Official Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Clinical Trial to Investigate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MK-6194 in Participants with Moderate to Severe Atopic Dermatitis
NCT number:	NCT05450198
Document Date:	12-Dec-2022

Title Page

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Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Clinical Trial to Investigate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MK-6194 in Participants with Moderate to Severe Atopic Dermatitis

This protocol amendment is applicable only to the United States.

Protocol Number: 008-04

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):

EudraCT	2022-001011-12
IND	142873

Approval Date: 12 December 2022

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
MK-6194-008-04	12-DEC-2022	This is the second US country specific amendment and includes the following modifications: 1) inclusion of monthly pregnancy testing from Day 85 through the end of the study, 2) clarification of subject and cohort stopping rules, and 3) clarification of requirements for initiation of the expansion panels.
MK-6194-008-03	26-SEP-2022	Canada added as a country.
MK-6194-008-02	07-JUL-2022	Belgium, Bulgaria, Romania, and Spain specific amendment to clarify a newly added test.
MK-6194-008-01	06-JUL-2022	This US country specific amendment modifies dose escalations to occur based on the review of safety data through at least one week following the final administered dose of MK-6194/placebo in the preceding dose escalation panel. Additional minor changes in this protocol amendment include an update of data from ongoing clinical studies through 01-JUL-2022, an updated study diagram to reflect the revised dose escalation criteria and clarify the study design, and clarification of screening testing.
Original Protocol	02-MAY-2022	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendments:

The purpose of this MK-6194-008-04 amendment to MK-6194-008-01 is to make the following modifications to the protocol:

1. To add monthly pregnancy testing after Day 85. This supplements the pregnancy testing that precedes each administration of MK-6194 and is performed at the final study visit (Section 1.3, Schedule of Activities).
2. CCI [redacted]
3. To clarify requirements to initiate expansion panels. The intent of the expansion panels is to evaluate dose levels for which the protocol-specified safety review from an equal or greater dose level in a primary escalation panel has been completed. This clarification is included in this amendment to clarify that the decision to dose an expansion panel is based upon primary escalation safety data experience at a greater or equal dose level, rather than based on a specifically named Panel (Section 4.1.2 Decision Regarding Dosing of Expansion Panels).

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Pregnancy testing has been added on Day 113 and Day 141.	The change was incorporated to increase the number of pregnancy tests to a monthly cadence after Day 85 through the end of the study.
4.1.2 Decision Regarding Dosing of Expansion Panels	The requirements for expansion panel dosing have been clarified to be based on safety review from a primary escalation panel at an equal or greater dose.	Clarification was made regarding data requirements for dosing the expansion panels.
6.6.1 Stopping Rules	Subject and cohort level stopping rules have been clarified.	Clarification was added to provide more explicit instructions regarding stopping rules. Please refer to point #2 in the Overall Rationale for Amendments above.
7.1 Discontinuation of Study Intervention	The criterion governing subject level discontinuation from dosing has been further clarified.	Clarification was added to provide more explicit instructions regarding subject level stopping rules. Please refer to point #2 in the Overall Rationale for Amendment above.
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events and 10.3.2 Definition of AE	Administrative changes	Revisions were made for alignment with the Merck Early Stage Development non-oncology protocol template standard language.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Dose Clinical Trial to Investigate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MK-6194 in Participants with Moderate to Severe Atopic Dermatitis

Short Title: Multiple Rising Dose Study of MK-6194 in Participants with Atopic Dermatitis

Acronym: NA

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study is to be conducted in adult participants with moderate to severe atopic dermatitis.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of MK-6194 in participants with atopic dermatitis, following multiple dose subcutaneous administration.	• AEs, discontinuation from dosing due to AEs
Secondary	
• To characterize serum PK for MK-6194 in participants with atopic dermatitis following multiple dose subcutaneous administration.	• CCI [redacted]

Objectives	Endpoints
• To characterize regulatory T-cell pharmacodynamics of MK-6194 in participants with atopic dermatitis following multiple dose subcutaneous administration. • Hypothesis: A tolerated multiple dose subcutaneous administration of CCI [redacted]	• Immunophenotyping of Tregs

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Atopic Dermatitis
Population	Patient: Adult participants with moderate to severe atopic dermatitis
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	CCI [redacted]

Number of Participants:

Up to 72 participants will be allocated/randomized.

CCI [redacted]

Duration of Participation	Each participant will participate in the study for approximately CCI [redacted] from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately CCI [redacted]

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 13.

1.2 Schema

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

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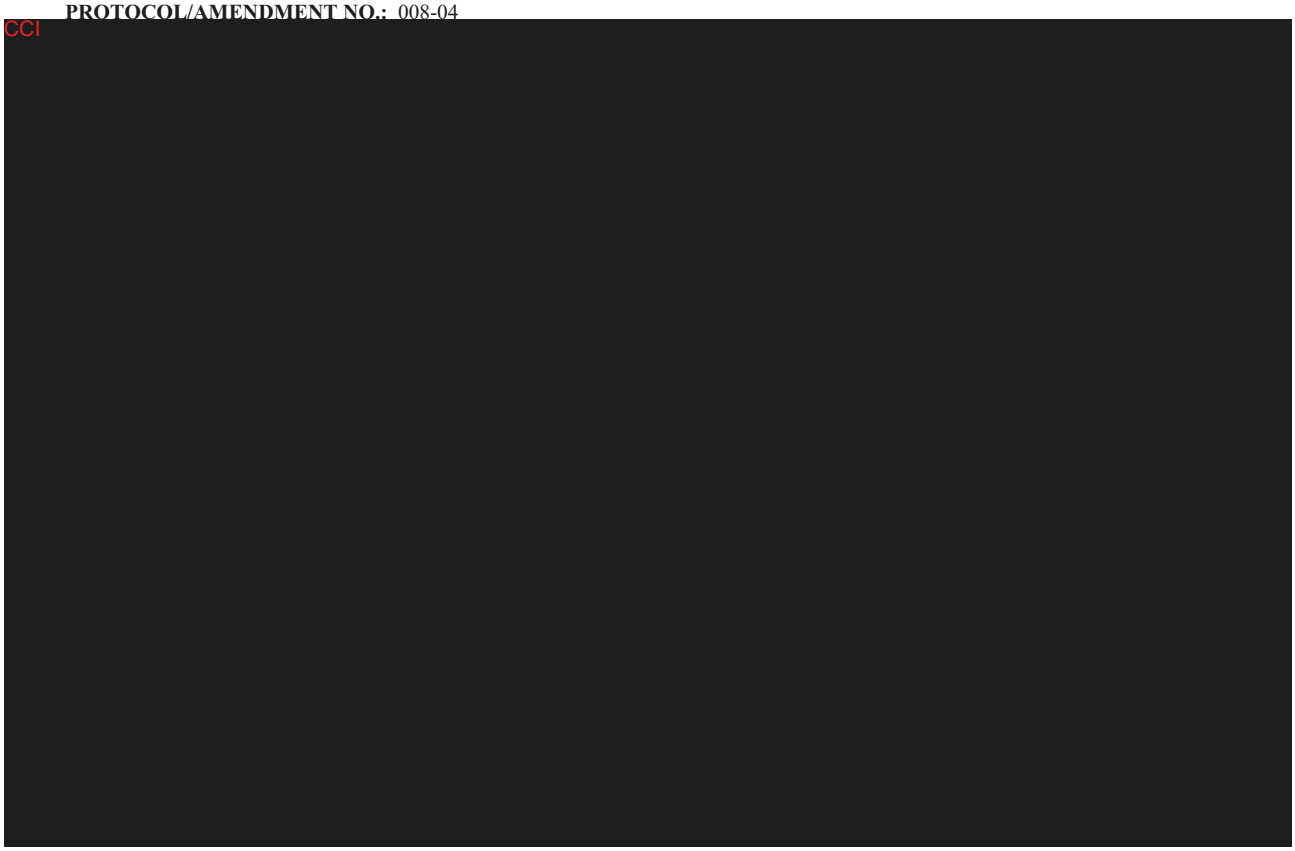


1.3 Schedule of Activities

Study Period:	**Screening**	**Intervention**															**Post-study**	**Notes**
Scheduled Day		**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**169**	
Administrative Procedures																		
Informed Consent	X																	Sec. 5.1, 8.1.1.1
Informed Consent for FBR	X																	Sec. 5.1, 8.1.1.2
Participant ID Card	X																	Sec. 8.1.3
Inclusion/Exclusion Criteria	X	X																Sec. 5.1, 5.2, 8.1.2 Review of IC/EC at Screening, only specific criteria will be reviewed at predose prior to randomization
Medical History	X																	Sec 8.1.4
Prior/Concomitant Medication Review	X----------																-X	Sec 5.2, 6.5, and 8.1.5
Assignment of Screening Number	X																	Sec 8.1.6
Assignment of Treatment/ Randomization Number		X																Sec 5.5, 8.1.7
CCI		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]							[redacted]
Safety Procedures																		
Full physical examination	X	X															X	Sec. 8.3.1 Day 1 at predose
Height	X																	Sec. 8.3.1
Weight	X																X	Sec. 8.3.1
VS (HR, BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.3.3.1 Days 1, 15, 29, 43, 57, 71 and 85: within 3h predose and 0.5 h postdose
VS (RR and Body Temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.3.3.1 Days 1, 15, 29, 43, 57, 71 and 85: within 3h predose and 0.5 h postdose
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.3.4, Appendix 9 Day 1: Predose and 12 hr postdose All other days: one ECG measurement Triplicate at Day 1 predose and Day 1 12 h postdose, single measurement at all other timepoints
Local injection site reaction assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sec. 8.3.2 Days 1, 15, 29, 43, 57, 71 and 85: predose and 0.5 h postdose

Study Period:	**Screening**	**Intervention**															**Post-study**	**Notes**
Scheduled Day		**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**169**	
AE/SAE review including assessment for systemic injection reaction	X----------X																	Sec 8.4, 10.3
Laboratory Procedures																		
Serum FSH - (WONCBP only)	X																	Sec. Appendix2, Appendix 5
Serum or urine β-hCG pregnancy test (WOCBP only)	X	X		X		X		X	X	X	X			X		X	X	Sec 8.3.6, Appendix 2 Day 1 predose serum pregnancy test may be obtained within 72 hours of dosing.
HIV, hepatitis B and C screen (per site SOP)	X																	Sec. 8.3.5, Appendix 2
Purified protein derivation (PPD) test or QuantiFERON®-TB Gold test (per site SOP)	X																	Sec 5.1, 5.2, Appendix 2 To assess IC/EC, performed at local or central lab
Urine Drug Screen (UDS)	X	X																Sec. 8.3.5, 8.10.5, Appendix 2 Mandatory at Screening and predose Day 1; any additional UDS are conducted per site SOP
Alcohol test	X	X																Mandatory at Screening; any additional tests are conducted per site SOP Section 8.10.5, Appendix 2
Hematology (Including CBC)	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	Sec. 8.3.5, Appendix 2 Days 1, 15, 29, 43, 57, 71 and 85: at predose
Urinalysis	X	X		X		X		X	X	X	X		X	X	X	X	X	Sec. 8.3.5, Appendix 2 Days 1, 15, 29, 43, 57, 71 and 85: at predose
Chemistry	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	Sec. 8.3.5, Appendix 2 Days 1, 15, 29, 43, 57, 71 and 85: at predose
Coagulation tests (PT/INR, aPTT)	X																	Sec. 8.3.6, Appendix 2
Pharmacokinetics																		
Blood for MK-6194 Assay[b]		X	X	X		X	X	X			X	X	X					Sec 8.9 Days 1 and 29: predose, and 12h postdose. Days 15, 43, 85: predose
Pharmacodynamics / Biomarker																		
Blood for ADA[b]		X		X							X						X	Sec 8.9 Days 1, 15 and 85 at predose

Study Period:	Screening	Intervention														Post-study	Notes
Scheduled Day		**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**169**	
CCI																		

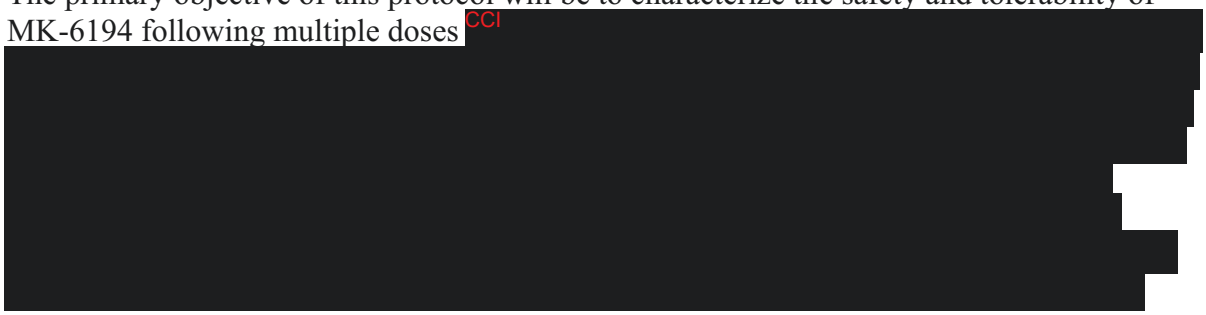
Study Period:	Screening	Intervention														Post-study	Notes
Scheduled Day		**1**	**8**	**15**	**22**	**29**	**36**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**169**	
CCI [redacted]																	

2 INTRODUCTION

2.1 Study Rationale

Human autoimmune disease results, in part from dysfunctional or insufficient numbers of Tregs that by not properly restricting immune responses, causes organ damage [Kolios, A. G. A., et al 2021]. MK-6194 is a novel IL-2 mutein that selectively expands regulatory T cells, without activating cytotoxic immune cell counterparts. This mechanism offers a unique opportunity to rebalance the dysregulated immune responses of patients with a wide range of autoimmune disease. Atopic dermatitis is an autoimmune disease area with significant unmet medical need for which published clinical trials have suggested significant clinical efficacy of IL-2 based treatment.

The primary objective of this protocol will be to characterize the safety and tolerability of MK-6194 following multiple doses CCI



2.2 Background

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

Rationale for Clinical Efficacy of MK-6194, an IL-2-mutein in Atopic Dermatitis:

Atopic dermatitis is a chronic, pruritic, inflammatory skin disease with an estimated prevalence of 10% in developed countries [Langan, S. M., et al 2020]. Dry skin and severe pruritus are hallmark features of the disease. A variety of causal mechanisms have been proposed, including epidermal barrier dysfunction, genetic factors, Th2 cell-skewed immune dysregulation, altered skin microbiome, and environmental triggers of inflammation. Atopic dermatitis typically follows a chronic, relapsing course over months to years. Patients with moderate to severe dermatitis rarely improve without treatment. Despite the availability of immunomodulatory therapies to treat patients with atopic dermatitis, such as dupilumab, (a monoclonal anti IL-4αR antagonist), topical and oral JAKis and tralokinumab, a monoclonal anti IL-13, atopic dermatitis continues to be a disease with significant unmet medical need. While a leading biologic therapy for the treatment of atopic dermatitis, ~20% of patients discontinue dupilumab treatment after 1 year [Silverberg, J. I., et al 2021], which may result in an unmet medical need.

Dupilumab is associated with a higher frequency of eye disorders (such as noninfectious conjunctivitis) and de novo psoriasis, while systemic JAKi used in the treatment of atopic dermatitis are associated with an increased risk of major adverse cardiovascular events and

cancer [Singh, J. A. 2022]. Therefore, a novel treatment for atopic dermatitis that offers both a significant clinical benefit and has an acceptable safety profile is urgently needed.

Clinical efficacy of low dose IL-2 in atopic dermatitis has been shown previously [Hsieh, K. H., et al 1991]. Nektar Therapeutics in partnership with Eli Lilly has developed a pegylated recombinant human IL-2 (NKTR-358). In December 2021, preliminary data from their Phase 1b in atopic dermatitis (NCT04081350) demonstrated a significant clinical benefit of NKTR-358 versus placebo, that persisted up to 36 weeks after treatment had concluded. These data are publicly available but are not yet published.

These supporting data indicate that MK-6194 may impart a significant and persistent clinical benefit among individuals with atopic dermatitis. Therefore, the primary and secondary objectives, respectively, of this multiple dose Phase 1b study are to determine the safety and tolerability, PK profile and T reg expansion profile following multiple doses of MK-6194 among participants with moderate to severe atopic dermatitis. Exploratory objectives will assess whether MK-6194 imparts a clinical benefit to participants with atopic dermatitis. Taken together, these results will determine whether further investigation of MK-6194 in atopic dermatitis is warranted in definitive Phase 2 clinical trials.

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. 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 trials in participants with a variety of autoimmune diseases, including SLE, UC, and chronic GVHD [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].

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MK-6194 was discovered by Pandion Therapeutics, Inc. (Pandion), which was acquired by the Sponsor in April 2021. Previous to the acquisition, MK-6194 was referred to as PT101.

2.2.2 Preclinical and Clinical Studies

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

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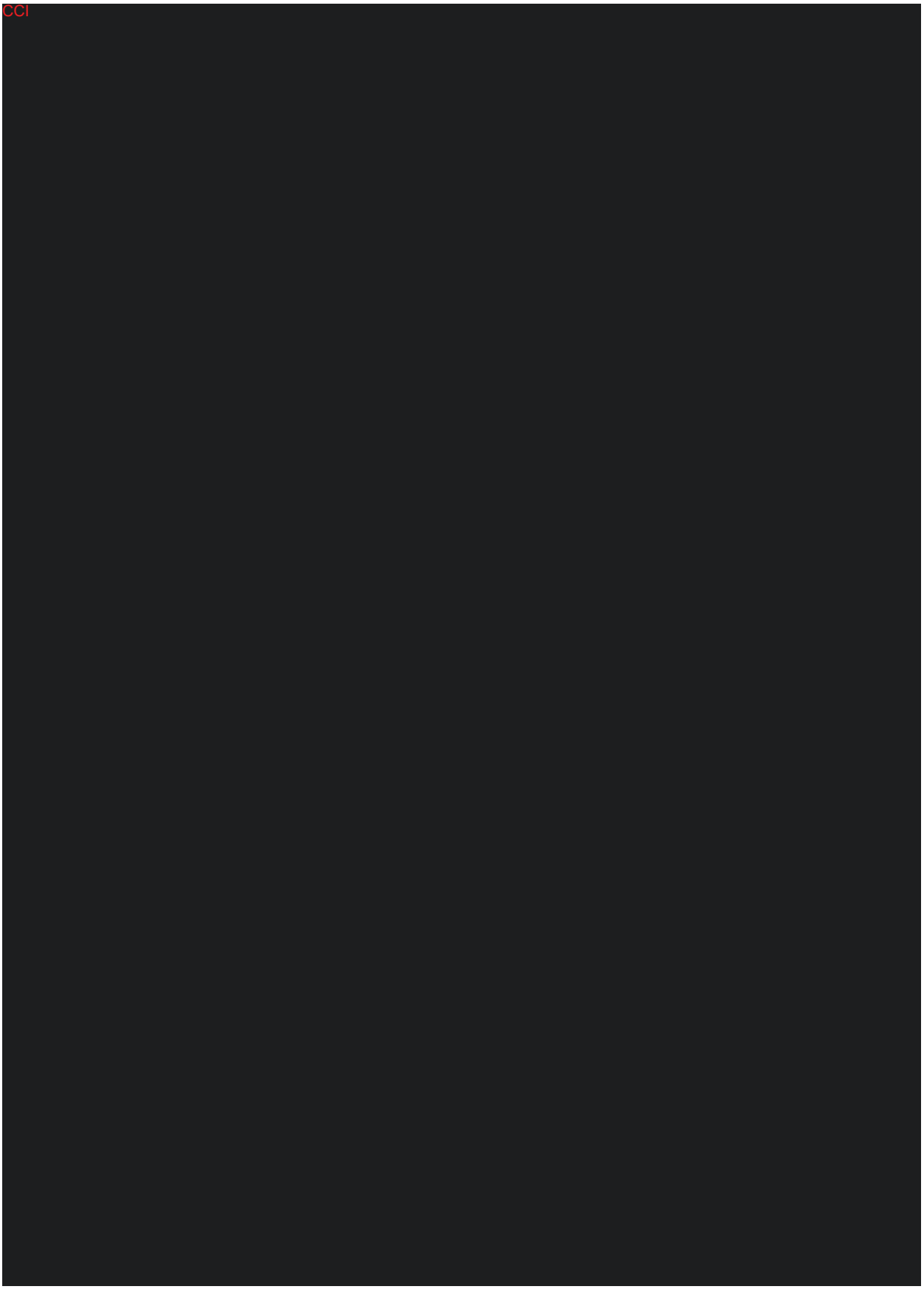

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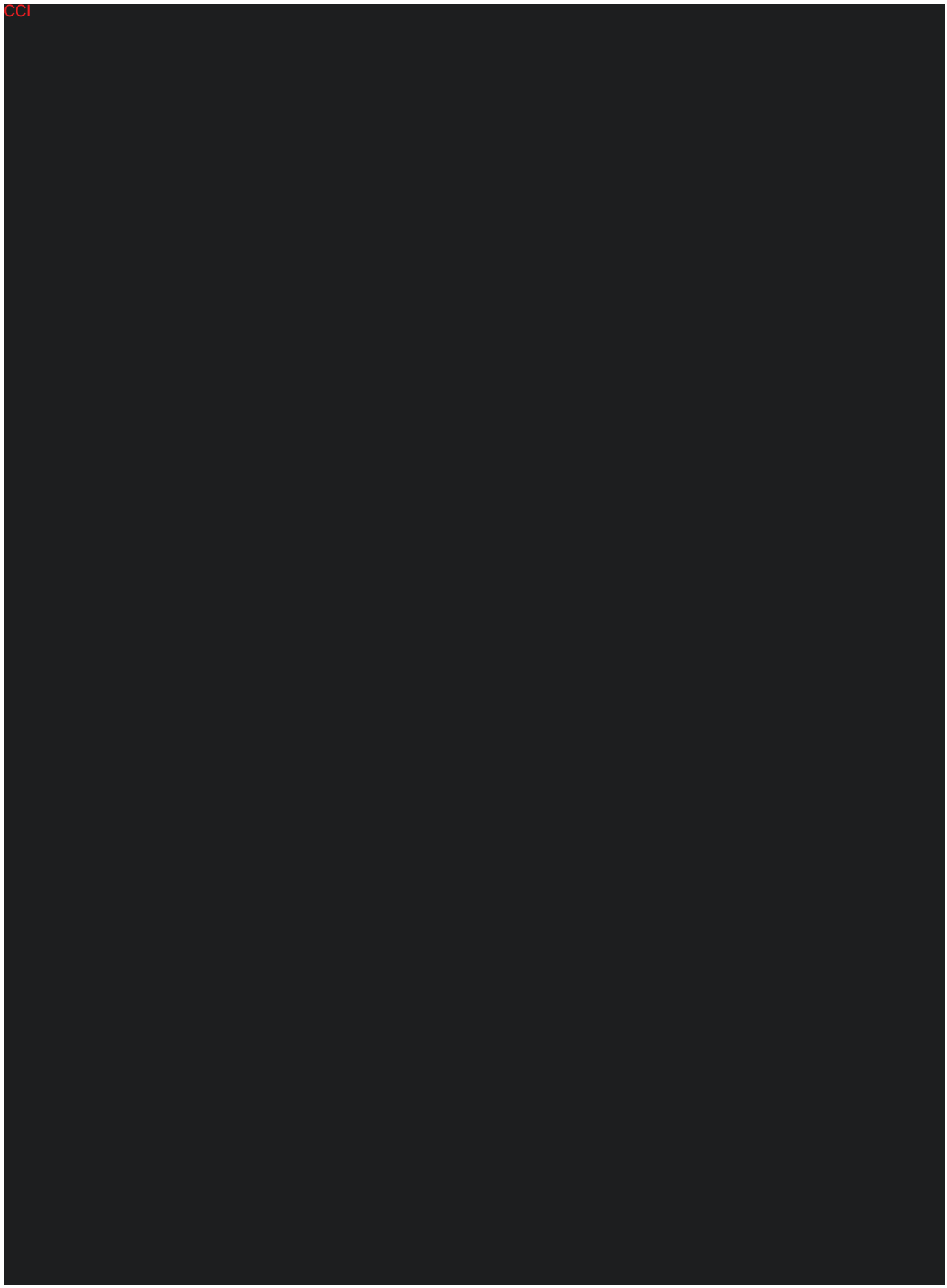

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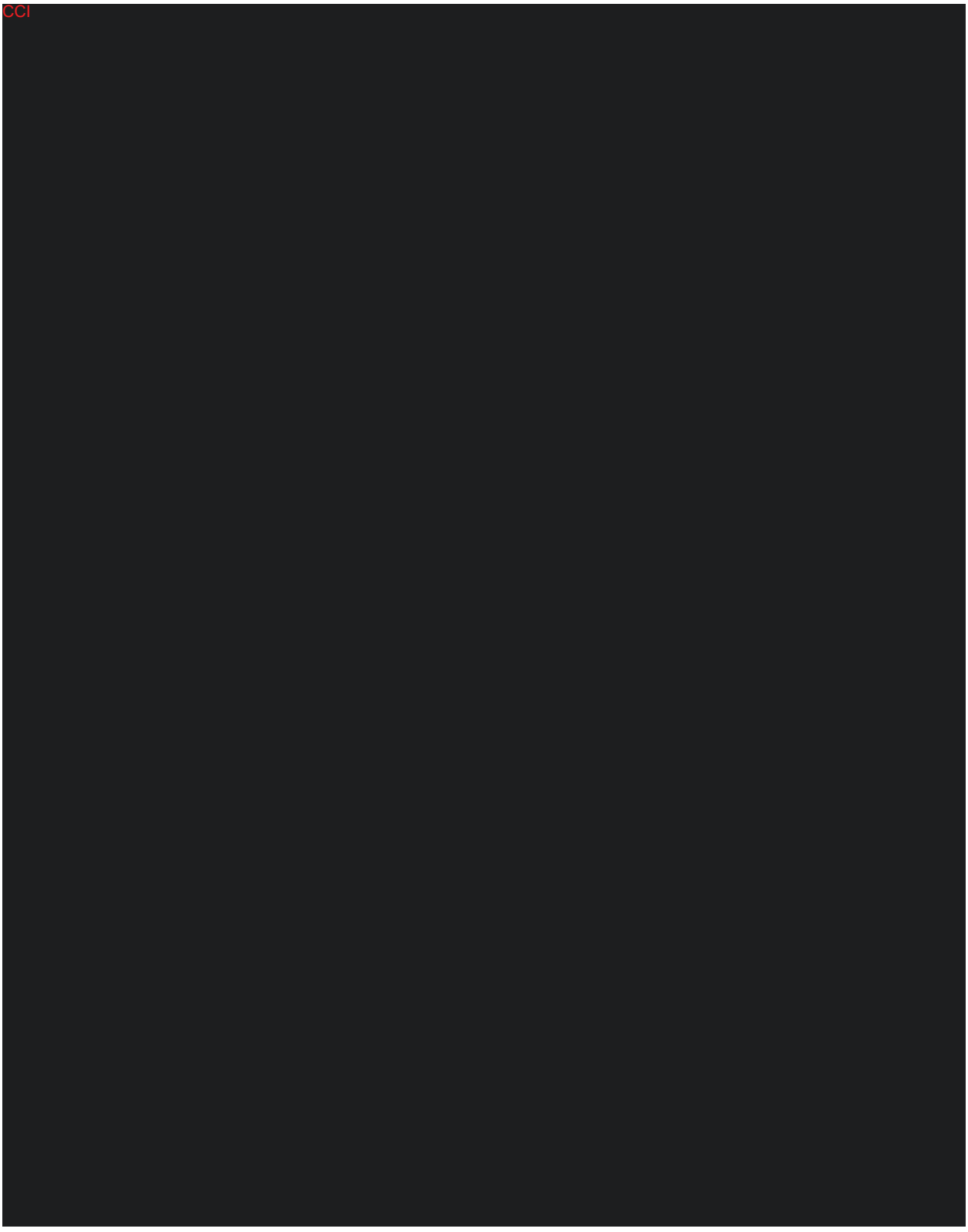

CCI [redacted]

The most notable non-cutaneous AE is mild eosinophilia across all panels to date (Panels A-F) in which 17 individuals of 46 have developed an AE of eosinophilia.CCI [redacted]

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[redacted]

2.3 Benefit/Risk Assessment

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

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study is to be conducted in adult participants with moderate to severe atopic dermatitis.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of MK-6194 in participants with atopic dermatitis, following multiple dose subcutaneous administration.	• AEs, discontinuation from dosing due to AEs
Secondary	
• To characterize serum PK for MK-6194 in participants with atopic dermatitis following multiple dose subcutaneous administration.	• CCI [redacted]

Objectives	Endpoints
• To characterize regulatory T-cell pharmacodynamics of MK-6194 in participants with atopic dermatitis following multiple dose subcutaneous administration. • CCI [redacted]	• Immunophenotyping of Tregs
Tertiary/Exploratory	
• Measures of Treatment Response	CCI [redacted]
• To assess emerging biomarkers of atopic dermatitis disease activity.	
• To identify molecular (genomic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, pharmacodynamic activity and/or the mechanism of action of MK-6194.	• Blood and/or skin biopsy biomarker parameters that may include but are not limited to DNA, RNA, protein-based analyses.

Objectives	Endpoints
• To characterize immunogenicity of MK-6194 in participants with atopic dermatitis following multiple dose subcutaneous administration	• ADA titers
• To explore the relationship between genetic variation and response to MK-6194 administration in relation to the recorded PK, pharmacodynamics, and clinical data.	• Germline genetic variation and association to PK, pharmacodynamics, and clinical data collected in this study
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

CCI

CCI [redacted]

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.

4.1.1 Decisions Regarding Dose Escalation

Dose Escalation from Panel A to Panel B: The participants in Panel A will be dosed with MK-6194 2.5 mg/ placebo once every 2 weeks. Dose escalation decisions to Panel B will be made after review of safety data, including adverse events, physical examination, vital signs, injection site reactions, laboratory tests and ECGs from participants through at least one week following the final dose of MK-6194/ placebo CCI [redacted] Review of data will be further supplemented with safety data from CCI [redacted]

Dose Escalation from Panel B to Panel C: CCI [redacted]

Dose escalation based on the safety data review outlined above is supported by:

CCI [redacted]

4.1.2 Decision Regarding Dosing of Expansion Panels

The safety data required for dosing of expansion panels at the same dose will be less than that required for dose escalation.

Expansion panels D, E, and F may initiate dosing following review of safety data from 4 participants from a primary escalation panel at an equal or greater dose that have been monitored for 7 days following the first dose (Day 8).

Expansion panels D, E and F may enroll up to 16 participants in each panel. Expansion panels will be administered doses that are the same (or lower) than the dose in the corresponding escalation panel.

4.2 Scientific Rationale for Study Design

Individuals with autoimmune disease are the intended recipients of MK-6194. Studying MK-6194 in participants with atopic dermatitis is a critical next step to define the impact of MK-6194 on safety, PK and pharmacodynamic measures in a population with an autoimmune disease. Patients with atopic dermatitis have already been shown to experience a clinical benefit from IL-2 based therapy in a published study [Hsieh, K. H., et al 1991] as well as in publicly available preliminary Phase 1b data released by Nektar Therapeutics.

Exposures anticipated in the proposed dose range are below those that were achieved and well tolerated in PN001. Close monitoring with pre-specified stopping rules will be implemented. Furthermore, the addition of participants in the expansion panels will permit the opportunity to more carefully investigate whether MK-6194 can provide meaningful clinical benefit to individuals with atopic dermatitis CCI

CCI

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

It is anticipated that administration of MK-6194 over the proposed dose range will be generally well-tolerated in participants with atopic dermatitis based on preclinical safety and toxicological testing in cynomolgus monkey and PN001. The most common adverse findings across all of these studies are cutaneous, including injection site reactions, which are monitorable and reversible. The other notable adverse finding reported across all studies is mild eosinophilia without evidence of eosinophilic end organ injury. Additionally, three participants in PN001 also reported dyspnea, which was not associated with changes in physical examination and resolved without intervention.

CCI

CCI

[redacted]

Among individuals with atopic dermatitis, mild eosinophilia often accompanies increased serum IgE levels, which can be found in up to 80 percent of patients. Therefore, based on the preclinical and clinical safety profiles, appropriate safety endpoints have been incorporated including monitoring for clinical AEs including physical examination supplemented by a targeted evaluation of injection site reactions, assessment of resting vital signs (BT, HR, BP, RR), 12-lead ECG, and laboratory safety tests (serum chemistry, hematology including CBC with differential to assess for eosinophilia, and urinalysis). Safety data from each dosing panel will be carefully reviewed before escalation to the next higher dose.

4.2.1.2 Pharmacokinetic Endpoints

CCI

[redacted]

4.2.1.3 Pharmacodynamic Endpoints

Whole blood will be collected for immunophenotypic analyses of circulating Treg frequency and absolute cell counts to evaluate MK-6194 pharmacodynamic effect under multiple dose conditions.

4.2.1.4 Efficacy Endpoints

The following clinical endpoints have been chosen as exploratory endpoints for this study:

CCI

[redacted]

CCI

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Exploratory Biomarker Research

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

Blood/Tissue protein 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 patient selection for therapy. This research would serve to develop such assays for future clinical use.

Blood/Tissue RNA analyses

Both genome-wide and targeted RNA-based expression profiling and sequencing in blood and/or tissue may be performed to define gene signatures that correlate with clinical response to treatment with therapy. Specific gene sets may be evaluated, and new signatures may be identified. Individual genes may also be evaluated (eg, IL-2. MicroRNA profiling may also be pursued as well as exosomal profiling).

4.2.1.5.2 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.

4.2.1.6 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.

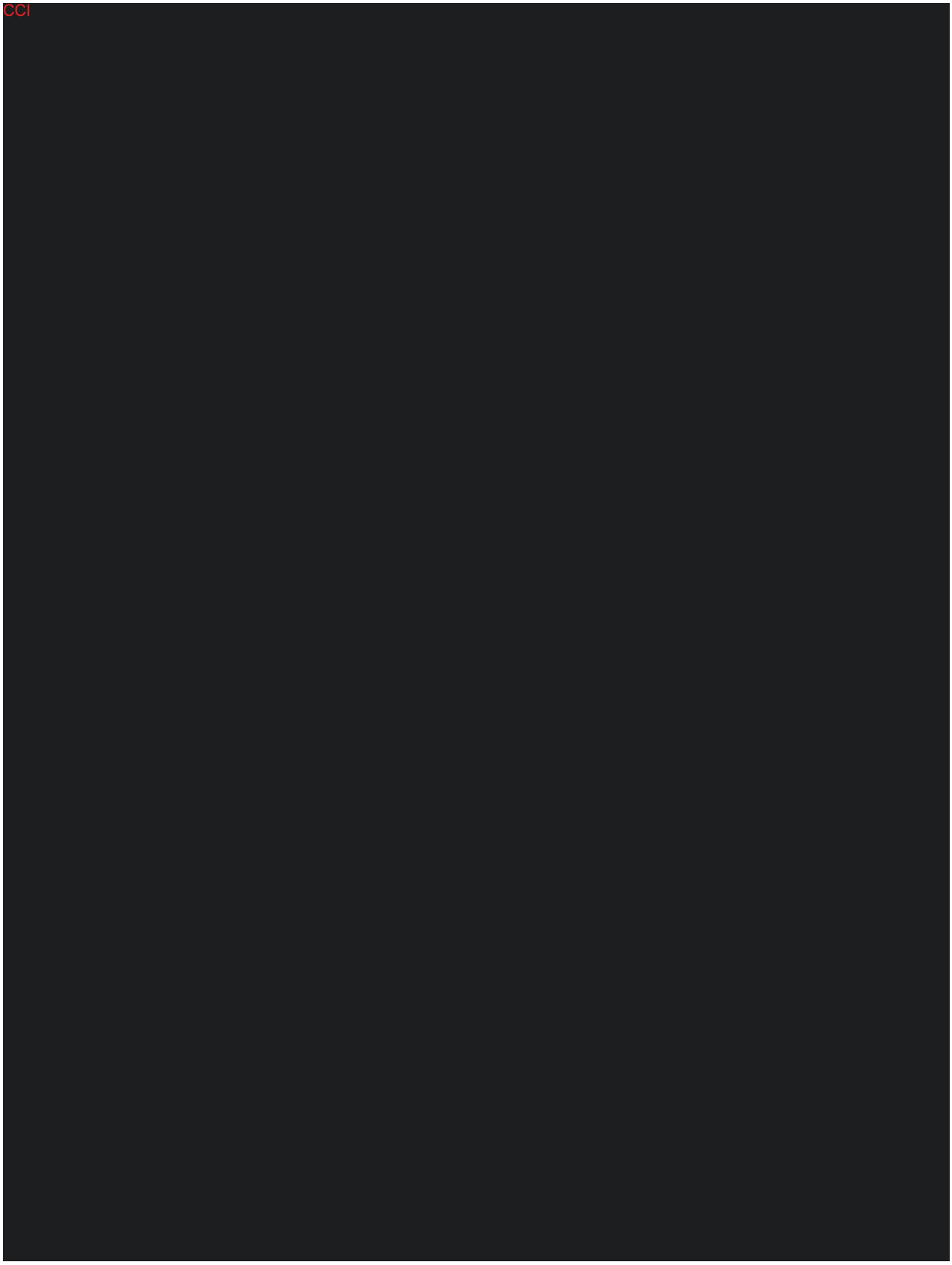
Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the 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 Comparator/Placebo

Placebo will be used in this study to allow for an appropriate assessment of the safety data of MK-6194 and to maintain study blinding to reduce bias.

4.3 Justification for Dose

CCI



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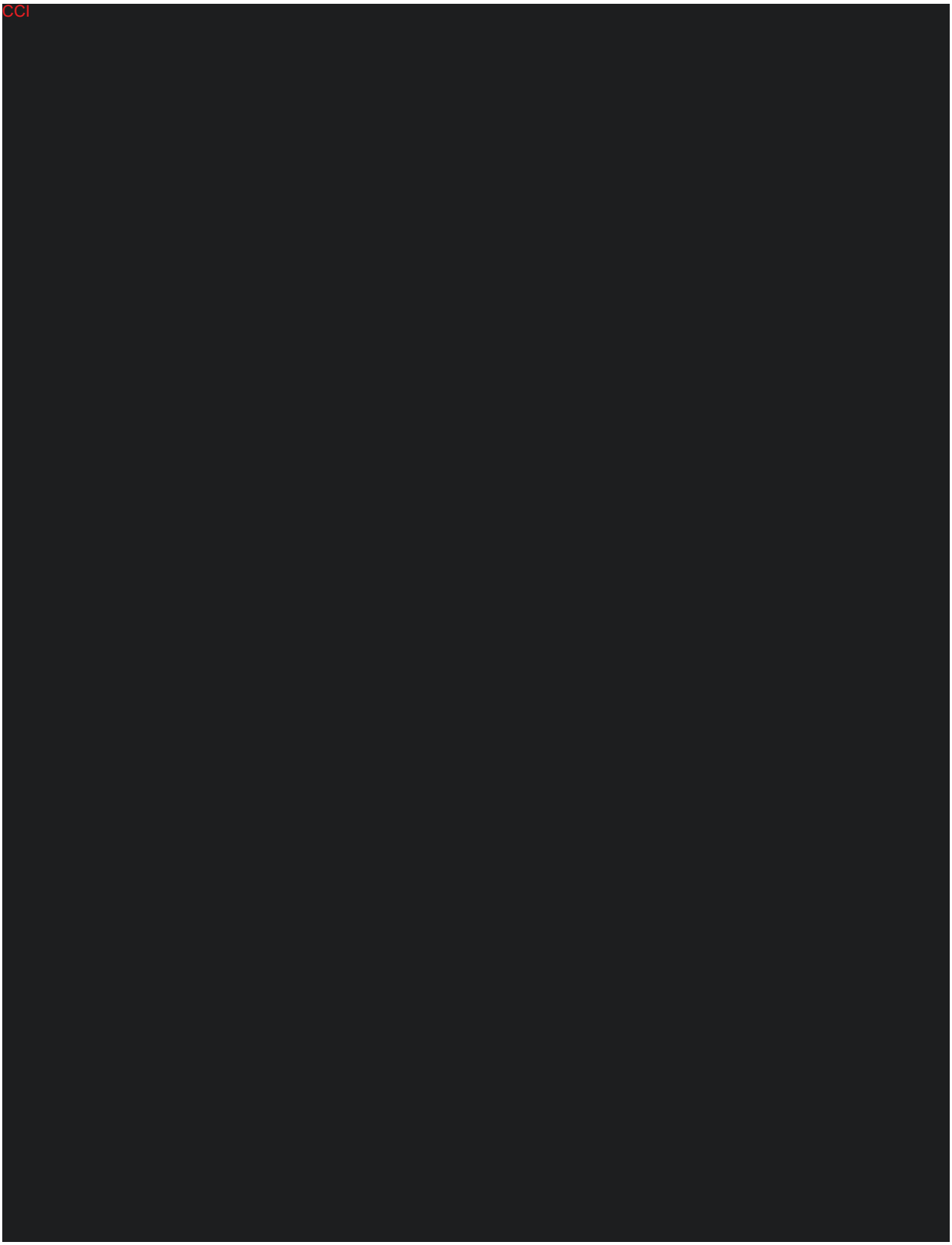


4.3.3 Rationale for Dose Interval and Study Design

CCI [redacted]

A dosing regimen of Q2W of modified forms of IL-2 was generally well-tolerated and resulted in preferential Treg expansion that was sustained in participants with autoimmune disease [Fanton, C., et al 2020], [Tchao, N., et al 2021]. CCI [redacted]

Together, this data supports that CCI [redacted]

The expansion panels (Panel D -F) will enroll up to CCI [redacted] per panel and may dose up to CCI [redacted], to obtain additional data at w es to support further development of MK-6194. It is expected that Panel D will be dosed at CCI [redacted]

Male contraception during clinical studies with MK-6194 is not warranted. Due to the physiology of the testes-blood barrier, the exposure to large protein therapeutics based on immunoglobin scaffolds in the semen is typically limited. In humans, it is estimated that the total concentration of immunoglobulins secreted in semen is 1% of that found in serum [Moldoveanu, Z., et al 2005]. Furthermore, the vaginal exposure to immunoglobulins is estimated to be 10% of that found in semen [Kuo, P. Y., et al 1998] [Sherwood, J. K., et al 1996]. Due to limited risk for genotoxicity and insufficient exposure to ejaculate, large protein therapeutics are not associated with an embryo-fetal risk to female partners.

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 (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory 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.

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

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/clinical endpoints 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 due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

A primary objective of this early Phase 1 study is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve PK, pharmacodynamic, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are to follow all local laws and guidelines in keeping with the needs for participant

confidentiality 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

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has a clinical diagnosis of atopic dermatitis (as defined by the criteria of Hanifin and Rajka; Appendix 11) for at least 6 months prior to the Screening visit as determined by participant interview to review patient's medical history and confirmation of diagnosis through physical examination by investigator.

2. Participant's disease is of at least moderate severity at the Baseline (Day 1 predose) Visit as defined by the following (see Section 10.12 Appendix 12):

CCI

[redacted]

4. Is considered to be a candidate for systemic treatment or phototherapy.

CCI

[redacted]

6. Have a Body Mass Index (BMI) ≥18 and ≤38 kg/m^2. BMI = weight (kg)/height $(m)^2$ at the prestudy (screening) visit. See Section 8.3 for criteria on rounding to the nearest whole number.

Demographics

7. Is male or female, from ≥18 years to ≤75 years of age inclusive, at the time of providing informed consent.

Female Participants

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

   - Not a WOCBP

     OR

   - A WOCBP and:

     - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual 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 ~84 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 women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

     - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) 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 8.3.6.

     - Abstains from breastfeeding during the study intervention period and for at least 84 days after study intervention MK-6194.

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

Informed Consent

9. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. Skin biopsy is optional for Panels A-C and it is required for Panels D, E and F.

10. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

11. Participant is eligible according to the following TB screening criteria:

    - No evidence of active TB, latent TB, or inadequately treated TB as evidenced by one of the following:

    - Negative QuantiFERON test or equivalent assay at screening or within 90 days prior to randomization date, OR

    - History of fully treated active or latent TB according to local standard of care. Investigator must verify adequate previous anti-TB treatment and provide documentation; these participants do not require QuantiFERON testing.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has known systemic hypersensitivity to the MK-6194 drug substance or other IL-2 based therapy, its inactive ingredients or the placebo.

2. Has a concurrent significant skin disease other than atopic dermatitis (such as psoriasis), 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 study investigator or sponsor, might confound the results of the study or poses an additional risk to the patient by their participation in the study.

3. Within 6 months prior to Screening, any significant organ dysfunction that is unstable or inadequately treated, including cardiac (see below), renal, liver, central nervous system, pulmonary, vascular, gastrointestinal, endocrine, psychiatric, ophthalmologic, or metabolic conditions or clinically significant laboratory abnormalities that place the patient at unacceptable risk for participation in a trial of an immunomodulatory therapy in the judgment of the investigator and sponsor.

4. Mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of

clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

5. History of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies that have been successfully treated ≥10 years prior to the screening visit).

6. History of myocardial infarction, congestive heart failure (New York Heart Association [NYHA] Class 3 or 4), uncontrolled arrhythmias, cardiac revascularization, stroke, uncontrolled hypertension, or uncontrolled diabetes within 6 months of Screening.

7. Has any clinically significant laboratory abnormality, which, in the opinion of the investigator, presents a safety concern to the participant, will prevent the participant from completing the study or will interfere with the interpretation of the study results
   - CCI [redacted]

8. Has a history of moderate to severe pulmonary function test abnormality, which, in the opinion of the investigator, presents a safety concern to the participant.

9. Has a history of organ or tissue allograft.

10. Has a history of symptomatic herpes zoster within 16 weeks of randomization, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or CNS zoster.

11. Has active clinically significant infection, or any infection requiring hospitalization or treatment with intravenous anti-infectives up to 8 weeks prior to Day 1 visit, or any infection requiring oral anti-infective therapy up to 6 weeks prior to Day 1 visit.

12. Has history of significant multiple and/or severe allergies (eg, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food. Participants who have history of severe allergies that do not present a safety concern to the participant may be enrolled in the study at the discretion of the investigator.

13. Has positive test(s) for HBsAg, hepatitis C antibodies or HIV, or has positive HBcAb with negative HBsAb serologies.

14. Has donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

15. Has had major surgery within 3 months prior to the prestudy (screening) visit or has a major surgery planned during the study.

CCI

[redacted]

Prior/Concomitant Therapy

17. Has had prior treatment with recombinant IL-2 or modified IL-2 therapy, including MK-6194 (see Section 6.5)

18. Is unable to refrain from treatment with topical (except provided low/medium potency topical corticosteroids with hydrocortisone 2.5% cream and triamcinolone acetonide 0.1% cream offered as rescue therapy) prior to week 6 or systemic therapy (including immunosuppressive agents, biologics, corticosteroids, or phototherapy) for atopic dermatitis during the entire trial. Refer to Section 6.5 for other not allowed medication.

19. Is unable to refrain from or anticipates the use of any other medication (see Section 6.5), including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study, until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

20. Has received a live or attenuated virus vaccine within 4 weeks prior to the Screening visit or intends to receive live or attenuated virus vaccination during the course of the study and for 12 weeks after the last dose of study drug.

21. Is currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, or atypical mycobacteria).

22. Is currently receiving lymphocyte depleting therapy.

Prior/Concurrent Clinical Study Experience

23. Is in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

    Note:

    - Participants in observational studies or non-interventional registry studies may be included in the study.

Diagnostic Assessments

24. Has a QTc interval ≥470 msec (males) or ≥480 msec (females) upon confirmation on recheck at screening or at Predose Day 1 (median), has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia, or is taking concomitant medications that prolong the QT/QTc interval.

Other Exclusions

25. Under the age of legal consent.

26. Is unwilling to comply with the study restrictions (see Section 5.3).

27. A regular user of any illicit drugs except cannabis, or has a history of drug (including alcohol) abuse within approximately 1 year. Participants must have a negative UDS, with the exception of cannabis or a medicine for which there is a current prescription from a licensed medical provider, prior to randomization.

28. The investigator has any concern regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

29. 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

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Dietary restrictions are not required.

5.3.1.2 Fruit Juice Restrictions

Fruit juice restrictions are not required.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will be instructed to avoid the ingestion of caffeine for at least 30 minutes before scheduled ECGs, HR, and BP procedures/assessments.

5.3.2.2 Alcohol Restrictions

Participants will be counseled as needed to limit alcohol use to ≤1 standard drink per day or less than approximately 7 standard drinks per week in females, and ≤2 standard drinks per day or less than approximately 14 standard drinks per week in males, on average. One standard drink is defined as any beverage containing 14 g of pure alcohol or as defined by local guidelines.

5.3.2.3 Tobacco Restrictions

Participants will be instructed to avoid the ingestion of nicotine-containing products for at least 30 minutes before scheduled ECGs, HR, and BP procedures/assessments. For all time during the study, tobacco restriction is not required.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study and until the poststudy visit.

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 may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention or withdraws from the study, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

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 (MK-6194 or placebo) will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

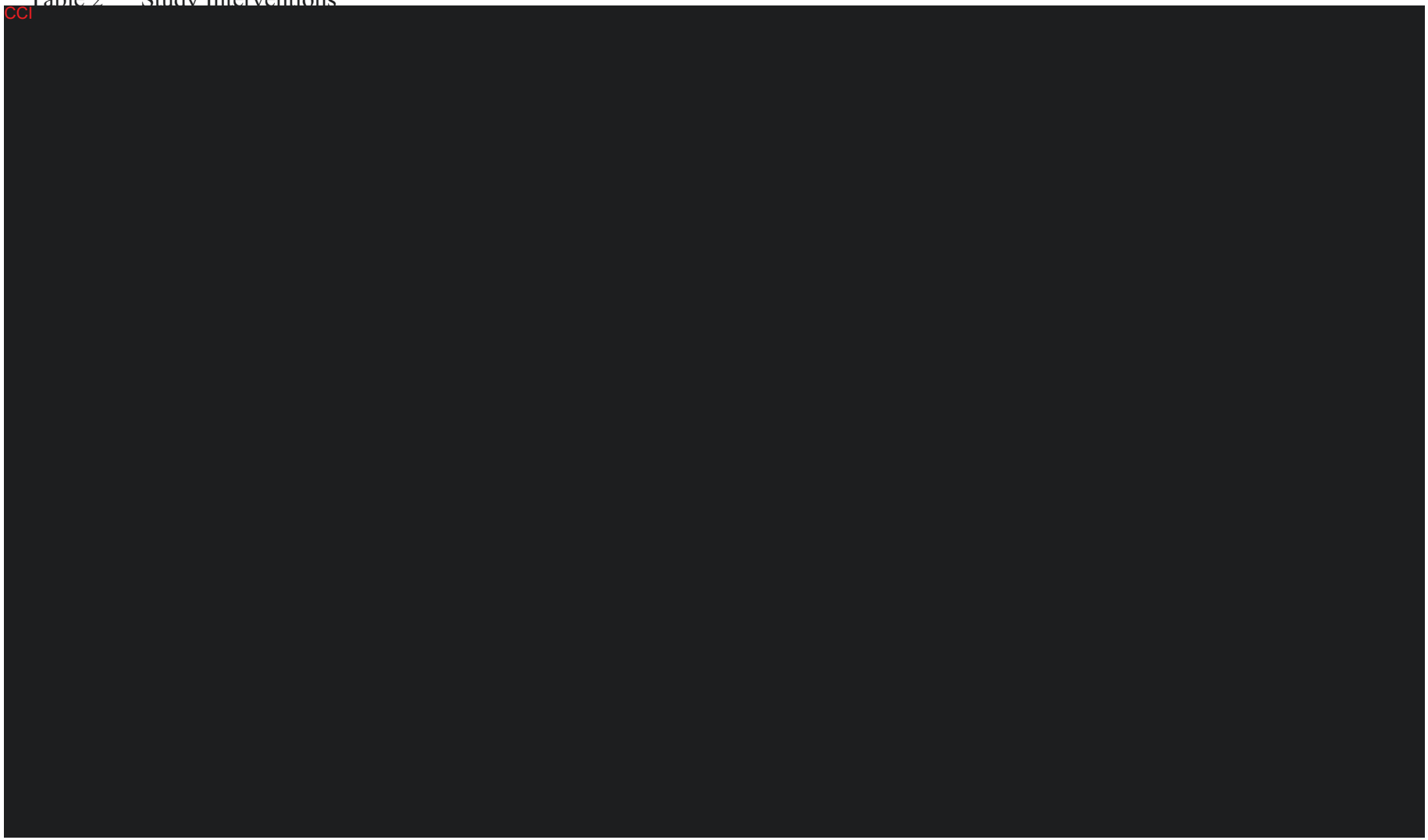
6.1 Study Intervention(s) Administered

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

Country-specific differences are noted in Appendix 7.

Table 2 Study Interventions

CCI




CCI

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 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.

MK-6194 sterile solution will be prepared and/or dosed per the instructions outlined in the Pharmacy Manual.

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

Participants will be assigned randomly according to a computer-generated allocation schedule.

A sample allocation schedule is provided in Table 3.

CCI

q2w=once every 2 weeks

[a] The suggested doses may be adjusted downward based on evaluation of safety, tolerability, PK, and/or pharmacodynamic data observed with previously administer doses.

[b] Panels D, E and F may enroll up to 16 participants.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

A double-blinding technique will be used. MK-6194 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study-site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

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

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study-site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

CCI

CCI

Vaccine Guidelines:

- There are no available data on the concurrent use of MK-6194 and its impact on immune responses following vaccination. Therefore, in accordance with local vaccination standards, it is recommended that the participant's vaccination be brought up to date according to local vaccination standards.
- Primary or booster doses of the SARS-CoV2 vaccination may be administered throughout the study.
- Inactivated vaccines (such as inactivated influenza vaccines) should be administered according to local vaccination standards whenever medically appropriate.
- Live or attenuated vaccines (including, but not limited to varicella, MMR, MMRV, LAIV, yellow fever, Ty21a oral typhoid, BCG, smallpox, and rotavirus) are prohibited within 4 weeks of screening, throughout the study, and for 12 weeks after the last dose of study drug.

6.5.1 Rescue Medications and Supportive Care

Rescue Treatment for Atopic Dermatitis:

CCI

Supportive Care for Injection Reaction:

Refer to Section 8.3.2 (Injection Reactions).

CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

6.6 Dose Modification (Escalation/Titration/Other)

All dose escalation decisions will be made jointly by the investigator and the Sponsor. Members of the Sponsor safety review team will include: the trial clinical director, trial clinical scientist, senior level clinical director and trial biostatistician. Additional Sponsor attendees may include the ESDS, ESDS lead, research associate and a pharmacologist. The Sponsor safety review team will obtain input from the investigator regarding investigators evaluation of safety and tolerability from the previous dosing period and investigators' recommendation to dose escalate in the next panel.

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If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, participants may:

- Receive the same dose level to further explore safety and tolerability at that level,
- Receive a lower dose of the study intervention (with or without food),
- Receive the same or lower dose as a divided dose, or
- Dosing may be stopped.

Participant discontinuation criteria are outlined in Section 7.

Enrollment and dosing of the expansion Panels D, E or F may be reduced or cancelled at the discretion of the Sponsor.

6.6.1 Stopping Rules

The following stopping rules will be used during the conduct of this study.

If any of the below stopping rules are met, the study will be paused, and no further dosing will occur until the Sponsor has reviewed the totality of data available. To continue the study (on joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

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If any of the below stopping rules are met, subsequent higher doses will be lowered based on joint agreement of the Sponsor and investigator in order for the study to continue.

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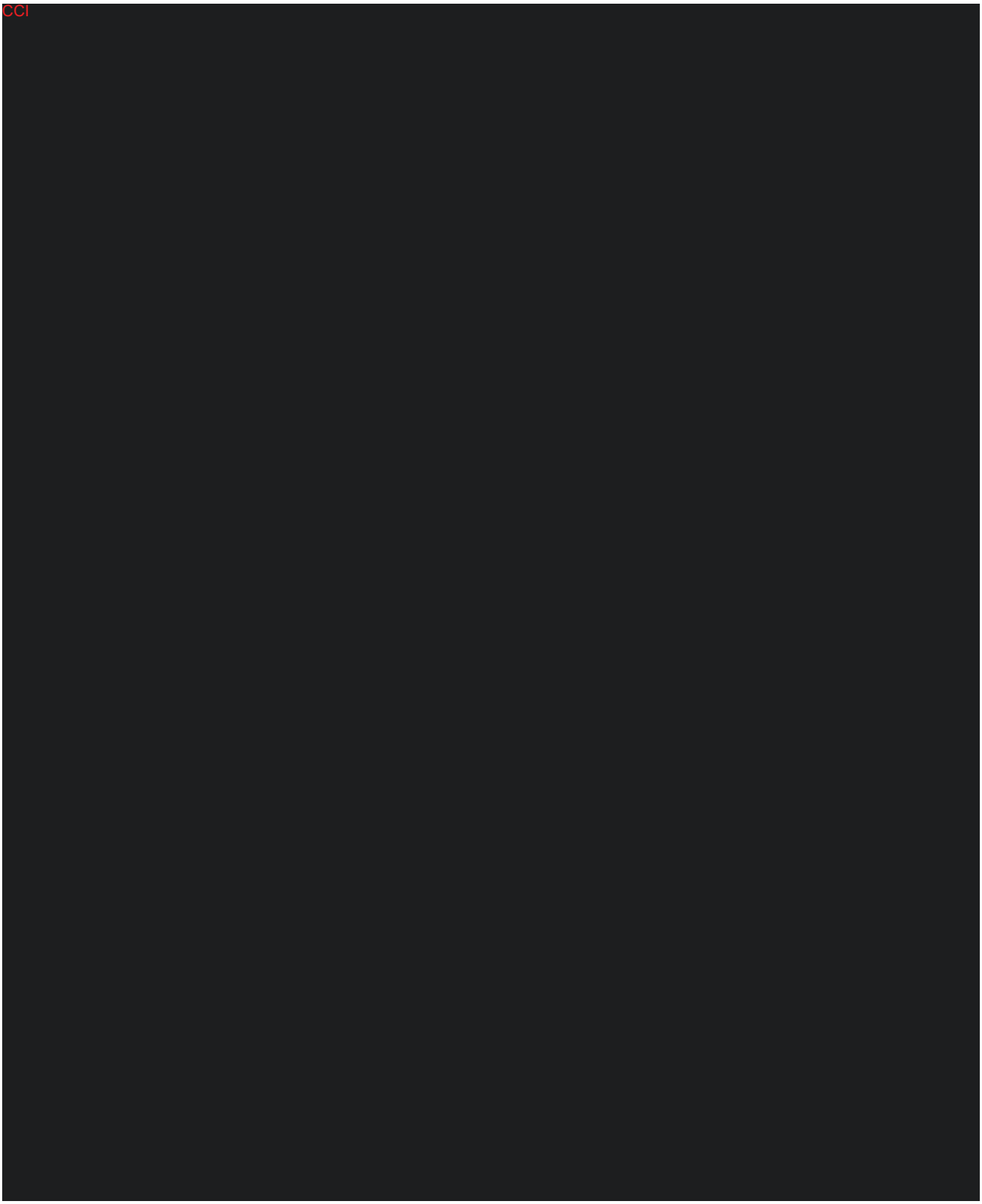

6.7 Intervention After the End of the Study

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 allocation/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 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

This study is blinded, but supplies are provided open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study. As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a PCL.

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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

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.
- Participants who receive a systemic rescue treatment or phototherapy

  Note: Participants who use topical corticosteroids prior to Week 6 will be permitted to continue in the study.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant missed four doses of study intervention within the first eight weeks of the study.
- The participant has a Grade 3 or higher AE (Grade 2 or higher for the system-organ class of Cardiac Disorders) considered related to study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a positive UDS, except for cannabis, at any time during the course of the study. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

Note: participants may be allowed to continue the study intervention with a positive UDS due to the use of specific medications (see Section 6.5) if they have an active prescription from a licensed health care provider and the Investigator and Sponsor both agree that the participant may continue to participate in the study.

- The participant meets at least one study specific stopping criterion as listed in Section 6.6.1

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

7.2 Participant Withdrawal From the Study

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.

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 8.1.9. 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.

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.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met 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 ~524 mL (Appendix 8 OR operations/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

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.

8.1.1.1 General Informed Consent

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 his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial 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. The participant or his/her 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.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, 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 identification 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.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

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 requirement, and record prior medication taken by the participant within 10 weeks before first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

8.1.8.1 Timing of Dose Administration

All doses of study intervention will be given in the morning at approximately the same time.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.10.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 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 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 qualified physician should make reasonable attempts to enter the toxicity grade 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.

8.1.11 Domiciling

Not applicable for this study.

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.

8.2 Efficacy/Disease Activity Assessments

There are no direct efficacy assessments in this study; surrogate markers of efficacy are outlined in Section 8.7.

8.2.1 Skin Biopsy and Dermatologic Photography

To participate in the skin biopsy and dermatologic photography, to capture lesions of interest or importance, the participant must be willing to give written consent for these specific procedures. Skin biopsies and/or photography must not be obtained on participants who refuse consent for biopsies and/or photography. A participant may be exempted from

participation in the biopsies at the discretion of the investigator and still participate in Panels A, B or C of the trial. Participation in the body photography is optional.

Detailed instruction for skin biopsy and dermatologic photography will be provided in the Study Operations/Laboratory Manual.

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 Appendix 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

BMI

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant’s shoes off and jacket or coat removed.

8.3.2 Injection Reactions

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8.3.3 Vital Signs

- Temperature, HR, RR, and BP will be assessed. The same method must be used for all measurements for each individual participant.
- BP and pulse measurements will be assessed in a semirecumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.
- VS is to be taken before blood collection for laboratory tests.

8.3.3.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent or supine position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and BT at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

The screening, predose (baseline) HR and BP will be a single measurement within 3 hours of dosing MK-6194/placebo. Postdose VS measurements will be single measurements.

Body Temperature

BT will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.4 Electrocardiograms

- All ECGs will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and potentially significant findings.

- Day 1 Predose ECGs will be obtained in triplicate at least 1to 2 minutes apart within 3 hours prior to dosing MK-6194/placebo. In addition, Day 1 12 hour ECG will be measured in triplicate. All other post-dose ECG measurements will be single measurements (Refer to Section 1.3).

- Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

- Participants should be resting in the semirecumbent position for at least 10 minutes before each ECG measurement.

- The correction formula to be used for QTc is Fridericia.

- If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

For Single ECG Measurement:

- During each treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

- During each treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

For Triplicate ECG Measurements:

- At each time point when triplicate ECGs are required, 3 individual ECG tracings should be obtained at least 1-2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

- Before each treatment administration on Day 1, predose ECGs will be obtained in triplicate approximately 1 to 2 minutes apart within 3 hours before dosing MK-6194/placebo. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

- During each treatment administration, if a participant demonstrates a median increase in QTc interval ≥60 msec compared to the median predose baseline measurement, the participant will continue to be monitored by at least single repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

- During each treatment period, if the median QTc interval is ≥500 msec for postdose measurements, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.5 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 84 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.

8.3.6 Pregnancy Testing

- Pregnancy testing:

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

    - Pregnancy testing (urine or serum as required by local regulations) should be conducted at timepoints indicated in the SoA during/after intervention.

    - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.

    - 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 subject's participation in the study.

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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 a 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

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator under any of the following circumstances:

- 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,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention randomization through ~ 84 days after cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside the period specified in the previous paragraph also 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 4.

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

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time 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
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

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do 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 24 hours 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 towards 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 SAE) 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 in a participant (spontaneously reported to the investigator or their designee) that occurs 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

Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are not applicable to this study.

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[redacted]

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

The decision as to which serum samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Serum MK-6194

Sample collection, storage, and shipment instructions for serum samples will be provided in the Study Operations Manual.

8.7 Pharmacodynamics

Please refer to Section 4.2.1.4 Pharmacodynamic Endpoints for details. Sample collection, storage, and shipment instructions for pharmacodynamic samples will be in Study Operations Manual.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for Planned Genetic Analysis
- Blood for Serum Biomarkers
- Blood for Paxgene RNA Biomarkers
- Blood for Paxgene DNA Biomarkers
- Blood for PBMC Biomarkers
- Skin Biopsy for Biomarkers

8.8.1 Planned Genetic Analysis Sample Collection

8.8.2 Exploratory Biomarkers

To further inform on MK-6194 pharmacodynamics and/or mechanism of action under multiple dose conditions the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA) and other circulating molecules will be collected from all participants in this study as specified in the SoA. Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Study Operations/Laboratory Manual.

8.8.3 Immunogenicity Assessments

Samples for ADA will be collected prior to administration of MK-6194 on each scheduled day of study intervention and at other specific timepoints as specified in the SoA. Detected ADA titers will be confirmed. Assaying to detect neutralizing antibodies may be performed.

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 DNA for future research
- Leftover main study serum from MK-6194 assay stored for future research

- Leftover main study serum from ADA assay stored for future research
- Leftover samples listed in Section 8.8 Biomarkers (including any extracted material from samples)

8.10 Visit Requirements

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

8.10.1 Screening

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

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention randomization if there are Day 1 procedures planned per protocol.

8.10.2 Treatment Period Visit

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1).

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

At any point if a participant discontinues from treatment but continues to be monitored in the study, all or a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy Visit

Participants will be required to return to clinic approximately 84 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 84 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 84 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-6194 is the critical procedure.

At any postdose time point, the blood sample for MK-6194 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK/pharmacodynamic and ADA Collection as outlined in Table 5

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8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MK-6194 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies.

Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum total biweekly dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel
- Interchange of doses between panels
- Entire panel(s) may be omitted
- Decrease in the duration of study intervention administration (eg, number of doses)
- Adjustment of the dosing interval (eg, q3w, but not to be more frequent than q2w)
- Remove a planned PK pause if agreed by Sponsor and investigator if no further increases in total daily dose
- Addition of study pause
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may use some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

Safety

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values either be computed on original scale (raw change from baseline) or on the log-scale and back-transformed for reporting (percent change from baseline) in the incidence of AEs and discontinuation of dosing due to AEs, as deemed clinically appropriate.

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[redacted]

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration

with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

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9.4 Analysis Endpoints

Primary Endpoints

Safety: AEs.

Secondary Endpoints

CCI

Pharmacodynamic: Immunophenotyping of Tregs

Exploratory Endpoints

CCI

9.5 Analysis Populations

The following populations are defined for the analysis and reporting of data in this study. All participants will be reported, and their data analyzed, according to the treatment(s) they received.

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[redacted]

9.6 Statistical Methods

Primary Analysis

Safety: Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values either be computed on original scale (raw change from baseline) or on the log-scale and back-transformed for reporting (percent change from baseline) in the incidence of AEs and discontinue of dosing due to AEs, as deemed clinically appropriate.

Secondary Analysis

CCI

[redacted]

CCI

[redacted]

Exploratory Analysis

CCI

[redacted]

9.7 Interim Analyses

During the in-life portion of the trial, descriptive summary level results (PK, pharmacodynmics, biomarkers and/or safety) will be prepared as needed to support decision-making meetings such as dose escalation meetings. The aggregate summaries will be presented only for each dose level as appropriate. CCI [redacted] change from

baseline EASI will be provided at the interim analysis at week 8 based on the availability of the data. Other clinical measures may also be summarized at the interim timepoints.

9.8 Multiplicity

No adjustment for multiplicity is needed since safety is the primary endpoint and only one hypothesis is for secondary endpoint will be tested.

9.9 Sample Size and Power Calculations

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CV=coefficient of variation; PP=posterior probability; SD=standard deviation.
SD in log-scale (s)= √log(CV2 + 1).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, 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 local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also 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. 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.

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. 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. 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.

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.

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 chart 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 his/her 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 his/her 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 his/her 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.

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

This section is not applicable as there are no study governance committees.

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 trial Directive 2001/20/EC, 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 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 directive 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 directive, 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.

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 7 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, 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 7 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
	Glucose	Calcium	Alkaline phosphatase	LDH
	Immunoglobulin E (IgE)	CRP		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)			

Laboratory Assessments	Parameters
Other Screening Tests	• Coagulation: PT and INR, aPTT • FSH (as needed in WONCBP only) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Alcohol test • Serology (HIV antibody, HBsAg, HBsAb, HBcAb, and hepatitis C virus antibody) per site SOP • Purified protein derivation (PPD test or QuantiFERON®-TB Gold test • All study-required laboratory assessments will be performed by a central laboratory, except pregnancy tests, TB test, Urine Drug Screen (UDS), and alcohol test, which may be performed centrally or locally.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; 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; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential	

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic 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 (also referred to as Sponsor's product) 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 /toxicity

- 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) according to the NCI CTCAE, version 5.0 (27 November 2017) . Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
    - Grade 4: Life threatening consequences; urgent intervention indicated.
    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product 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 medical 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 Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product 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 Sponsor's product? 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 Sponsor's product 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 Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product 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, or (2) the study is a single-dose drug study; or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT 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 Sponsor's product 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 Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (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 e-mail 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: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and 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.

Women in the following categories are not considered WOCBP:

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian 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 female
  - 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 women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal 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.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female 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, Mullerian 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 female
  - 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 women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
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[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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 are 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 which 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 utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according

to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not Applicable.

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10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   a. The participant may be excluded from the study;

   b. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   c. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

   OR

   a. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

      - If the repeat test value is within the normal range, the participant may enter the study.

      - If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: Guideline for the Diagnosis of Atopic Dermatitis

The information below outlines *examples* of clinical outcome assessment measures to be used in this trial. Trial-specific source documents will be provided to sites.

Screening

Hanifin and Rajka Criteria for Atopic Dermatitis

Table 2.2. Diagnostic criteria for atopic dermatitis in children and adults* (Modified from Hanifin & Rajka, 1980)

Major criteria
Pruritus
Flexural eczema and lichenification
Chronic relapsing course
Personal or family history of atopic disease
Minor criteria
Dry skin (xerosis)/ichthyosis vulgaris/hyperlinear palms
Immediate (type 1) skin test reactivity, elevated radioallergosorbent tests
Elevated total serum IgE
Tendency towards skin infection (*Staphylococcus aureus*, herpes simplex)
Tendency toward nonspecific hand or foot dermatitis
Infraorbital fold (of Dennie–Morgan)
Periocular darkening
Pityriasis alba
Itch when sweating
Intolerance of irritants
Perifollicular accentuation
Food allergies (e.g. urticarial reactions)

*A patient should have at least three major criteria accompanied by at least three minor ones.

[Williams, H.C., Textbook: Atopic Dermatitis: The Epidemiology, Causes and Prevention of Atopic Eczema, Cambridge University Press, 2000]

10.12 Appendix 12: Clinical Outcome Assessment Measures

10.12.1 Eczema Area and Severity Index (EASI)

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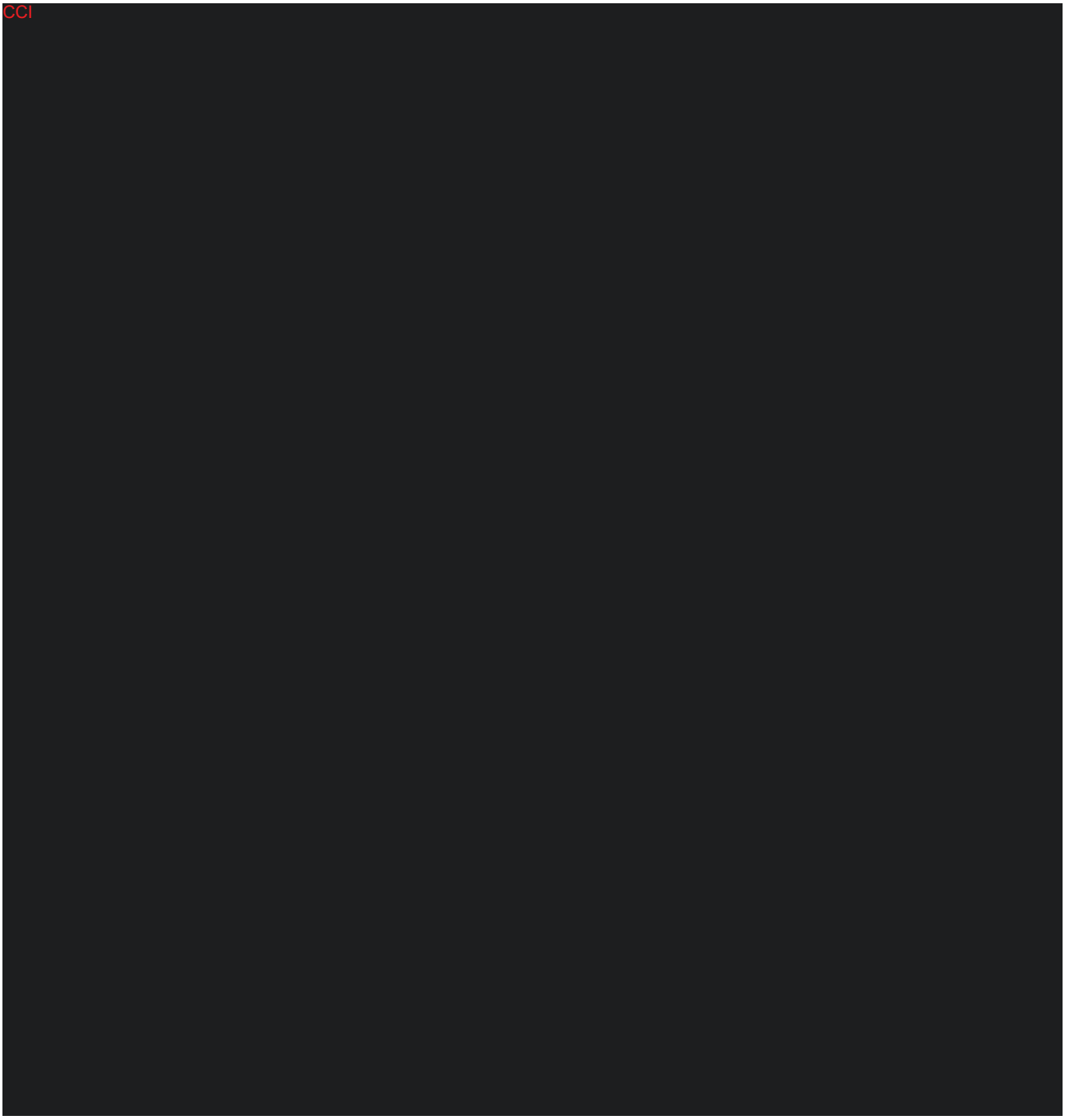

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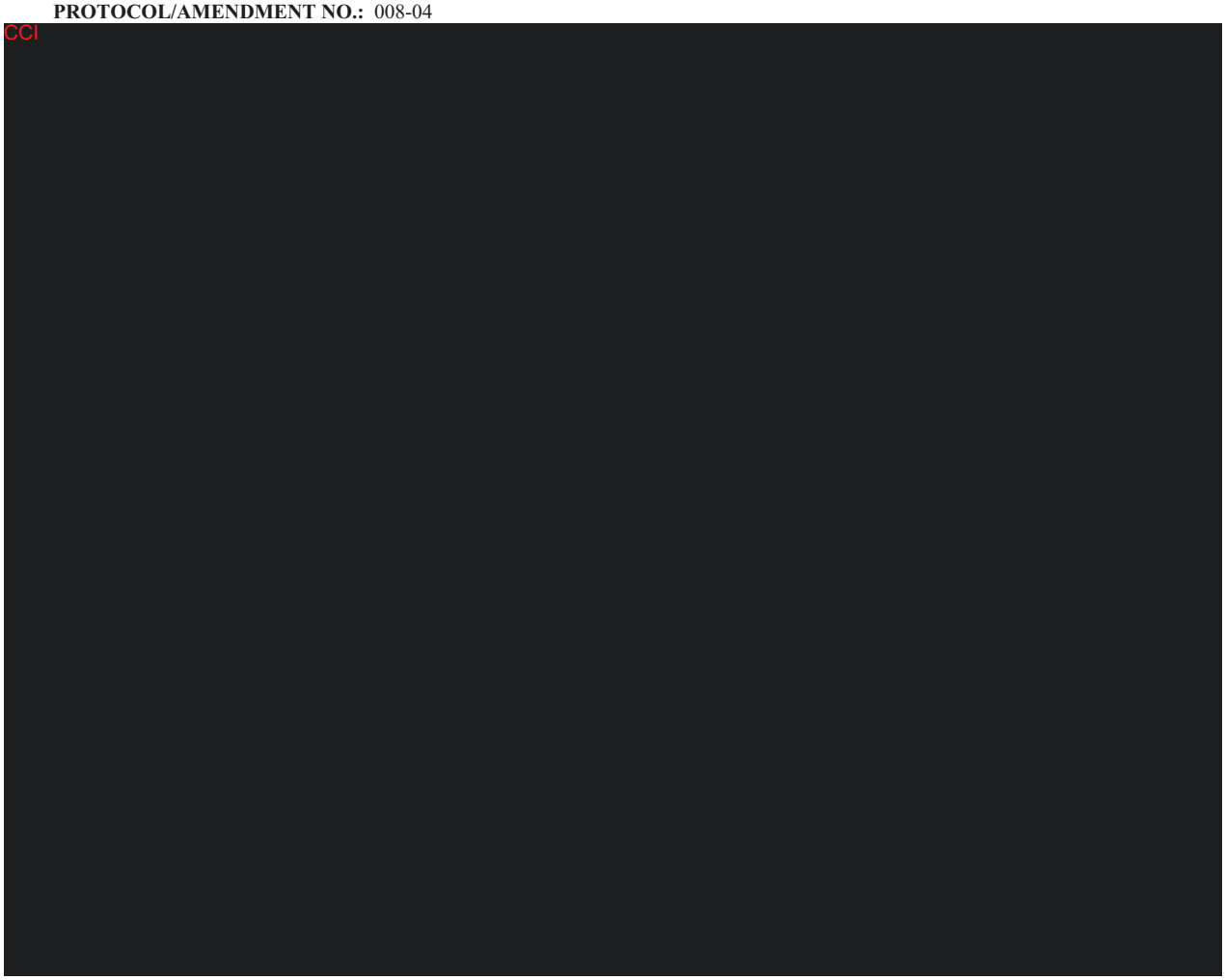

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10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
ADA	anti drug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEC	absolute eosinophil count
ALT	alanine aminotransferase
aPTT	Activated partial thromboplastin
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
AUC0-inf	area under the curve from 0 to infinity
AUC0-last	area under the curve from 0 to last
BCG	bacille Calmette-Guerin
BDS	blood drug screen
BMI	body mass index
BP	blood pressure
BSA	body surface area
BT	Body temperature
CBC	Complete blood count
CCU	Cardiac care unit
CI	confidence interval
CL/F	clearance
Cmax	maximum plasma concentration
Cr	creatinine
CrCl	creatinine clearance
CRF	Case Report Form
CRP	C-reactive protein
CRU	clinical research unit
CSD	Cough Severity Diary
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CV	coefficient of variation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DRC	Data review committee
CCI [redacted]	
EC	Exclusion criteria
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
EM	Exposure margin

Abbreviation	Expanded Term
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
E-R	exposure response
ESDS	early stage development scientist
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GVHD	Graft-versus-host disease
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBsAb	hepatitis B surface antibody
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSSB	Hepatic-specific Safety Board
HCT	Hematocrit
IA(s)	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
iCRO	imaging CRO
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
CCI [redacted]	
IgE	immunoglobulin E

Abbreviation	Expanded Term
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
CCI [redacted]	
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IO	immune-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWG	International Working Group
IWRS	integrated web response system
JAKi(s)	Janus kinase inhibitor(s)
KPS	Karnofsky performance status
LAM	lactational amenorrhea method
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
LIAV	live attenuated influenza vaccine
LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella
MMRV	measles, mumps, and rubella plus varicella
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval

Abbreviation	Expanded Term
MTX	methotrexate
NCI	National Cancer Institute
NCS	not clinically significant
NDA	New Drug Application
NEAB	noneosinophilic bronchitis
NHP	nonhuman primates
NIMP	noninvestigational medicinal product
NK	Natural killer
NOAEL	no observed adverse effect level
NSAIDS	nonsteroidal anti-inflammatory drugs
NUVB	narrow band ultraviolet B
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over-the-counter
PBMC	Peripheral blood mononuclear cell
PBO	placebo
PBPK	physiologically-based PK
PCL	Protocol Clarification Letter
PE	Physical examination
PK	pharmacokinetic
CCI	[redacted]
PP	per-protocol
PPD	purified protein derivation
PQC	product quality complaint
PRO	patient-reported outcome
PT	Prothrombin time
PUVA	psoralen + ultraviolet A
Q2W	every 2 weeks
QoL	quality of life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RCC	refractory chronic cough
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
RR	respiratory rate
SAC	Scientific Advisory Committee
SAD	Single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase

Abbreviation	Expanded Term
SGPT	Serum glutamic pyruvic transminase
siDMC	Standing Internal Data Monitoring Committee
SLAB	Supplemental laboratory test(s)
SLE	Systemic lupus erythematosus
SoA	schedule of activities
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
SVR12	sustained viral response
TARC	Thymus-and Activation-Regulated Chemokine
TB	tuberculosis
Tconv	conventional T cells
TEA	Treatment Eligibility Assessment (form)
Teff	Effector T cells
Tmax	Time to maximum plasma concentration
TMDD	target-mediated drug disposition
Tregs	regulatory T cells
t1/2	half life
UACS	upper airway cough syndrome
UC	Ulcerative colitis
UCC	unexplained chronic cough
UDS	urine drug screen
ULN	upper limit of normal
URTI	upper respiratory tract infection
UVB	untraviolet B
UVA1	ultraviolet A1
VAS	Visual Analog Scale
Vd	volume of distribution
CCI	[redacted]
VS	vital signs
Vz/F	Volume of distribution
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZAP70	zeta-chain-associated protein kinase

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