emotional and physical functioning [Batchelor, J. M., et al 2016]. Items are scored using a 7-point Likert scale (0 – 6), with lower scores indicating better HRQL. The VitiQoL includes items from the Dermatology Life Quality Index (DLQI), Skindex-16, and adapted items from the Brief Fear of Negative Evaluation scale (BFNE), as well as several de novo items.

Vitiligo Noticeability Scale

The VNS is the participant's assessment of how 'noticeable' vitiligo patches are after treatment. The noticeability of vitiligo after treatment is an important indicator of treatment success from a patient's perspective [Lilly, E., et al 2013]. The VNS is a single-item measure that asks patients to rate the noticeability of their vitiligo compared with before they started treatment on a 5-point scale ranging from 1 (more noticeable) to 5 (no longer noticeable). Scores of 4 – 5 are considered indicative of treatment success.

Both the VitiQoL and the VNS measure exploratory endpoints and will be assessed at several timepoints.

PGI-S and PGIC/M

The following global assessments will be performed in this study to assess impact of treatment intervention from the participant's perspective: 1) Patient Global Impression of Change/Meaningfulness (PGIC/M), and 2) Patient Global Impression of Severity (PGI-S). Both of these assessments range from "none" to "very severe" for severity and "much better" to "much worse" for change. The assessment of severity and change in vitiligo at several timepoints are exploratory endpoints. The PGIC/M also includes 2 follow-up questions for patients who respond that their vitiligo is either "a little better" or "much better", or "a little worse" or "much worse". The follow-up question (dependent on the response) asks if this change is important to the patient (Yes/No).

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 SoA (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.

In MK-6194 studies, absolute eosinophil counts will be measured at baseline and monitored during treatment. Participant discontinuation criteria related to clinically significant elevated eosinophil counts and/or evidence of eosinophil-related organ injury have been implemented (Section 7.1).

4.2.1.3 Pharmacokinetic Endpoints

PK samples will be collected from all participants at select visits as described in the SoA (Sections 1.3.1 and 1.3.2). On dosing days, PK samples will be collected before administration of study intervention. At selected timepoints PK samples post dosing will also be collected from all participants. At selected sites, additional PK/PD/Biomarker samples will be collected in >15 participants per treatment arm (Section 1.3.3). 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 pharmacometric 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 (Sections 1.3.1 and 1.3.2). At selected sites, additional PK/PD/Biomarker samples will be collected in >15 participants per treatment arm (Section 1.3.3), allowing more frequent PD sample collection during the study. 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 before the 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 participants. Thus, to aid future participants, it is important to investigate the determinants of response or resistance to the treatments administered, as well as determinants of AEs during 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. 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/Tissue RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tissue and/or 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/Tissue Protein biomarker analyses

Tissue and/or 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- and/or tissue-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 participant 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.

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.

4.2.2 Rationale for the Use of Placebo

This study will be placebo-controlled to avoid bias in the collection and evaluation of efficacy and safety data during the Double-Blind portion of the study, and to assess whether any observed effects are treatment-related or an effect of study participation. Participants may discontinue the study intervention at any time. Given that there are limited approved treatments for vitiligo, and no clear standard of care for treatment, the use of a placebo is justified.

4.3 Justification for Dose

MK-6194 will be administered as a 3-mg dose by subcutaneous injection Q2W or Q4W based on the available PK, PD, and safety results from Phase 1 SAD and MAD studies in healthy participants, participants with ulcerative colitis, and participants with atopic dermatitis. MK-6194 PK and PD has been generally similar between UC patients and healthy adults.

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]. A 3-mg dose will result in the majority of participants achieving a peak Treg expansion of 2-fold change from baseline while minimizing expansion of CD4+ T conventional cells, CD8+ cells, and NK cells. The correlation of Treg expansion and efficacy with MK-6194 in autoimmune diseases has not yet been studied.

Doses up to 5 mg Q2W of MK-6194 have been generally well tolerated and resulted in preferential Treg expansion over effector cell populations in participants with UC when administered for 12 weeks. Low-dose IL-2 clinical studies have used dosing regimens that resulted in sustained or intermittent Treg expansion. Both Q2W and Q4W regimens of MK-6194 will be studied in this trial to evaluate the impact of sustained or intermittent Treg expansion, respectively, on clinical efficacy. A 3-mg dose is anticipated to be generally well tolerated when administered Q2W or Q4W.

Thus, dosing regimens of 3 mg Q2W and 3 mg Q4W will be studied to evaluate whether either of these MK-6194 dosing regimens have a therapeutic impact among participants with vitiligo.

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.

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

1. Has a clinical diagnosis of non-segmental vitiligo

   Note: Vitiligo diagnosis must be made by a trained physician who is a board-certified dermatologist (or local equivalent)

2. Has non-segmental vitiligo with disease duration of at least 6 months

   Note: Disease duration is defined as the length of time since onset of symptoms

3. Has depigmentation contributing to F-VASI ≥ 0.3 at screening and baseline

4. Has depigmented facial BSA ≥0.3% at screening and baseline

5. Has T-VASI ≥4 at screening and baseline

6. Has total body vitiligo area ≥4% at screening and baseline excluding hands and feet involvement

7. Is candidate for systemic therapy based on investigator judgment at screening and baseline

Demographics

8. 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

9. 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

10. 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

11. 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 segmental vitiligo
2. Has ≥50% leukotrichia on face or body
3. Has any other dermatological diseases that would interfere with vitiligo assessments
4. Has history of or current inflammatory condition other than vitiligo that, in the opinion of the investigator, could interfere with the evaluation of vitiligo
5. 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.
6. Has a known history of hypereosinophilic syndrome or an eosinophil-related condition (eg, eosinophilic pulmonary disease including eosinophilic asthma, eosinophilic esophagitis, eosinophilic nephritis, eosinophilic granulomatosis with polyangiitis [formerly known as Churg-Strauss syndrome], etc)
7. Has an active or clinically significant infection requiring hospitalization or treatment with IV anti-infectives within 4 weeks prior to Randomization, or oral/intramuscular anti-infective therapy within 2 weeks prior to Randomization
8. 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
9. Has a severe chronic pulmonary disease requiring oxygen therapy
10. Has a transplanted organ, which requires continued immunosuppression
11. Has a history of any malignancy, except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix
12. 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.

Note: 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).

- Participants with positive HCV antibodies 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.

See Appendix 7 for country-specific requirements.

13. Has evidence of active TB, latent TB, or inadequately treated TB (for participants with history of TB) as evidenced by one of the following:

    - Positive QuantiFERON-TB Gold 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 QuantiFERON testing. CXR is still required at Screening; normal CXR or CT within 90 days prior to Screening is acceptable.

14. 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.

15. Has history of drug or alcohol abuse within 6 months prior to Screening (can be participant reported)

16. Has had major surgery within 3 months prior to Screening OR has a major surgery planned during the study

17. 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

Prior/Concomitant Therapy

18. Has had an inadequate response (as evaluated by a dermatologist or local physician specialist equivalent) to previous treatment with a JAKi after an appropriate treatment duration (eg, ≥12 weeks)

    Note: Up to approximately 50% of participants with previous JAKi use study wide are eligible if the following criteria are met:

    - Response to previous treatment with a JAKi after an appropriate treatment duration (ie, ≥12 weeks)

    - History of previous JAKi use for <12 weeks regardless of response status

    For these participants, the last dose of the JAKi should be ≥4 weeks prior to Randomization.

19. Has received prohibited medications within the specified timeframes prior to Randomization (Table 1). These medications are also prohibited during the study:

Table 1 Prohibited Medications

Medication Category	**Prohibited Period Prior to Randomization and Any Time During the Study[a]**
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). See Appendix 8 Permanent skin bleaching agents	Any time
T-cell depleting therapies (eg, alemtuzumab, antithymocyte globulin)	12 months
B-cell depleting therapies (eg, rituximab, ocrelizumab)	6 months

Medication Category	**Prohibited Period Prior to Randomization and Any Time During the Study[a]**
Biologics with immunosuppressive potential. See Appendix 8 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 (JAK1, JAK2, JAK3) (including selective inhibition) TYK2 inhibitors PDE4 inhibitors S1P modulators See Appendix 8 for examples of these medications	4 weeks
Medications Used to Treat Vitiligo	
Any drug inducing photosensitivity such as including, but not limited to certain antibiotics (eg, tetracyclines), certain NSAIDs	2 weeks
Antioxidants (eg, polypodium leucotomas, superoxide dismutase, alpha-lipoic acid, Ginko Biloba)	No newly initiated 3 month prior to Randomization, and the dose should remain stable during the study duration
Other topical treatments or any procedures (eg, needling) that could affect vitiligo	4 weeks (or 5-drug half-lives)
Systemic or topical non-biologic immunomodulators/immunosuppressants (eg, corticosteroids, calcineurin inhibitors, tacrolimus/pimecrolimus)	4 weeks for systemic, and 2 weeks for topical
Any kind of phototherapy (eg, UV/UVB phototherapy, PUVA therapy, tanning beds, laser therapy)	4 weeks
Any other prescription or over-the-counter medication, traditional Chinese medicine, herbal supplement, or other therapy used to treat vitiligo	4 weeks
Other Therapies	
Any investigational drug	4 weeks or 5 half-lives of the investigational drug (whichever is longer)
Live vaccines Note: JYNNEOS for prevention of smallpox and mpox, (also known as monkeypox disease) is allowed. JYNNEOS is a live, non-replicating vaccine. See Appendix 8 for examples of live and non-live vaccines.	4 weeks (or longer if required locally)
CTLA-4=cytotoxic T-lymphocyte-associated protein 4; JAK=Janus kinase; IL-2=interleukin 2; NSAIDs= nonsteroidal anti-inflammatory drugs; PD-1= programmed cell death protein 1; PDE4= phosphodiesterase-4 enzyme; PD-L 1= programmed cell death ligand 1; PUVA=psoralen and ultraviolet rays A; S1P= sphingosine 1 phosphate; TYK2= tyrosine kinase 2; UV/UVB=ultraviolet/ultraviolet rays B. [a] Medication use is prohibited until the last dose of study intervention is administered (study completion or early discontinuation).	

See Appendix 7 for country-specific requirements.

Prior/Concurrent Clinical Study Experience

20. Has participated in another investigational clinical study within 4 weeks (see Table 1 for prohibited period) prior to Randomization

Diagnostic Assessments

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

- Hemoglobin <8.5 g/dL
- WBC $<3.5 \times 10^3/\mu L$
- Absolute neutrophil count $<1.5 \times 10^3/\mu L$
- Absolute lymphocyte count $<0.5 \times 10^3/\mu L$
- Absolute eosinophil count >1000 cells/µL
- Absolute platelet count $<100 \times 10^3/\mu L$
- >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

  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.

Other Exclusions

22. Has donated or lost ≥1 unit of blood (approximately 500 mL) within 4 weeks prior to the Screening Visit
23. Has received cosmetic or other procedures that could interfere with evaluation of vitiligo during the study
24. 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

Blood Donation

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

Sun or Light Exposure

Study participants should be instructed to avoid prolonged exposure to the sun (ie, without sufficient SPF protection or in sun conditions where skin could be impacted). The use of tanning booths, sun lamps, or other ultraviolet light sources are prohibited during the study.

Makeup/Tattooing/False Eyelashes/Self-Tanning

- Permanent and semipermanent makeup is not permitted. Cosmetic makeup is permitted; however, must be removed for clinical assessments at all study visits.

- Tattooing, including procedures such as microblading and micropigmentation, are not permitted during the study. Existing tattoos are allowed as long as the assessment of vitiligo is not impaired per investigator clinical judgment.

- False eyelashes are permitted; however, should be removed for clinical assessments at all study visits.
- Self-tanning and dyes are not permitted during the study.
- Laser treatment: intense pulsed light therapy and any laser treatment, including for hair removal and skin pigmentation, is not permitted during the study.
- Needling is not permitted during the study.
- Existing beards are allowed as long as the assessment of vitiligo is not impaired per investigator clinical judgment.

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 as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
MK-6194 Q2W	Experimental	MK-6194	Biological/Vaccine	Injection, Solution	3 mg	3 mg	SC	Double-Blind Treatment and Blinded Extension Periods	Test Product	IMP	Provided centrally by Sponsor
MK-6194 Q4W	Experimental	MK-6194	Biological/Vaccine	Injection, Solution	3 mg	3 mg	SC	Double-Blind Treatment and Blinded Extension Periods	Test Product	IMP	Provided centrally by Sponsor
MK-6194 Q4W	Experimental	Placebo	Biological/Vaccine	Injection, Solution	0 mg	0 mg	SC	Double-Blind Treatment and Blinded Extension Periods	Placebo	IMP	Provided centrally by Sponsor
Placebo Q2W	Placebo Comparator	Placebo	Biological/Vaccine	Injection, Solution	0 mg	0 mg	SC	Double-Blind Treatment Period	Placebo	IMP	Provided centrally by Sponsor

EEA= European Economic Area; IMP= investigational medicinal product; NIMP/AxMP= noninvestigational/auxiliary medicinal product; Q2W= every 2 weeks; Q4W= every 4 weeks; 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: To maintain the blind for MK-6194 Q4W, alternating placebo will be administered between the MK-6194 doses. Participants randomized to the placebo arm Q2W during the Double-Blind Treatment Period will be rerandomized to MK-6194 Q2W or MK-6194 Q4W during the Blinded Extension Period.

All supplies indicated in Table 2 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 MK-6194 3 mg Q2W, MK-6194 3 mg Q4W, or placebo during the Double-Blind Treatment Period.

During the Blinded Extension Period, participants who were assigned to the placebo arm during the Double-Blind Treatment Period will be rerandomized 1:1 to MK-6194 3 mg Q2W or MK-6194 3 mg Q4W and will be given new randomization numbers. Participants who were assigned to either of the MK-6194 arms during the Double-Blind Treatment Period will continue to receive 3 mg MK-6194 with the same dosing schedule; however, will be assigned new randomization numbers in order to maintain the study blind during the Blinded Extension Period.

In order to maintain the blind, all participants will self-administer study intervention Q2W. Participants in the 3 mg MK-6194 Q4W group will alternate between placebo and MK-6194.

If futility criteria are met at the IA in both treatment arms, the study will stop early. If futility criteria are met for one treatment arm, participants who complete the Double-Blind Treatment Period of the study, but have not started the Blinded Extension Period, will be switched to the nonfutile arm for the Blinded Extension Period.

If a dose arm is found to be subefficacious during the Week 24 primary endpoint analysis, participants in the Blinded Extension who are already part of the subefficacious dose arm may continue on that dose; however, there will be no new enrollment to the subefficacious dose arm (Section 9.6). Participants who are still receiving the subefficacious dose in the Double-Blind Treatment Period will finish the Double-Blind Treatment Period as randomized but will receive the efficacious dose in the Blinded Extension Period.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. *Stable vs active vitiligo*

Treatment response in active versus stable vitiligo might be different.

- Active vitiligo is defined as new/extending lesion(s) in the 6 months prior to Screening Visit (confirmed by photographs or medical record/history) and/or; confetti-like lesion(s); trichrome lesion(s); Koebner phenomenon/phenomena (excluding Type 1 [history based on isomorphic reaction]), inflammatory vitiligo.
- Stable vitiligo is defined as an absence of signs of active disease (no signs of new or extending lesions).

2. *Previous JAKi exposure (yes or no)*

- It is unknown whether exposure to JAKi may affect response to an IL-2 mutein or if an inadequate response to JAKi may predict an inadequate response to MK-6194.

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 for the duration of the study (ie, through Week 54). Only selected Sponsor personnel involved in performing and reviewing the results of the Week 24 analyses will be unblinded at the time of the Week 24 database lock.

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 on the Participant Reminder Log. Compliance will be assessed by direct questioning during review of the Participant Reminder Log and 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 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.

6.5 Concomitant Therapy

Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are also prohibited during the study. Please refer to Table 1 (in Section 5.2) for medications which are 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. See Appendix 8 for examples of live vaccines and Appendix 7 for country-specific requirements.

Any prescription or over-the-counter medication, traditional Chinese medicine, herbal supplement, or other therapy used to treat vitiligo (or could affect vitiligo) are prohibited during the study to avoid confounding of results.

If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should 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.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

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 Management of Eosinophilia

For participants with AEC ≤650 cells/µL at Screening:

- If AEC is >1000 cells/µL at a scheduled or unscheduled visit after Randomization, another CBC with differential must be performed before the next dose. It is recommended to perform the CBC with differential close to the next dosing day and at least 10 days after the prior dose.
- If AEC is still >1000 cells/µL, a CBC with differential may be repeated the day before the dosing day or on the dosing day, prior to administration of study intervention.
- If AEC remains >1000 cells/µL, study intervention should be interrupted. Study intervention may be restarted once AEC is ≤1000 cells/µL.

For participants with AEC >650 cells/µL at Screening:

- If AEC at a scheduled or unscheduled visit after Randomization has an increase of ≥500 cells/µL above the Screening value, another CBC with differential must be performed before the next dose. It is recommended to perform the CBC with differential close to the next dosing day and at least 10 days after the prior dose.
- If AEC is >1000 cells/µL, a CBC with differential may be repeated the day before the dosing day or on the dosing day, prior to administration of study intervention.
- If AEC remains >1000 cells/µL, study intervention should be interrupted. Study intervention may be restarted once AEC is ≤1000 cells/µL.

Hypereosinophilic syndrome and eosinophil-associated organ injury are described in Appendix 9.

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 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

6.9.1 Study Site Retention Samples

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.
- 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, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has AEC >1500 cells/μL and has confirmed or suspected hypereosinophilic syndrome or eosinophil-associated organ injury; see Appendix 9 for details.
- The participant has a persistent moderate increase in eosinophils for ≥8 weeks, defined as AEC ≥1500 cells/μL on at least 3 consecutive tests. The interval between the tests should be at least 1 week.
- The participant has AEC >5000 cells/μL at a single time point.
- The participant develops active or latent TB.
- 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.
- The participant is diagnosed with HBV, HCV, or HIV.
- The participant has HBV-DNA ≥LLOQ.

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.

See Appendix 7 for country-specific requirements.

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 or participant's legally acceptable representative who consented for the Subpopulation procedures, may withdraw consent for the additional PK/PD/Biomarker sample collection. 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 main 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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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 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 at selected sites will explain the consent for additional PK/PD/Biomarker sample collection to participants, 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 (Sections 5.1 and 5.2) will be reviewed at the Screening and Randomization Visits as outlined in the SoA (Section 1.3.1) by the investigator, or subinvestigator delegate, who is a qualified physician, to ensure that the participant qualifies for the study.

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.

For the Blinded Extension Period, each participant who completes the Double-Blind Treatment Period per protocol requirements will receive a new participant identification card at Visit 10; the rerandomization number will be added to the new participant identification card. The participant identification card from the Double-Blind Treatment Period 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, surgical procedures, or other medical conditions. Additionally, a complete vitiligo 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 1, Section 6.5, and Appendix 8), and record prior medications taken by the participant. All treatment with JAKi and vitiligo treatments or other prohibited medications, regardless of timing, must be recorded.

All other medications taken within 30 days prior to Screening should be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the participant during the study. Prohibited concomitant medications, therapies, and products, as outlined in Section 5.2 (Table 1), Section 6.5, and Appendix 8, should not be administered from the indicated period before Randomization to 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 individual who is screened twice will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1. Prestudy 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 randomization number. The randomization number identifies the participant for all procedures occurring after Randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

All participants who complete the Double-Blind Treatment Period per protocol requirements will be rerandomized to MK-6194 3 mg Q2W or MK-6194 3 mg Q4W and will be assigned a new randomization number for the Blinded Extension Period.

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 will be assigned a randomization number via IRT at Visit 2 (Day 1). A second randomization number will be assigned via IRT at Visit 10 for all participants who complete the Double-Blind Treatment Period per protocol requirements.

IRT will allow randomization of up to approximately 50% of participants study wide with previous JAKi use. IRT will manage the participant's stratification as outlined in Section 6.3.2 and the Blinded Extension rerandomization of the placebo group 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 52 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/family member is permitted. Self-administration should be in one of the approved injection 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. See Appendix 7 for country-specific requirements.

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). In order to maintain the blind, all participants should administer study intervention doses approximately every [redacted] days (and at a minimum of [redacted] Enough study intervention supplies will be provided to the participant to allow for self-administration of required doses in between clinic visits. Participants will be instructed to review the "MK-6194 Instructions for Use" when administering injections of study intervention at home.

Contact the Sponsor 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/family members will be trained by the appropriate study staff on the proper administration of study intervention technique before the participant's first injection. Training or retraining 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. See Appendix 7 for country-specific requirements.

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 and/or study staff during visits as outlined in the SoA. Self-administration of study intervention by the participant, or administration by a caregiver/family member, should occur *after* completion of all study procedures, including collection of all blood samples. The study site staff will ensure proper self-administration technique. Participants will document dosing in the Participant Reminder Log.

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 medication 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.

8.1.10.2 Withdrawal From Additional PK/PD/Biomarker Subpopulation

Participants may withdraw consent for the Subpopulation procedures (Section 1.3.3) 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.

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 >15 participants per treatment arm, as outlined in the SoA (Section 1.3.3), in addition to the samples listed in the Double-Blind Treatment and Blinded Extension Periods (Sections 1.3.1 and 1.3.2).

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 vitiligo.

8.2 Efficacy Assessments

8.2.1 PROs

All PROs should be completed in the order listed in the SoA ***before*** laboratory tests or any other efficacy or safety procedures, except for Visit 2 (Randomization) where PROs can be completed after confirming eligibility. Participants will be trained by site personnel on the use of an electronic tablet for PRO completion and are to complete the questionnaires on their own at the study site using the provided electronic tablet.

VitiQoL

The VitiQoL is a 16-item validated, disease-specific instrument that measures the impact of vitiligo on patients' social, emotional and physical functioning [Lilly, E., et al 2013]. Items are scored using a 7-point Likert scale (0 – 6), with lower scores indicating better quality of life.

Vitiligo Noticeability Scale

The VNS is a single-item measure that asks patients to rate the noticeability of their vitiligo compared with before they started treatment on a 5-point scale ranging from 1 (more noticeable) to 5 (no longer noticeable). Scores of 4 – 5 are considered indicative of treatment success.

Patient Global Impression of Severity

The PGI-S is a 2-item measure asking the participant to rate the severity of their vitiligo on their facial area and on their total body area right now, with response options of none, mild, moderate, severe, and very severe.

Patient Global Impression of Change/Meaningfulness

The PGIC/M is a 2-part measure asking the participant to rate the change in their vitiligo since they started taking the study medication, with response options ranging from "much better" to "much worse". Based on the response to the initial question, the participant is

asked a follow-up question to evaluate the meaningfulness of the improvement or worsening, with response options of "yes" or "no" indicating whether the improvement or worsening was important to the participant or not.

8.2.2 ClinROs

All ClinROs should be completed in the order listed in the SoA. The investigator or medically qualified designee are to complete the questionnaires using the provided electronic tablet. Separate instructions on how to complete the ClinROs will be available if needed.

Investigator qualifications, training, and applicable certification processes are established in a separate document. It is strongly encouraged that the same investigator evaluates the same participant for the duration of the study to improve continuity and reliability of the assessments.

Clinical Global Impression of Severity

The CGI-S is a 2-item measure asking the investigator to rate the severity of participant's vitiligo on their facial area and on the total body area right now, with response options of none, mild, moderate, severe, and very severe.

Clinical Global Impression of Change

The CGI-C is a 2-item measure asking the investigator to rate the change in the participant's vitiligo on their facial area and on the total body area since they started taking the study medication, with response options ranging from "much better" to "much worse".

Facial Vitiligo Area Scoring Index (F-VASI) and Total Vitiligo Area Scoring Index (T-VASI)

The VASI is a validated scoring method that assesses the extent and severity of areas of vitiligo depigmentation. There are 2 region-specific VASI scores that will be calculated for the study; the F-VASI, which measures vitiligo involvement of the facial area, and the T-VASI, which measures vitiligo involvement for the total body. Both are scored by measuring the total area of depigmentation, as measured by a standard unit, multiplied by the percent of depigmentation of the affected areas.

F-VASI is defined as the sum of the area(s) of all vitiligo lesions on the Face X Average Degree of Depigmentation (%).

The FACE is defined as the area between the hairline, chin, and up to the ears. This area includes the eyelids, cheeks, and nose, but DOES NOT INCLUDE the lips, scalp, ears, or neck.

Vitiligo lesions on face will be estimated by using a fingertip unit (1 FTU), a finger (3 FTUs), or a thumb (3 FTUs) depending on the lesion size. One FTU is equivalent to 0.03% of the body surface are (BSA) and a finger and thumb are considered 0.1% BSA. The degree of depigmentation for each vitiligo involvement site is determined and estimated to

the nearest of the following percentages: 0% (no depigmentation), 10%, 25%, 50%, 75%, 90%, or 100% (complete depigmentation). The F-VASI is derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each site on the face and summing the values of all sites together. Possible scores range from 0-3.5.

The T-VASI determines the degree of vitiligo involvement of the whole body. The total body is separated into 6 mutually exclusive areas: 1. Head/Neck (Including the Face), 2. Hands, 3. Upper extremities (Excluding the hands), 4. Trunk (Including genitalia; Excluding buttocks), 5. Lower extremities (Including buttocks; Excluding the feet), and 6. Feet. The area of depigmentation will be measured by using the palmar method, whereupon one hand unit (comprised of the patient's palm + 5 digits, with fingers tucked together & thumb tucked to the side) = 1% Body Surface Area. As for the F-VASI, the degree of depigmentation for each vitiligo involvement site is determined and estimated to the nearest of the following percentages: 0% (no depigmentation), 10%, 25%, 50%, 75%, 90%, or 100% (complete depigmentation). Where there are multiple lesions within a body region, the degree of depigmentation within each body region should be estimated using the above percentages and then averaged to the closest overall percentage. For example, if there are 3 vitiligo lesions within a body region, with degrees of depigmentation of 75%, 50% and 100%, the estimated average degree of depigmentation for that region would be 75%.

The area of percent depigmentation scores for each body region are summed to derive the T-VASI score, which ranges from 0 to 100, with 0 indicating no vitiligo and 100 indicating vitiligo on the entire body. Note that, when a lesion crosses over more than one region, the scoring for the lesion is not split between regions; the investigator will select one of the regions to include that lesion in to calculate the VASI for that region, always including that lesion in the same region for all future assessments.

Body Surface Area

The participant's right or left hand should be selected as the measuring device. For purposes of clinical estimation, the total surface of the palm plus 5 digits, with fingers tucked together and thumb tucked to the side, will be assumed to be approximately equivalent to 1% BSA. Measurement of the total area of involvement by the physician is aided by clinical judgment (ie, if specks of pigment were moved so that they were next to each other and then estimating the total area involved). The site should make every attempt to have the same qualified investigator or designee perform all BSA assessments on a given participant throughout the study.

CCI

8.2.3 Photography

Photography of the face and/or body areas affected with vitiligo will be obtained at the times outlined in the SoA using the provided electronic tablet to support the F-VASI, T-VASI, and CCI Photographs will be anonymized to the extent possible in order to protect participant's identity. Additional instructions and a full description of the methodology for obtaining photographs are provided in a separate manual. Photographs will not be used for formal assessments of efficacy; however, may be included in the CSR or other publications.

The F-VASI and T-VASI photographs will be reviewed centrally; however, it is the investigator's VASI score that will be used for efficacy calculations. If the photographs obtained at Screening are deemed sufficient by the central reviewer, no additional photographs are required at the randomization visit.

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 (rash, injection site). Other body systems may be examined at the discretion of the investigator.

Note that a urinary/genital examination is not required; however, visual inspection of the urinary/genital area for areas of depigmentation is expected.

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, RR, and BP will be assessed. The same method should be used for all measurements for each individual participant.
- HR and BP 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 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 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 QuantiFERON Gold Test or equivalent as outlined in the TB screening eligibility criterion in Section 5.2. The QuantiFERON Gold Test or equivalent must be performed and read by trained and licensed personnel according to local guidelines. 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, exam 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 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 PPD in the past should not be reexposed 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 10) 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 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.

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

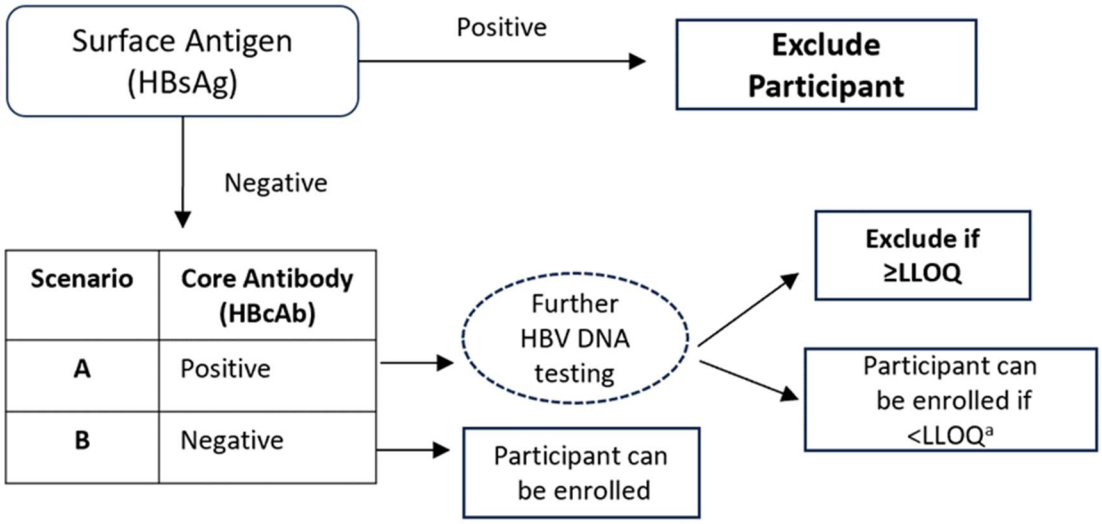
All participants will be tested for the presence of HBV at Screening using the following tests:

- 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 2.

- A positive result for HBsAg will be exclusionary.
- 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 at any timepoint, the participant will require discontinuation of study intervention (Section 7.1).
- A negative test result for HBcAb does not require HBV-DNA PCR qualitative testing and the participant may be enrolled (Scenario B).

Figure 2 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 at any timepoint, the participant will require discontinuation of study intervention (Section 7.1).

See Appendix 7 for country-specific requirements.

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 3.

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

Table 3 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

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).
2. AEC >5000 cells/µL at a single time point
3. AEC >1500 cells/µL and confirmed or suspected hypereosinophilic syndrome or eosinophil-associated organ injury; see Appendix 9 for definitions and examples.

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

For purposes of this study, an overdose will be defined as 2 or more doses of study intervention administered <10 days apart.

If an overdose occurs, a CBC with differential to assess absolute eosinophil counts (see Section 6.6.3 and Appendix 9) 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.

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.

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 Laboratory Manual. Blood samples collected may be stored and further analysis may be performed, if required.

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 SoA Section 1.3. Additional samples will be collected from participants that are part of the PK/PD/Biomarker Subpopulation as outlined in Section 1.3.3.

Blood collected for immunophenotyping will be assessed using the Treg - immunophenotyping assay and TBNK assay. For all participants, blood will be collected for use in the TBNK assay. For participants in the Subpopulation, blood will be collected to use in both Treg-immunophenotyping and TBNK assays.

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 genetic analysis
- Blood for immunophenotyping
- 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.

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 predose 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 Laboratory Manual.

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, except for blood for immunophenotyping

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.

Except for Visit 2, all PROs should be completed in the order listed in the SoA before laboratory tests or any other efficacy or safety procedures (Section 8.2.1).

8.10.1 Screening/Rescreening Visits

Screening

Up to 4 weeks before intervention randomization, potential participants will be evaluated to determine whether they fulfill the entry requirements as set forth in Section 5.

Rescreening

Participants are allowed to rescreen once. 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 4-week window) during which time screening procedures will be repeated. If the participant's original screening laboratory results and procedures were not exclusionary and rescreening is completed within 4 weeks of the initial Screening Visit date, the screening laboratory assessments or 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 Double-Blind Treatment Period

Each visit should be performed as specified in the SoA.

Participants who satisfy all entry criteria will be randomized (via IRT) to double-blind study intervention at Visit 2 (Day 1). Participants will complete PROs in the order listed in the SoA and specified in Section 8.2.1, before any other procedures are completed, except for Visit 2 (Randomization) where PROs can be completed after confirming eligibility.

Participants will be educated by a trained member of the site staff on appropriate administration of study intervention (Section 8.1.9.3). 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.

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Week 24 Visit

At Visit 10 (Week 24), all procedures for the Double-Blind Treatment Period (Section 1.3.1) need to be completed BEFORE the Week 24 study intervention administration as the Week 24 dosing will be part of the Blinded Extension Period (Section 1.3.2).

8.10.3 Blinded Extension Period

The Blinded Extension Period begins with the participant's Week 24 administration of study intervention. Study procedures are outlined in Section 1.3.2. Participants who were assigned to the placebo group during the Double-Blind Treatment Period will be rerandomized to an active arm as outlined in Section 6.3.1.

Participants who permanently discontinued study intervention will continue to be monitored in the study 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 1.3.3) in addition to the activities listed in the Double-Blind Treatment and Blinded Extension Periods (Sections 1.3.1 and 1.3.2).

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.

Participants who discontinue study intervention will no longer be part of this Subpopulation.

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 in that period (Section 7.1) as outlined in the SoA with the following exceptions, which are not applicable after study intervention is discontinued.

- Efficacy data, including photographs
- 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, [Table 1], and Appendix 8) while the participant was on study intervention are no longer prohibited after discontinuation of study intervention, except for live vaccines. See Appendix 7 for country-specific requirements.

Note: At the Discontinuation Visit, IRT will be contacted for closeout 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, AE and concomitant medication 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 SAP 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 for the Double-Blind Treatment Period (at Week 24) will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. Only the clinical database and sponsor personnel directly involved in the Week 24 analysis and reporting will become unblinded at the time of the Week 24 database lock.

The extension period of this study will also be conducted as a blinded study. The database of the extension period will be unblinded after the end of the Blinded Extension Period (Week 52). Additional efficacy and safety analyses will be performed based on the data acquired from the completion of the extension period.

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

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

- Percent change from baseline in F-VASI at Week 24

Secondary Efficacy Endpoint

- Percent change from baseline in T-VASI at Week 24

Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are stated in Section 3 of the protocol.

9.3.2 Safety Endpoints

Safety endpoints are stated in Section 3 of the protocol.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values, and vital signs.

9.4 Analysis Populations

9.4.1 Efficacy Analysis Population

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.

9.4.2 Safety Analysis Population

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

9.4.3 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.

9.4.4 Pharmacodynamic Analysis Population

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

9.4.5 Immunogenicity Analysis Population

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

9.5 Statistical Methods

9.5.1 Estimand(s)

Estimand for the Primary Efficacy Analysis

The estimand for the primary objective of this study contains 5 attributes:

- Treatment Regimen: MK-6194 or matching placebo
- Target population: Adult Participants with Non-Segmental Vitiligo
- Endpoint: The percent change from baseline in F-VASI at Week 24
- The population-level summary: the difference in the mean percent change from baseline in F-VASI at Week 24 between the treatment group and placebo
- Intercurrent events: Detailed below:

Number	Intercurrent Events	Handling Strategy
Intercurrent Event #1	Discontinuation of MK-6194 or placebo	Treatment Policy Strategy
Intercurrent Event #2	Usage of any medication for the treatment of Vitiligo as listed in Protocol Section 5.2 # 19	Treatment Policy Strategy

9.5.2 Statistical Methods for Efficacy Analyses

All efficacy endpoints will be analyzed based on the FAS population. Unless otherwise specified, all efficacy data will be included in efficacy analyses. A Hochberg testing procedure will be implemented in this study for multiplicity adjustment. LDA method will be used for the analysis of the continuous endpoints, and stratified M&N method will be used for the analysis of the binary endpoints.

Primary Efficacy Analysis

The primary endpoints, the percent change from baseline in F-VASI score at Week 24, will be analyzed using a LDA model for repeated measures. This model will use all available data on F-VASI at baseline and all post-baseline timepoints. In this model, time will be treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will adjust for treatment, visit, treatment by visit, and baseline vitiligo status (stable, active) and previous JAK inhibitor use (yes, no). Point estimates, 95% CI and p-value for the treatment differences will be provided. If there are a small number of responses in one or more strata, for the purpose of analysis, strata will be combined to ensure a sufficient number of participants and responses in each stratum. Details regarding the

combining of strata will be specified in the SAP prior to database lock based on a blinded review of response by stratum. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Sensitivity Analyses

In addition to the analysis approach specified above for the primary endpoint analysis section, the following sensitivity analyses will be used to assess the robustness of the primary analysis approach.

Multiple-imputation Analysis

For all participants with missing baseline F-VASI assessment, single imputation (only once) will be implemented based on baseline stratification factors. All post-baseline missing F-VASI assessments will be handled using multiple imputation (MI) under the missing-at-random (MAR) assumption.

Tipping-point Multiple-imputation Analysis

Tipping point as described in Ratitch et al. (2013) [Ratitch, B., et al 2013] will be conducted. In this approach, missing data are first imputed for all visits under the MAR assumption, and then the worsening/shift is applied. This is repeated with increasing the delta-shift (worsening) until the result is no longer statistically significant.

Secondary Efficacy Analysis

The secondary efficacy endpoint, the percent change from baseline in T-VASI at Week 24, will be analyzed similarly as the primary endpoint.

Table 4 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint/Hypothesis 1				
Percent change from baseline in F-VASI at Week 24	P	LDA	FAS	Model based
	S	LDA	FAS	Multiple Imputation
	S	LDA	FAS	Tipping Point Multiple Imputation
Secondary Endpoint 2				
Percent change from baseline in T-VASI at Week 24	P	LDA	FAS	Model based
FAS=Full Analysis Set; F-VASI= Facial Vitiligo Area Scoring Index; LDA=longitudinal data analysis; MI=multiple imputation; P=Primary approach; S=Supportive approach; T-VASI= Total Vitiligo Area Scoring Index.				

The efficacy analysis mentioned above will be performed at the end of the Double-Blind Treatment Period (Week 24). Additional descriptive analyses will be performed at the end of the Blinded Extension Period (Week 52). Details of the analysis plan will be finalized in the SAP before the final database lock.

9.5.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory tests, and vital signs.

The overall safety evaluation will include a summary (ie, frequency and percentage) by treatment group of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, 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 with events 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 group.

Table 5 summarizes analysis strategy for safety endpoints in this study.

Table 5 Analysis Strategy for Safety Parameters

Safety Endpoint	Descriptive Statistics	95% Between-group CI	Graphical Display
Any AE	X	X	
Any serious AE	X	X	
Any drug-related AE	X	X	
Any serious drug-related AE	X	X	
Discontinued study treatment due to AE	X	X	
AE that resulted in death	X		
Specific AEs or SOCs (incidence ≥ 4 participants in any treatment group)	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.			

The safety analysis mentioned above will be performed at the end of the Double-Blind Treatment Period (Week 24). Additional descriptive analyses will be performed at the end of the Blinded Extension Period (Week 52). Details of the analysis plan will be finalized in the SAP before the final database lock.

9.6 Interim Analyses

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9.7 Multiplicity

Due to the interim analysis for futility, an α-spending of 0.0001 will be applied to the 2-sided Type I error rate of 5% for the primary hypothesis based on the Haybittle-Peto method [Haybittle, J. L. 1971] [Peto, R., et al 1976]. Multiplicity adjustment will be made for testing 2 doses on the primary endpoint for the analysis, i.e., for testing a family of the following hypotheses:

- H1(1): 3 mg MK-6194 Q4W dose is superior to placebo in the percent change from baseline in F-VASI at Week 24.

- H1(2): 3 mg MK-6194 Q2W dose is superior to placebo in the percent change from baseline in F-VASI at Week 24.

To strongly control the Type-I error rate for this family, the Hochberg procedure [Hochberg, Y. 1988] will be applied.

9.8 Sample Size and Power Calculations

This study will randomize 55 participants into each treatment group and has >80% power to demonstrate the superiority of at least 1 dose of MK-6194 over placebo at an overall 2-sided 0.0499 alpha-level, if the underlying treatment difference in percent change from baseline at Week 24 in F-VASI score is -20%. The power and sample size are based on the following assumptions: 1) a 15% drop out rate, 2) a standard deviation of 33%, pooled across treatment groups.

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 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.

10.1.4.2 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.

10.1.5 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 6 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 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety 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	
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) • TSH • Serology (HIV antibody, HBsAg, HBcAb, HCV antibody)[a]. See Appendix 7 for country-specific requirements. • QuantiFERON- TB Gold test • PCR test (only required for participants exhibiting COVID-19 symptoms)			

[a] Further testing will be needed for:

- Participants with negative HBsAg and positive HBcAb 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, COVID-19 PCR tests, and local TB tests, as applicable.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; COVID-19=coronavirus disease 2019; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; POCBP=persons of childbearing potential; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cells.

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

See Appendix 7 for country-specific requirements.

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.

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 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.

See Appendix 7 for country-specific requirements.

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

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

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.

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Country specific Requirements for Argentina

Section 1.3 Schedule of Activities

HBV, HCV, TB, and HIV testing at Screening is mandatory.

Section 1.3 Schedule of Activities and Section 8.3.5 Pregnancy Testing

Pregnancy testing must be performed monthly during treatment as well as at the end of study intervention.

10.7.2 Country specific Requirements for the Czech Republic

Section 6.5 Concomitant Therapy

In addition to all restrictions or concomitant medications listed in Section 6.5, specific concomitant therapies or vaccinations noted below are prohibited during the study:

- Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 90 days after the last dose of study intervention.

Section 8.3.5 Pregnancy Testing

Pregnancy testing is to be conducted every 30 days during the treatment period.

10.7.3 Country-specific Requirements for Germany

Sections 1.1, 4.4, 5.1, 7.1, 7.2, 8.1.1, 8.1.1.1, 8.1.1.2, 8.1.1.3

For a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Section 8.3.7 Chest X-ray

Chest x-rays and/or CT scans will not be implemented in Germany. Participants will be screened for TB using the QFT Test or equivalent as outlined in Section 8.3.7.

10.7.4 Country-specific Requirements for Japan

Section 1.3.1 Double-Blind Treatment Period

Study Period:	**Screen**	**Double-Blind Treatment Period**												**Notes**
Visit Number/Title:	**1 Screen**	**2 Rand**	**3**	**4**	**5**	**TC**	**6**	**7**	**8**	**9**	**TC**	**10[a]**	**Discon**	
Scheduled Day/Week	Up to 4 wks	Day 1 Wk 0	Day 2	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk12 +1d	Wk 18	Wk 20	Wk 24		
Day		1	2	15	29	43	57	85	86		141	169		
Recommended Window			±12h	±3d	±3d	±3d	±7d	±7d	±12h	±7d	±3d	±7d		
Safety Procedures														
HBV-DNA testing	X							X				X	X	Only for participants with positive HBcAb and/or positive HBsAb and HBV-DNA <LLOQ at Screening

Section 1.3.2 Blinded Extension Period

Study Period:	**Blinded Extension Period**										**Notes**
Visit Number/Title:	**10[a]**	**11**	**12**	**13**	**14**	**15**	**TC**	**16**	**Discon**	**F/U TC**	
Scheduled Day/Week	Wk 24	Wk 26	Wk 28	Wk 32	Wk 36	Wk 44	Wk 48	Wk 52		28 Days after Last Dose	
Day	169	183	197	225	253	309	337	365			
Recommended Window:	±7d	±3d	±3d	±7d	±7d	±7d	±3d	±7d		+7d	
Safety Procedures											
HBV-DNA testing					X	X		X	X		Only for participants with positive HBcAb and/or positive HBsAb and HBV-DNA <LLOQ at Screening

Section 10.2

HBV Testing

Table Protocol-required Safety Laboratory Assessments

Other Screening Tests	• HBsAb

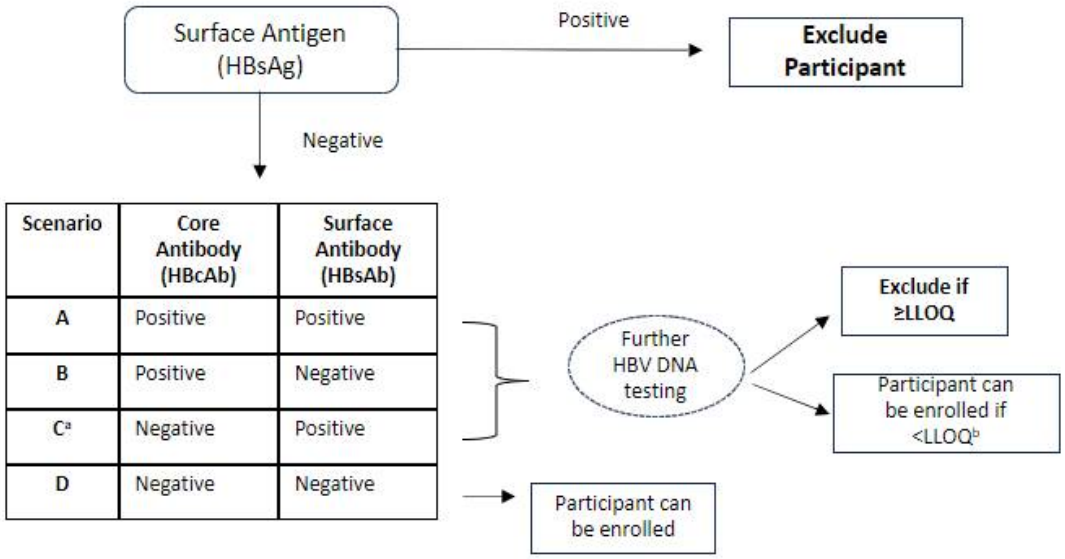
HBsAb= hepatitis B surface antibody

Section 5.2: Exclusion Criteria and Section 8.3.8 HBV, HCV, and HIV Testing

12. Is known to be infected with HBV, HCV, or HIV:

- Participants with positive HBsAg are excluded from the study.
- For participants with positive HBsAb and negative HBcAb, HBV-DNA testing at screening is required. If HBV-DNA is ≥LLOQ, the participant must be excluded. If HBV-DNA is <LLOQ, participant may be enrolled and HBV-DNA testing should be performed approximately every 12 weeks (in correlation with a scheduled visit) and at last scheduled visit. If subsequently, HBV-DNA is ≥LLOQ, the participant will require discontinuation of study intervention (Section 7.1).
- For participants with positive HBcAb and/or positive HBsAb and HBV-DNA is <LLOQ at Screening, HBV-DNA testing should be performed approximately every 12 weeks (in correlation with a scheduled visit) and at last scheduled visit. If HBV-DNA is ≥LLOQ, the participant will require discontinuation of study intervention (Section 7.1).

HBV, HCV, HIV Testing



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

a. For participants with positive HBsAb and negative HBcAb who have had a HBV vaccination, HBV-DNA testing is required at Screening. However, HBV-DNA monitoring after randomization is not required. The vaccination history must be documented in the medical records.

b 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).

Sections 4.1, 8.1.9, 8.1.9.3, 8.1.9.4

In Japan, administration of study intervention is not be permitted by a caregiver.

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 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 2 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 - A SAE occurring in a participant (and/or the associated person) in a 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 Country-Specific Requirements for France

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: Examples of Commonly Used Medications/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 7.

Table 7 Commonly Used Immune Checkpoint Inhibitors

PD-1 Inhibitors	PD-L1 Inhibitors	CTLA-4 Inhibitors
Cemiplimab Nivolumab Pembrolizumab	Atezolizumab Avelumab Durvalumab	Ipilimumab Tremelimumab

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 with the exception of T and B cell depleting therapies(Table 1). Examples of prohibited biologics include, but are not limited to, the medications in Table 8.

Table 8 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 (JAK1, JAK2, JAK3 isoforms), 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 9.

Table 9 Commonly Used Advanced Immunosuppressive Small Molecule Medications

JAK Inhibitors		**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.

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

10.9 Appendix 9: Hypereosinophilic Syndrome or Eosinophil-Associated Organ Injury

Definition of Hypereosinophilic syndrome [Valent, P., et al 2012]

1. Absolute eosinophil count ≥1500 cell/µL on 2 examinations (interval ≥ 1 month*) and
2. Organ damage and/or dysfunction attributable to tissue hypereosinophilia† and
3. Exclusion of other disorders or conditions as major reason for organ damage

* In the case of evolving life-threatening end-organ damage, the diagnosis can be made immediately to avoid delay in therapy.

† HE-related organ damage: organ dysfunction with marked tissue eosinophil infiltrates and/or extensive deposition of eosinophil-derived proteins (in the presence or absence of marked tissue eosinophils) and 1 or more of the following: (1) fibrosis (lung, heart, digestive tract, skin and others); (2) thrombosis with or without thromboembolism; (3) cutaneous (including mucosal) erythema, edema/angioedema, ulcerations, pruritus, and eczema; and (4) peripheral or central neuropathy with chronic or recurrent neurologic deficit. Less commonly, organ damage in liver, pancreas, kidney, and other organs can be judged as HE-related pathology. HES can manifest in 1 or more organ systems.

Eosinophil-associated organ injury can also occur as single organ diseases. Table 10 provides a list of single-organ diseases accompanied by HE [Valent, P., et al 2012].

Table 10 Organ-Restricted (Inflammatory) Conditions Accompanied by Hypereosinophilia

Eosinophilic ascites	Eosinophilic nephritis
Eosinophilic asthma	Eosinophilic ocular disorders
Eosinophilic bronchitis	Eosinophilic pancreatitis
Eosinophilic colitis	Eosinophilic panniculitis
Eosinophilic cystitis	Eosinophilic pleuritis
Eosinophilic endometritis	Eosinophilic pneumonia
Eosinophilic esophagitis	Eosinophilic pustular folliculitis: all variants
Eosinophilic fasciitis (Shulman syndrome)	Eosinophilic synovitis
Eosinophilic gastroenteritis	Eosinophilic ulcer of the oral mucosa
Eosinophilic hepatitis	Eosinophilic vasculitis
Eosinophilic mastitis	Pachydermatous eosinophilic dermatitis
Eosinophilic myocarditis	Wells syndrome (eosinophilic cellulitis)
Eosinophilic myometritis	

10.10 Appendix 10: 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)

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
Ab	antibody
ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEC	absolute eosinophil count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	antiretroviral therapy
AST	aspartate aminotransferase
BFNE	Brief Fear of Negative Evaluation
bid	twice daily
BP	blood pressure
BSA	body surface area
CBC	complete blood count
CCL22	chemokine ligand 22
CD4+	cluster differentiation 4 expressing cells
CD25	cluster of differentiation 25, IL-2Rα subunit
CD122	cluster differentiation 122, IL-2Rβ subunit
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
C_{max}	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CL	clearance
ClinROs	clinician reported outcomes

Abbreviation	Expanded Term
CRF	Case Report Form
CSR	Clinical Study Report
CT	computer tomography
C-terminus	carboxyl-terminus
C_{trough}	trough concentration
CXR	chest x-ray
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	External Data Monitoring Committee
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FAS	Full Analysis Set
FBR	future biomedical research
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FOXP3	forkhead box protein 3
FSH	follicle-stimulating hormone
FTU	fingertip unit
F-VASI	Facial Vitiligo Area Scoring Index
GCP	Good Clinical Practice
GI	gastrointestinal

Abbreviation	Expanded Term
GWAS	genome-wide association study
hCG	human chorionic gonadotropin
H1, (H2)	hypothesis 1, (hypothesis 2)
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HE	hypereosinophilia
HES	hypereosinophilic syndrome
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IgG1	immunoglobulin G1
IL-2	interleukin 2
IL-2M	interleukin-2 mutein
IL-10	interleukin 10
IA	interim analysis(ses)
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
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology

Abbreviation	Expanded Term
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
JAK	Janus kinase
JAKi	Janus kinase inhibitor
LDA	longitudinal data analysis
LLOQ	lower limit of quantitation
MAD	maximum administered dose
M&N	Mietinnen and Nurminen
MAR	missing-at-random
MCAR	missing completely at random
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputations
MNAR	missing not at random
mRNA	messenger RNA
NK	natural killer cells
N-terminus	amino-terminus
PBMC	peripheral blood mononuclear cell
PBO	placebo
PCR	polymerase chain reaction
PD	pharmacodynamic
PDE4	phosphodiesterase 4
PGIC/M	Patient Global Impression of Change/Meaningfulness
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
po	orally
POCBP	participants of childbearing potential
PP	per-protocol

Abbreviation	Expanded Term
PPD	purified protein derivative
PQC	product quality complaint
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QFT	QuantiFERON-TB Gold®
QoL	quality of life
RNA	ribonucleic acid
RR	respiratory rate
S1P	sphingosine 1-phosphate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAD	single ascending dose
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLAB	supplemental laboratory test(s)
SNP	single-nucleotide polymorphism
SPF	sun protection factor
SoA	schedule of activities
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TB	tuberculosis
TBNK	T, B, and natural killer cell surface marker assay
TC	telephone call
Tconv	conventional T cells, CD24+CD25-cells
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine

Abbreviation	Expanded Term
Teff	effector T cell
T_{max}	time to maximum concentration
Tregs	regulatory T cells
T-VASI	Total Vitiligo Area Scoring Index
TYK2	tyrosine kinase 2
UC	ulcerative Colitis
ULN	upper limit of normal
VASI	Vitiligo Area Scoring Index
CCI [redacted]	[redacted]
VitiQoL	Vitiligo-Specific Quality of Life Instrument
VNS	Vitiligo Noticeability Scale
VS	vital signs
WBC	white blood cell
WT	wild type

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