Official Protocol Title:	A Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1654 in Pre-Term and Full-Term Infants
NCT number:	NCT03524118
Document Date:	30-Jul-2020

Title Page

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Protocol Title: A Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1654 in Pre-Term and Full-Term Infants

Protocol Number: 002-04

Compound Number: MK-1654

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	130,097
EudraCT	2017-005062-21

Approval Date: 30 July 2020

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	30-JUL-2020	The purpose of Amendment 04 is: • to modify the blood collection schedule for Panels D and E to add a Day 545 post-dose blood draw for ADA and SNA collection for participants enrolled in Panels D and E prior to Amendment 04 who choose to participate in the modified blood collection schedule and Panel D and E participants enrolled under Amendment 04. The SAE follow-up period for these participants has been extended to Day 545 accordingly; • to discontinue the collection of microsample blood for ADA for all Panels; • to discontinue the collection of microsample blood for PK for Panels D and E; • to document 100 mg as the selected dose for Panels D and E; • to allow the oral polio vaccine to be administered concomitantly with MK-1654
Amendment 3	18-DEC-2019	The purpose of Amendment 03 was to remove the restrictions for the administration of rotavirus vaccine.
Amendment 2	12-DEC-2018	The purpose of Amendment 02 was to ensure that all instances of hives or welts are evaluated to ensure consistent follow-up of potential allergic reactions.

Document	Date of Issue	Overall Rationale
Amendment 1	27-JUL-2018	The purpose of Amendment 01 was to extend the scope and duration of post-dose safety monitoring to support the safety evaluation of MK-1654.
Original Protocol	16-FEB-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 002-04

Overall Rationale for the Amendments:

To modify the blood collection schedule for Panels D and E to add a Day 545 post-dose blood draw for ADA and SNA collection for participants enrolled in Panels D and E prior to Amendment 04 who choose to participate in the modified blood collection schedule and Panel D and E participants enrolled under Amendment 04. The SAE follow-up period for these participants has been extended to Day 545 accordingly; to discontinue the collection of microsample blood for ADA for all Panels; to discontinue the collection of microsample blood for PK for Panels D and E; to document 100 mg as the selected dose for Panels D and E; to allow the oral polio vaccine to be administered concomitantly with MK-1654.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design Section 4.3.3 Rationale for Dose Interval and Study Design Section 6.3.1 Intervention Assignment	• Removed the word "optional."	• Panel D is now an established study Panel.
Section 1.1 Synopsis Section 1.2 Schema Section 1.3.2 SoA for Panels D2 and E2 Section 3 Hypothesis,	• Updated text to describe additional study visit at Day 545 to collect ADA and SNA blood samples, for participants in Panels D and E prior to Amendment 04 who choose to participate in the modified blood collection schedule and for newly	• To characterize ADA and SNA beyond one-year post-dose.

Section # and Name	Description of Change	Brief Rationale
Objectives, and Endpoints Section 4.2.1.1 Safety Endpoints Section 8.1.9 Discontinuation and Withdrawal Section 8.3.4 Safety Follow-up Telephone Calls Section 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information Section 8.13.3 Discontinued Participants Continuing to be Monitored in the Study and Post-study Visit Section 9.1 Statistical Analysis Plan Summary Section 9.4.1 Safety Endpoints Section 9.4.2 Pharmacokinetic Endpoints Section 9.4.3 Other Endpoints	enrolled Panels D and E participants under Amendment 04. • The SAE follow-up period for participants in Panels D2 and E2 has been extended to Day 545 accordingly. • A new SoA, Section 1.3.2, was created to provide a new blood sampling schedule (Group 3) for participants enrolled in Panels D and E prior to Amendment 04 who choose to participate in the modified blood collection schedule and for all Panels D and E participants enrolled under Amendment 04. This new SoA includes a Day 545 visit (Visit 8). • The objectives and endpoints were updated accordingly to distinguish the time points for Panels A, B, and C, and Panels D and E.	• Modifications were made to the blood sampling schedule for Panels D and E to include the timepoints of greatest interest for each assay and to extend ADA and SNA testing to 18 months (Visit 8, Day 545). • To provide time point clarifications.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Updated estimated study duration from approximately 2 years to approximately 4 years. Updated the approximate length of time Panel D2 and E2 participants will be in the study.	Time adjustment due to enrollment delays and the addition of a Day 545 post-dose visit for participants in Panels D2 and E2.
Section 1.1 Synopsis Section 1.2 Schema Section 4.1 Overall Design Section 4.3.2 Maximum Dose/Exposure for This Study Section 4.3.3 Rationale for Dose Interval and Study Design Section 6.1 Study Intervention(s) Administered Section 6.2.1 Dose Preparation Section 6.3.1 Intervention Assignment Section 8.1.8 Study Intervention Administration Section 9.1 Statistical Analysis Plan Summary	Changed the dose for Panels D and E from "up to 100 mg" to "100 mg."	Per siDMC, the 100 mg dose was selected for Panels D and E.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 6.1 Study Intervention Section 6.2.1 Dose Preparation Section 8.1.8 Study Intervention Administration	Added the following dosing instructions: Panels D and E: 100-mg dose - 1 mL split into 2 IM injections o 0.5 mL administered in the right thigh o 0.5 mL administered in the left thigh	To clarify the selected dose volume and administration.
Section 1.3 Schedule of Activities (SoA) Section 3 Hypothesis, Objectives, and Endpoints Section 4.1 Overall Design Section 4.2.1.2.2 Blood Microsampling Assay Section 8.7.2 Blood Microsampling for ADAs Section 9.4.3 Other Endpoints	The collection of microsample blood for ADA was removed. Text was added to clarify that microsample blood for MK-1654 pharmacokinetics will only be collected from infants in Panels, A, B, and C. Section 8.7.2 was removed.	The study will no longer collect microsample blood for ADA for infants in ALL panels, as the microsample ADA assay is not technically feasible. Microsample blood for MK-1654 PK will not be collected for infants in Panels D and E, as sufficient data are available based on microsamples already collected in the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1 SoA for Panels A, B, C, D1 and E1 Section 1.3.2 SoA for Panels D2 and E2	The weekly RSV surveillance telephone calls should be made through 1 week after the site-designated RSV season end date. The participant's legally acceptable representative will no longer be instructed to return the Electronic Diary Card Device after Day 30 *via mail*.	To clarify the duration of RSV surveillance telephone calls. To allow individuals to return the device in ways other than *via mail* (eg, in person if they live close to the site).
Section 2 Introduction	Updated background information on the burden of RSV infection in infants.	Updates are based on a systematic review and modeling study of RSV in children under 5 years of age published in The Lancet.
Section 2.1 Study Rationale	Removed references to targeted trough drug level.	The objective is no longer only to achieve the preclinical target.
Section 2.2.3 Completed Clinical Studies	Updated section header from "Ongoing Clinical Studies" to "Completed Clinical Studies." Changed "Most AEs have been mild" to "Most AEs have been transient and mild to moderate in intensity."	The language was updated for alignment with final study data.
Section 4.1 Overall Design Section 8 Study Assessments and Procedures	Updated total blood volume drawn per participant.	The blood sampling volume was adjusted. Blood volume updates are based on the discontinuation of the ADA microsample blood collection for Panels A-C, and modification of the blood collection for Panels D and E (discontinuation of PK and ADA microsamples; creation of new blood collection schedule, including addition of Day 545 blood draw).

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 4.2.1.2 Pharmacokinetic Endpoints Section 6.3.1 Intervention Assignment	Revised text to indicate that only participants enrolled prior to Amendment 04 will be assigned to 1 of 4 blood sampling schedules. Added text to indicate that Panel D and E participants enrolled under Amendment 04 will be assigned to a separate blood sampling schedule. Panel D and E participants enrolled prior to Amendment 04 will have the option of transitioning to this blood sampling schedule (D2/E2) or remaining on their current schedule (D1/E1).	Blood sampling groups were clarified based on the new blood sampling schedules for Panels D and E.
Section 4.2.1.5 Future Biomedical Research Section 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research Section 8.11 Biomarkers Section 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Removed the word “substudy” from the description of future biomedical research.	Future biomedical research is not a separate substudy.
Section 4.3.3 Rationale for Dose Interval and Study Design	Corrected the expected number of Panel D participants.	Updates match the number stated in other sections.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria Section 6.5 Concomitant Therapy	Removed restrictions pertaining to concomitant oral rotavirus (Section 5.2) and oral polio vaccines (Sections 5.2 and 6.5).	Oral rotavirus and oral polio vaccine may be administered concomitantly with MK-1654 without interference expected and do not require additional injections for the participant. This amendment removes the restriction on oral polio vaccine. The restriction on oral rotavirus vaccine was removed with the previous amendment (AM03); however, exclusion criterion 19 was not updated, so this change is being made to align the exclusion criterion with what is stated in Section 6.5.
Section 8.6.1 Blood Collection for MK-1654 Pharmacokinetics	Removed the following sentence: "Leftover specimens will be stored after the study for future research for all participants whose legally acceptable representative provides informed consent."	This information is also provided in Section 8.9 Future Biomedical Research Sample Collection.
8.9 Future Biomedical Research Sample Collection	Updated language to clarify the types of specimens to be collected for Future Biomedical Research.	The language in this section was updated to clarify the types of specimens to be collected.
Various Sections	Added editorial clarifications.	To improve the clarity of the protocol instructions.

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1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Double-blind, Randomized, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1654 in Pre-Term and Full-Term Infants

Short Title: Phase 1b Study of MK-1654 Safety and PK in Pre-Term and Full-Term Infants

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in healthy pre-term and full-term infants receiving a single ascending dose of MK-1654 or placebo intramuscularly. No formal hypotheses will be tested in the study.

Primary Objectives	Primary Endpoints
- To evaluate the safety and tolerability of MK-1654 through Days 365 (Panels A through C, D1, and E1) and Day 545 (Panels D2 and E2)	- Solicited injection site adverse events (AEs) Day 1 through Day 5 post-dose - Solicited systemic AEs Day 1 through Day 5 post-dose - Serious adverse events (SAEs) from Day 1 through Days 365 (Panels A through C, D1, and E1) and Day 545 (Panels D2 and E2) post-dose
Secondary Objectives	Secondary Endpoints
- To estimate the serum pharmacokinetic (PK) profile of MK-1654 on Days 7, 14, 90, 150, and 365 (Panels A through C, D1, and E1) and Days 7, 150, and 365 (Panels D2 and E2)	- For Panels A through C, D1, and E1: the MK-1654 PK variables $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, and concentration (C7days, C14days, C90days, C150days, and C365days) - For Panels D2 and E2: the MK-1654 PK variables $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, and concentration (C7days, C150days, and C365days)
- To describe the incidence of anti-drug antibodies (ADAs) to MK-1654 on Days 14, 90, 150, and 365 (Panels A through C, D1, and E1) and Days 150, 365, and 545 (Panels D2 and E2)	- For Panels A through C, D1, and E1: titer of ADAs to MK-1654 on Days 14, 90, 150, and 365 - For Panels D2 and E2: titer of ADAs to MK-1654 on Days 150, 365, and 545

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Prevention
Indication	Prevention of lower respiratory tract infections (LRI) and hospitalizations caused by respiratory syncytial virus (RSV) A and B strains in infants born at 29 weeks gestational age or older and of up to 8 months chronological age.
Population	Healthy pre-term infants (born at 29 to 35 weeks gestational age) and healthy full-term infants (born at over 35 weeks gestational age). All participants will have chronological age of 2 weeks to 8 months.
Study Type	Interventional
Intervention Model	Single Group This is a multi-site single ascending dose study.
Type of Control	Placebo
Study Blinding	Double-blind
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 4 years from the time that written informed consent is provided for the first participant until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result.

Number of Participants:

Approximately 180 participants will be randomized such that a sufficient number of evaluable participants in each panel complete the study, as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Panel	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen
Panel A (Pre-term infants)	MK-1654	20 mg	Once	IM	Single 0.2 mL injection on Day 1
	Placebo[a]	NA			
Panel B (Pre-term infants)	MK-1654	50 mg	Once	IM	Single 0.5 mL injection on Day 1
	Placebo[a]	NA			
Panel C (Pre-term infants)	MK-1654	75 mg	Once	IM	0.75 mL dose divided into 0.5 mL (in the right thigh) + 0.25 mL (in the left thigh) injections on Day 1
	Placebo[a]	NA			
Panel D (Pre-term infants)	MK-1654	100 mg	Once	IM	1 mL dose (divided into 0.5 mL in the right thigh + 0.5 mL in the left thigh) injections on Day 1
	Placebo[a]	NA			
Panel E (Full-term infants)	MK-1654	100 mg	Once	IM	1 mL dose (divided into 0.5 mL in the right thigh + 0.5 mL in the left thigh) injections on Day 1
	Placebo[a]	NA			

IM=intramuscular; NA=not applicable.
a Placebo product is 0.9% sodium chloride, USP sterile saline.

Total Number	6 intervention arms (5 active, 1 placebo)
Duration of Participation	Each participant will participate in the study for approximately 365 days or 545 days (depending on Panel) from the time the participant's legally acceptable representative signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 2 weeks, each participant will receive the assigned intervention on Day 1. After the intervention, participants in Panels A, B, C, D1, and E1 will be followed through Day 365, and participants in Panels D2 and E2 will be followed through Day 545.

Study Governance Committees:

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

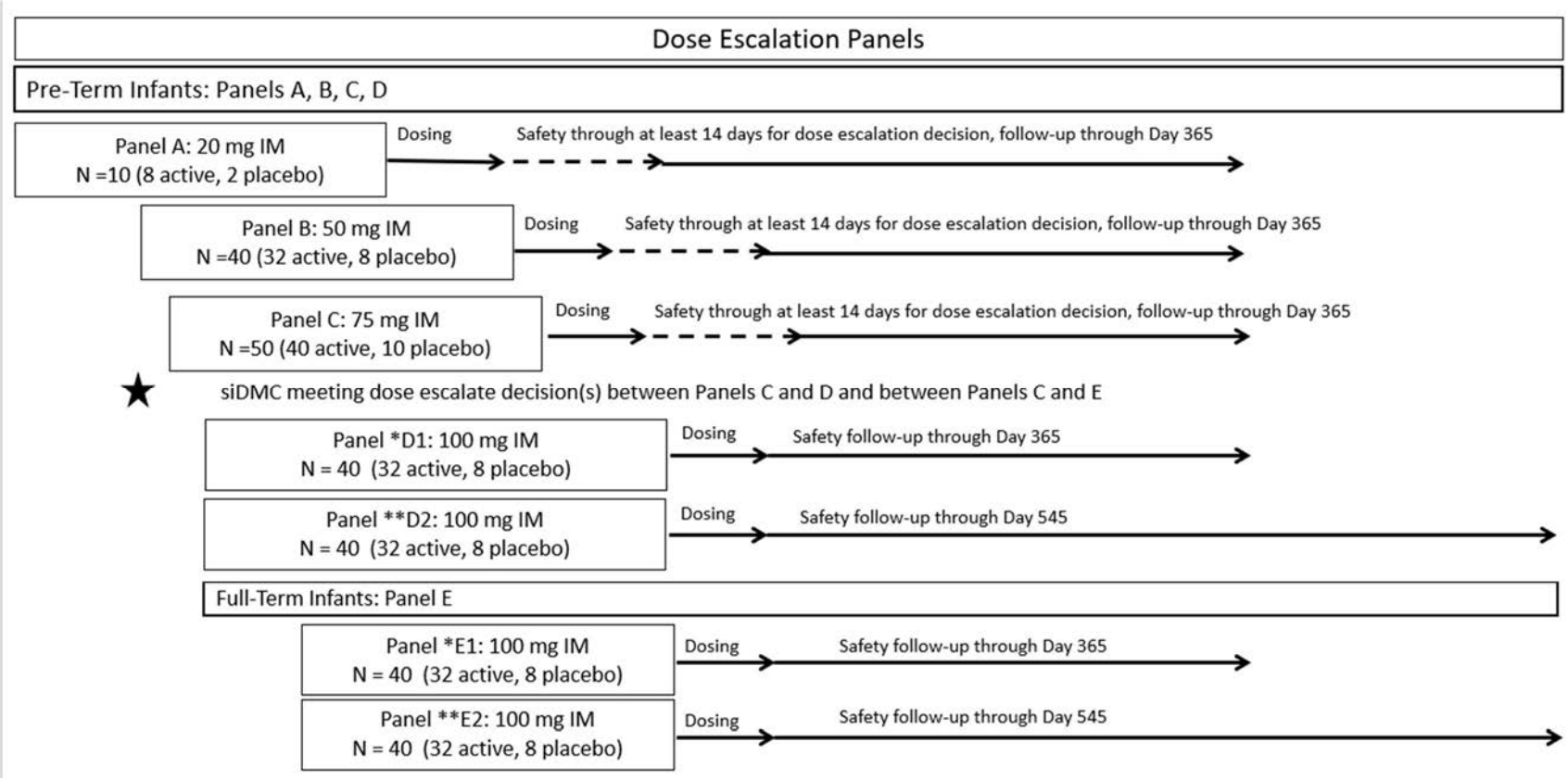
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Dose Escalation Diagram



IM = Intramuscularly, N = total number of participants enrolled in the panel, siDMC = standing Internal Data Monitoring Committee
Participants in Panels D and E will be separated into two groups to distinguish participation, dependent on time of enrollment and consent.
*D1 and E1: Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA.
**D2 and E2: Participants enrolled in Panels D and E prior to Amendment 04 choosing to participate in the modified schedule will follow the D2 and E2 SoA.
Participants enrolled in Panels D and E under amendment 04 must follow the D2 and E2 SoA.

1.3 Schedule of Activities (SoA)

1.3.1 SoA for Panels A, B, C, D1, and E1

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
	Administrative Procedures																
Informed Consent	X																
Informed Consent for Future Biomedical Research	X																
Inclusion/Exclusion Criteria	X	X															Prior to randomization on Day 1, confirm that the participant continues to meet eligibility criteria.
Participant Identification Card	X																
Medical History	X	X															Record on the Medical History eCRF any condition not already recorded at the screening baseline medical history or as AEs (on the AEs eCRF).

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
Prior/Concomitant Medication Review	X	X			X	X	X	X	X	X	X	X	X	X	X	X	All concomitant medications taken on Days 1 through 30 will be recorded; only concomitant medications related to a respiratory event or SAE will be recorded from Day 31 through Day 365.
Intervention Randomization		X															Randomization (allocation) number is assigned at the time of study intervention administration. Participants will be assigned by IRT to 1 of 4 different blood sampling schedules (1a, 1b, 2a, or 2b).
MK-1654 or Placebo Administration			X														Refer to Section 6.1 Study Intervention Administration and Section 6.6 Dose Modification (Escalation) for details.
Electronic Diary Card Device Given to and Collected from Participant's Legally Acceptable Representative				X													Participant's legally acceptable representative will be instructed to return the device after Day 30.

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
	Safety Procedures																
Full Physical Examination including Weight and Length	X														X		
Weight and Length		X						X	X		X	X					
Directed Physical Examination							X									X	Symptom-directed physical examination, as deemed necessary by the investigator.
Systemic and Local Treatment Reaction Assessment				X	X		X	X								X	Participants will be monitored at the study site for 2 hours post-dose on Day 1 and have safety monitoring visits on Days 3 and 7.
Vital Signs	X	X		X			X	X	X		X	X			X	X	Repeat vital signs at 1- and 2-hours post-dose for all participants. Refer to Section 8.3.2 Vital Signs for details.
Hematology and Chemistry	X																Refer to Sec 10.2 Appendix 2: Clinical Laboratory Tests for details.

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All AEs through Day 14; solicited AEs of allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) through Day 30; respiratory AEs (see row below) and SAEs through Day 365.
	Respiratory Virus Assessments																
Respiratory AEs Collection									←Per criteria in Section 8.8.2→								Observed/reported symptoms of respiratory infection will be collected as respiratory AEs on the AEs eCRF. If the symptoms meet the criteria for acute respiratory infection (ARI; see Section 8.8.2), participants will be evaluated at the earliest available unscheduled visit.

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
RSV Surveillance Weekly Telephone Calls									←Weekly RSV surveillance TC through 1 week after site designated RSV season end date→								RSV weekly surveillance starts on Day 14 until Sponsor deems that RSV season has ended. From Day 14, sites will conduct weekly surveillance calls to the legally acceptable representative to determine if any respiratory symptoms have occurred in the previous week. If the symptoms meet the criteria for ARI (see Section 8.8.2), participants will be evaluated at the earliest available RSV assessment visit, within 10 days after symptom onset.

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
Nasal Mucosal Sample for Respiratory Virus RT-PCR									←Per criteria in Section 8.8.5→							X	If ARI symptoms are confirmed, nasal swab will be obtained (see Section 8.8.5 and the operations/laboratory manual).
	Pharmacokinetics/Pharmacodynamics/Biomarkers																Different PK and microsample blood draw schedules reduce the number of blood samples required of each individual participant.
	Schedule 1a:																
Schedule 1a Blood for MK-1654 PK	X							X			X	X					
Schedule 1a Blood for ADAs	X										X	X					
Schedule 1a Blood for RSV SNA	X											X					
Schedule 1a Microsample Blood for MK-1654 PK	X							X									As of Amendment 04, microsample blood for PK will no longer be collected from Panel D1 and E1 infants.

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
	Schedule 1b:																
Schedule 1b Blood for MK-1654 PK	X							X			X	X					
Schedule 1b Blood for ADAs	X										X	X					
Schedule 1b Blood for RSV SNA	X											X					
Schedule 1b Microsample Blood for MK-1654 PK	X											X					As of Amendment 04, microsample blood for PK will no longer be collected from Panel D1 and E1 infants.
	Schedule 2a:																
Schedule 2a Blood for MK-1654 PK	X								X			X			X		
Schedule 2a Blood for ADAs	X								X			X			X		
Schedule 2a Blood for RSV SNA	X											X			X		
Schedule 2a Microsample Blood for MK-1654 PK	X											X					As of Amendment 04, microsample blood for PK will no longer be collected from Panel D1 and E1 infants.

Study Period	**Screening**	**Intervention (Panel A, B, C, D1, E1)**				**Follow-up (365 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the D1 and E1 SoA (See Section 4.1).**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**per investigator discretion**	
	Schedule 2b:																
Schedule 2b Blood for MK-1654 PK	X								X			X			X		
Schedule 2b Blood for ADAs	X								X			X			X		
Schedule 2b Blood for RSV SNA	X											X			X		
Schedule 2b Microsample Blood for MK-1654 PK	X														X		As of Amendment 04, microsample blood for PK will no longer be collected from Panel D1 and E1 infants.

ADAs=anti-drug antibodies; AEs=adverse events; ARI=acute respiratory infection; eCRF=electronic case report form; IRT=Interactive Response Technology; PK=pharmacokinetics; Post-dose pm=in the evening of Day 1 post-dose; RSV=respiratory syncytial virus; RT-PCR=reverse transcription polymerase chain reaction; SAEs=serious adverse events; SNA=serum neutralizing antibodies; TC=telephone call; UNSCH=unscheduled visit.

1.3.2 SoA for Panels D2 and E2

Study Period	**Screening**	**Intervention (Panel D2, E2)**				**Follow-up (545 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing to participate in the modified schedule will follow the D2 and E2 SoA.** **Participants enrolled in Panels D and E under Amendment 04 must follow the D2 and E2 SoA.** **See Section 4.1**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**8**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**545 ±10**	**per investigator discretion**	
	Administrative Procedures																	
Informed Consent	X																	
Informed Consent Addendum		←						X								→		For participants enrolled in Panels D & E prior to Amendment 04 who choose to participate in the modified schedule, obtain consent with the Informed Consent Addendum.
Informed Consent for Future Biomedical Research	X																	
Inclusion/Exclusion Criteria	X	X																Prior to randomization on Day 1, confirm that the participant continues to meet eligibility criteria.
Participant Identification Card	X																	
Medical History	X	X																Record on the Medical History eCRF any condition not already recorded at the screening baseline medical history or as AEs (on the AEs eCRF).

Study Period	**Screening**	**Intervention (Panel D2, E2)**				**Follow-up (545 days post dose)**												**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing to participate in the modified schedule will follow the D2 and E2 SoA.** **Participants enrolled in Panels D and E under Amendment 04 must follow the D2 and E2 SoA.** **See Section 4.1**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**8**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**545 ±10**	**per investigator discretion**	
Prior/Concomitant Medication Review	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	All concomitant medications taken on Days 1 through 30 will be recorded; only concomitant medications related to a respiratory event or SAE will be recorded from Day 31 through Day 545.
Intervention Randomization		X																Randomization (allocation) number is assigned at the time of study intervention administration.
MK-1654 or Placebo Administration			X															Refer to Section 6.1 Study Intervention Administration and Section 6.6 Dose Modification (Escalation) for details.
Electronic Diary Card Device Given to and Collected from Participant's Legally Acceptable Representative				X														Participant's legally acceptable representative will be instructed to return the device after Day 30.
	Safety Procedures																	
Full Physical Examination including Weight and Length	X															X		
Weight and Length		X						X				X			X			
Directed Physical Examination							X										X	Symptom-directed physical examination, as deemed necessary by the investigator.

Study Period	**Screening**	**Intervention (Panel D2, E2)**				**Follow-up (545 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing to participate in the modified schedule will follow the D2 and E2 SoA.** **Participants enrolled in Panels D and E under Amendment 04 must follow the D2 and E2 SoA.** **See Section 4.1**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**8**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**545 ±10**	**per investigator discretion**	
Systemic and Local Treatment Reaction Assessment				X	X		X	X									X	Participants will be monitored at the study site for 2 hours post-dose on Day 1 and have safety monitoring visits on Days 3 and 7.
Vital Signs	X	X		X			X	X	X		X	X			X	X	X	Repeat vital signs at 1- and 2-hours post-dose for all participants in panels. Refer to Section 8.3.2 Vital Signs for details.
Hematology and Chemistry	X																	Refer to Sec 10.2 Appendix 2: Clinical Laboratory Tests for details.
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All AEs through Day 14; solicited AEs of allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) through Day 30; respiratory AEs through Day 365 (see row below), and SAEs through Day 545.
	Respiratory Virus Assessments																	
Respiratory AEs Collection									←Per criteria in Section 8.8.2→								←Per criteria in Section 8.8.2→	Observed/reported symptoms of respiratory infection will be collected as respiratory AEs on the AEs eCRF. If the symptoms meet the criteria for acute respiratory infection (ARI; see Section 8.8.2), participants will be evaluated at the earliest available unscheduled visit.

Study Period	**Screening**	**Intervention (Panel D2, E2)**				**Follow-up (545 days post dose)**											**Notes:** **Participants enrolled in Panels D and E prior to Amendment 04 choosing to participate in the modified schedule will follow the D2 and E2 SoA.** **Participants enrolled in Panels D and E under Amendment 04 must follow the D2 and E2 SoA.** **See Section 4.1**
Visit Number/Title	**Screening**	**1**			**TC**	**TC**	**2**	**3**	**4**	**TC**	**5**	**6**	**TC**	**TC**	**7**	**8**	**UNSCH**	
Scheduled Day and Window (days):	**Up to 14 prior to Day 1**	**1 Pre-dose**	**1 Dose**	**1 Post-dose**	**1 Post-dose pm**	**2**	**3 +1**	**7 +2**	**14 ±2**	**31 ±3**	**90 ±5**	**150 ±5**	**210 ±5**	**270 ±5**	**365 ±7**	**545 ±10**	**per investigator discretion**	
RSV Surveillance Weekly Telephone Calls									←Weekly RSV surveillance TC through 1 week after site designated RSV season end date→									RSV weekly surveillance starts on Day 14 until Sponsor deems that RSV season has ended. From Day 14, sites will conduct weekly surveillance calls to the legally acceptable representative to determine if any respiratory symptoms have occurred in the previous week. If the symptoms meet the criteria for ARI (see Section 8.8.2), participants will be evaluated at the earliest available RSV assessment visit, within 10 days after symptom onset.
Nasal Mucosal Sample for Respiratory Virus RT-PCR									←Per criteria in Section 8.8.5→								X	If ARI symptoms are confirmed, nasal swab will be obtained (see Section 8.8.5 and the operations/laboratory manual).
	Pharmacokinetics/Pharmacodynamics/Biomarkers																	
Schedule 3 Blood for MK-1654 PK	X							X				X			X			
Schedule 3 Blood for ADAs	X											X			X	X		
Schedule 3 Blood for RSV SNA	X											X			X	X		

ADAs=anti-drug antibodies; AEs=adverse events; ARI=acute respiratory infection; eCRF=electronic case report form; IRT=Interactive Response Technology; PK=pharmacokinetics; Post-dose pm=in the evening of Day 1 post-dose; RSV=respiratory syncytial virus; RT-PCR=reverse transcription polymerase chain reaction; SAEs=serious adverse events; SNA=serum neutralizing antibodies; TC=telephone call; UNSCH=unscheduled visit.

2. INTRODUCTION

Burden of RSV Infection in Infants

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis, lower respiratory tract infections (LRI), and hospitalization in infants. An estimated 74,000 to 126,000 infant hospitalizations in the United States result from RSV each year, representing an annual rate of 25 to 40 per 1000 infants [Hall, C. B., et al 2013] [Shay, D. K., et al 1999] [Holman, R. C., et al 2004]. RSV infection has been associated with 43% to 74% of bronchiolitis and 19% to 54% of pneumonia cases in hospitalized children [Shay, D. K., et al 1999]. In 2015, RSV was estimated to have caused 28% of acute LRIs and 2.7 to 3.8 million hospitalizations globally in children under 5 years of age. Almost half of the hospitalizations (45%) occurred in infants younger than 6 months. Mortality from RSV infection was significant, with an estimated 94,600 to 149,400 childhood deaths worldwide [Shi, T., et al 2015]. The overwhelming majority of RSV-associated deaths occur in developing countries. In contrast, in the United States, the death rate in infants due to RSV is low, likely due to quality supportive care [Nair, H., et al 2010].

Beyond hospitalization and death, RSV infection is a significant driver of outpatient health care utilization in infants, leads to the development of some chronic respiratory illnesses, and results in workdays missed by caregivers [Bourgeois, F. T., et al 2009]. An estimated 2.2% (1.7 million visits) of all United States primary care visits of children ≤5 years old in 2000 were due to RSV infection. Pre-term infants with RSV averaged 12.4 physician office visits for any cause and 5 visits for respiratory causes during their first 2 years of life, whereas children without RSV averaged 9.4 visits for any cause and 2.9 visits for respiratory causes during their first 2 years of life [Diez-Domingo, J., et al 2014]. Compared to influenza, children with RSV were more likely to receive intensive medical care, medications, including antibiotics, and radiologic studies [Bourgeois, F. T., et al 2009]. Children previously infected with RSV also have a higher risk of developing some chronic conditions, including allergic rhino-conjunctivitis [Diez-Domingo, J., et al 2014], recurrent wheezing, and asthma [Polack F. P. 2015]. Taken together, these data highlight the burden of RSV for infants, caregivers, and healthcare providers and systems.

Pre-term infants, and those with underlying medical conditions, are pre-disposed to severe RSV infection. A prophylactic monoclonal antibody (mAb) targeting the RSV fusion (F) protein, palivizumab (Synagis™, MedImmune), is approved for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk for RSV disease [U.S. Prescribing Information 2009] [American Academy of Pediatrics Committee on Infectious Diseases 2014]. However, the majority of infants hospitalized with RSV infection have no predisposing risk factors and are otherwise healthy (only a younger age and prematurity have been independently associated with RSV illness requiring hospitalization) [Hall, C. B., et al 2009]. The infant population in which palivizumab is recommended has narrowed considerably due to limited clinical benefit and high cost [American Academy of Pediatrics Committee on Infectious Diseases 2014]; monthly dosing to cover the entire RSV season also limits the wide application of palivizumab. Therefore, there is a need for prophylaxis to

prevent RSV infection and related complications in infants not recommended to receive palivizumab, which represents the overwhelming majority of healthy pre-term and full-term infants.

Passive immunization with a neutralizing mAb against the RSV F protein, ie, palivizumab, is a proven prophylaxis approach in infants. This approach provides near-immediate protection at birth [American Academy of Pediatrics Committee on Infectious Diseases 2014] and accommodates the immature immune system and high safety requisites of this infant population [Acosta, P. L., et al 2015] [David Snydman (Tufts) 2013]. Similarly, MK-1654 is also a neutralizing mAb against RSV, with additional attributes to facilitate its application as an RSV prophylactic for infants currently not receiving palivizumab, as outlined in Section 2.1.

2.1 Study Rationale

This study is being conducted to assess the safety, tolerability, and serum PK following administration of MK-1654 IM to healthy pre-term and full-term infants. The main objective is to identify a well-tolerated dose in infants that is expected to provide high protection against RSV through 5 months post-injection.

Similar to the completed Phase 1a study in healthy adult participants (P001), this study is randomized, placebo-controlled, double-blind, and uses a single ascending dose design. Information on the safety and PK of MK-1654 in pre-term and full-term infants will further facilitate dose selection and clinical development in the target infant population.

The study will enroll healthy pre-term infants born at 29 to 35 weeks gestational age and healthy infants born at over 35 weeks gestational age (throughout this protocol, defined as “full-term” in order to distinguish from the pre-term infant population, acknowledging that this differs from accepted definitions of full-term infants). All participants will have chronological age between 2 weeks and 8 months at the time of consent, consistent with the peak age of hospitalization for RSV (2-3 months chronological age) and increased risk for RSV infection in infants. The full-term infants will be the final cohort within the study, after dose escalation and confirmation of short-term safety in pre-term infants.

RSV prophylaxis is currently unavailable for most infants. Palivizumab is approved in the United States, the European Union, and more than 80 countries globally for RSV prophylaxis in infants at high risk for RSV disease. However, the American Academy of Pediatrics recommends limiting use of palivizumab for infants born <29 weeks gestation and infants with certain chronic illnesses such as congenital heart disease or chronic lung disease, due to its modest efficacy, high cost, and the need for 5 separate monthly injections [American Academy of Pediatrics Committee on Infectious Diseases 2014] [Joffe, S., et al 1999].

2.2 Background

Refer to the IB for detailed background information on MK-1654.

2.2.1 Pharmaceutical and Therapeutic Background

MK-1654 is a fully human mAb targeting the RSV F protein, which the virus utilizes to enter host cells and fuse infected cells with adjacent cells, spreading by forming syncytia. The F protein is considered a key antigen for protective immunity, based on natural immunity studies and active and passive vaccine approaches (ie, palivizumab) [American Academy of Pediatrics Committee on Infectious Diseases 2014] [Graham, B. S., et al 2015]. MK-1654 binds to the F protein and neutralizes RSV infection of cells in vitro and reduces viral load in the nose and lungs of cotton rats infected with RSV A or B when administered prophylactically [Wyde PR, Moore DK, Hepburn T, Silverman CL, Porter TG, Gross M, 1995]. Compared to palivizumab, MK-1654 exhibits greater potency both in vitro and in the preclinical cotton-rat model (see IB). Mutations in the Fc region of MK-1654 result in an extended half-life such that PK modeling suggests that a single dose of MK-1654 will sustain therapeutic levels for 5 months in the majority of infants entering their first RSV season (see IB for details).

2.2.2 Preclinical and Clinical Studies

Refer to the IB for preclinical information on MK-1654.

2.2.3 Completed Clinical Studies

The FIH study, P001, was a 1-year, randomized, placebo-controlled, double-blind, single ascending dose study to assess the safety, tolerability, and PK of MK-1654 administered as a single IM (100, 300 mg) or IV (300, 1000, 3000 mg) dose to healthy adult participants. One hundred and fifty-two healthy male and female (non-child bearing potential) participants aged 19 to 59 years were enrolled (enrollment completed FEB-2018). Preliminary results from this study were used to confirm that the safety and PK profile and dose levels of MK-1654 in healthy adults warranted initiating this Phase 1b study in healthy pre-term and full-term infants. No acute safety reactions to MK-1654 were noted through completion of the highest dose (3000 mg IV) in Study P001. Most AEs were transient and considered mild to moderate in intensity by the investigator. No MK-1654-related SAEs were reported. See the IB for additional information.

2.2.4 Information on Other Study-related Therapy

Not applicable.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from intervention 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 ICF documents.

3. HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

The following objectives and endpoints will be evaluated in healthy pre-term and full-term infants receiving a single ascending dose of MK-1654 or placebo intramuscularly. No formal hypotheses will be tested in the study.

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of MK-1654 through Day 365 (Panels A through C, D1, and E1) and Day 545 (Panels D2 and E2)	• Solicited injection site adverse events (AEs) Day 1 through Day 5 post-dose • Solicited systemic AEs Day 1 through Day 5 post-dose • Serious adverse events (SAEs) from Day 1 through Day 365 (Panels A through C, D1, and E1) and Day 545 (Panels D2 and E2) post-dose
Secondary	
• To estimate the serum pharmacokinetic (PK) profile of MK-1654 on Days 7, 14, 90, 150, and 365 (Panels A through C, D1, and E1) and Days 7, 150, and 365 (Panels D2 and E2)	• For Panels A through C, D1, and E1: the MK-1654 PK variables $AUC_{0\text{-inf}}$, C_{max}, T_{max}, $t_{1/2}$, and concentration (C7days, C14days, C90days, C150days, and C365days) • For Panels D2 and E2: the MK-1654 PK variables $AUC_{0\text{-inf}}$, C_{max}, T_{max}, $t_{1/2}$, and concentration (C7days, C150days, and C365days)
• To describe the incidence of anti-drug antibodies (ADAs) to MK-1654 on Days 14, 90, 150, and 365 (Panels A through C, D1, and E1) and Days 150, 365, and 545 (Panels D2 and E2)	• For Panels A through C, D1, and E1: titer of ADAs to MK-1654 on Days 14, 90, 150, and 365 • For Panels D2 and E2: titer of ADAs to MK-1654 on Days 150, 365, and 545

Objectives	Endpoints
Tertiary/Exploratory	
• To describe any associations between ADA titer and PK, safety, and RSV serum neutralizing antibody titer	• Associations between ADA titer, PK parameters, safety endpoints, and RSV serum neutralizing antibody titer
• To evaluate the effect of MK-1654 on RSV serum neutralizing antibody titers on Days 150 and 365 (Panels A through C, D1, and E1) and Days 150, 365, and 545 (Panels D2 and E2) after a single IM dose of MK-1654	• RSV serum neutralizing antibody titers
• To evaluate the PK profile of MK-1654 in blood microsamples (Panels A through C)	• Blood microsample PK profile after a single IM dose of MK-1654 (Panels A through C)
• To estimate the PK profile of MK-1654 in different segments of the target population with respect to body weight	• Associations between PK parameters and body weight
• To describe the incidence of viral acute respiratory infection (ARI) in the study, as determined by reverse transcription polymerase chain reaction (RT-PCR) detection and presence of symptoms, including RSV-associated outpatient lower respiratory tract infection (LRI) or hospitalization	• RSV, influenza, and human metapneumovirus (hMPV) in nasal swab in infants with symptoms consistent with respiratory infection • RSV-associated ARI • RSV-associated LRI • RSV-associated hospitalization • RSV-associated medically attended LRI (including office or clinic visit, emergency department, urgent care, or hospitalizations)

4. STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, single ascending dose, multi-site, double-blind, safety, tolerability, and PK study of MK-1654 in healthy pre-term and full-term infants.

Approximately 180 healthy male and female infants will be enrolled in the study, including 140 pre-term (born at 29 to 35 weeks gestational age) and 40 full-term (born at over 35 weeks gestational age) infants. All participants will have chronological age of 2 weeks to 8 months.

Pre-term infants will be enrolled worldwide and allocated to 1 of 4 dose escalation panels (Panel A, B, C, or D). Within each sequential dose escalation panel, participants will be randomized by IRT in a 4:1 ratio (active:placebo) to receive one of the following active doses or placebo:

- Panel A: 20 mg,
- Panel B: 50 mg,
- Panel C: 75 mg, or
- Panel D: 100 mg.

Panel A will enroll a total of 10 participants (8 active, 2 placebo) at the lowest dose level; Panel B will enroll a total of 40 participants (32 active, 8 placebo) at 50 mg; Panel C will enroll 50 participants (40 active, 10 placebo) at 75 mg to cover the expected target clinical dose; and Panel D will enroll 40 participants (32 active, 8 placebo) to receive 100 mg, the highest possible dose. Available safety, tolerability, and PK data from Panels A, B, and C will be analyzed to inform the final dose level and allocation of participants in Panel D per Sponsor siDMC Meeting decision, as detailed in Section 6.6. Treatment allocation/randomization of pre-term infants in Panels B, C, and D will be stratified by weight using IRT, as described in Section 6.3.2.

Full-term infants will be enrolled worldwide into Panel E. Within this panel, participants will be randomized by IRT in a 4:1 ratio (active:placebo) to receive either the following active dose or placebo:

- Panel E: 100 mg

Panel E will enroll 40 participants (32 active, 8 placebo) at 100 mg, the highest possible dose. The dose level in Panel E will be determined as in Panel D per Sponsor siDMC.

All participants will receive the assigned study intervention (MK-1654 or placebo [0.9% sodium chloride, USP sterile saline]) administered via IM injection(s) on Day 1. Participants in panels A and B will receive study intervention administered as a single IM injection, as specified in the pharmacy manual. Participants in panels C, D, and E will receive 1 dose of study intervention divided and administered as 2 IM injections, as specified in the pharmacy manual and Section 8.1.8.

After randomization to MK-1654 or placebo within a panel, participants enrolled prior to Amendment 04 will also be randomized by IRT to 1 of 4 different blood sampling schedules (Group 1a, Group 1b, Group 2a, or Group 2b). These differ in the schedule of venous and microsampling, as outlined in SoA 1.3.1 and the operations/laboratory manual. This

approach provides sufficient safety and PK data to support dose escalation decisions and to meet study objectives while minimizing the number of blood draws and total blood volume drawn from each participant at each visit and during the study overall. The approximate total blood volume drawn per participant is approximately 9.0 mL, as detailed in the operations/laboratory manual.

As of Amendment 04, 2 SoAs have been created for participants in Panels D and E to distinguish their participation in the modified schedule, as follows:

- Panels D1 and E1 (Section 1.3.1):
    - Participants enrolled in Panels D and E prior to Amendment 04 choosing not to participate in the modified schedule will follow the Panels D1 and E1 SoA.
- Panels D2 and E2 (Section 1.3.2):
    - Participants enrolled in Panels D and E prior to Amendment 04 choosing to participate in the modified schedule will follow the Panels D2 and E2 SoA (Group 3).
    - Participants enrolled in Panels D and E under Amendment 04 must follow the Panels D2 and E2 SoA.

See the Dose Escalation Diagram in Figure 1 and the dose escalation procedures and decision criteria in Section 6.6 Dose Modification (Escalation) and Section 4.4.2 Clinical Criteria for Study Pause.

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

In addition to the interim safety and PK assessments for dose escalation decisions between panels, an interim safety and PK analysis will also be performed when the PK data are available for all evaluable pre-term infant participants in Panels A and B and at least 10 pre-term infant participants in Panel C through Day 150 and will include available safety and PK data from Panels D and E , as described in Section 9.7. The study will be complete once all participants have completed their final safety visit.

4.2 Scientific Rationale for Study Design

Rationale for selection of the primary safety endpoint and of the secondary and tertiary PK, pharmacodynamic, and other exploratory endpoints in this study is discussed below. See Section 4.3.3 and the IB for additional details on the scientific rationale for the study design.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

As this is an early clinical investigation of MK-1654, safety and tolerability of MK-1654 will be the primary endpoints and will be carefully monitored. AEs, systemic and local injection reaction assessments, physical examinations, and VS will be assessed during the intervention and follow-up periods, with assessment collection times optimized based on the expected PK properties of MK-1654 in infants and the typical timing of reactions to mAbs. All AEs will be assessed for intensity.

Participants will be observed at the study site for 2 hours post-dose for safety monitoring for any immediate AEs, then will return to the study site for visits and for safety and PK assessments as set out in Section 1.3 SoA. In addition, on the evening of Day 1 and on Days 2, 31, 210 (7 months) and 270 (9 months), participants will receive safety follow-up telephone calls for review of concomitant medications and any AEs/SAEs specified in Section 8.3.4. Instructions for supportive care are outlined in Section 6.5.1. Temperature and AEs will also be documented on a validated diary card administered via handheld electronic device, with entries reviewed with the legally acceptable representative during the follow-up safety visit on Days 7 and 14 and telephone call on Day 31.

The safety follow-up period will be 365 days post-dose for Panels A through C, D1, and E1 and 545 days post-dose for Panels D2 and E2. The safety parameters for this study will include the proportion of participants with the following:

1. Elevated temperature (≥102.2°F [39.0°C] rectal or ≥101.7°F [38.7°C] axillary equivalent) from Day 1 through Day 5 post-dose;

2. Solicited systemic treatment reaction AEs (irritability, drowsiness, fever, and appetite lost) from Day 1 through Day 5 post-dose;

3. Solicited local injection reaction AEs (redness/erythema, swelling, and pain/tenderness) reported using the electronic diary card from Day 1 through Day 5 post-dose;

4. Solicited AEs of allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) from Day 1 through Day 30 post-dose;

5. Respiratory AEs from Day 1 post-dose through Day 365 post-dose;

6. Any other unsolicited non-serious AEs occurring from Day 1 through Day 14 post-dose;

7. SAEs throughout the study duration (from the time the consent form is signed through Day 365 (Panels A through C, D1, and E1)/Day 545 (Panels D2 and E2) post-dose and/or completion of the participant's participation in the study; for complete details on SAE data collection, refer to Section 10.3.4).

As with all biologic medications, MK-1654 carries a risk of acute systemic reactions upon exposure. These reactions can be categorized as common acute systemic injection reactions, acute hypersensitivity reactions, and high cytokine release reactions. For other biologic medications, these reactions have been best described in adults. In adults, common acute systemic injection reactions are usually mild, and may manifest with rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate or blood pressure. Acute hypersensitivity reactions typically occur after repeated exposures but can occur with the first dose. In addition to signs similar to common acute systemic injection reactions, participants may develop urticaria, wheezing, coughing, facial swelling, angioedema, and more significant changes in VS. Following initial exposure or re-exposure to palivizumab, cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported. An anaphylactic reaction is a severe type of acute systemic injection reaction characterized by cutaneous and mucosal symptoms such as generalized hives, pruritus or flushing, swollen lips-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor, or hoarseness) and/or changes in blood pressure (hypotension), per the 2006 Sampson criteria for anaphylaxis (Grade 4 reaction) [Sampson, H. A., et al 2006].

The risk of any of these acute systemic injection reactions to the MK-1654 antibody is considered very low as it contains only human elements. The MK-1654 antibody has no endogenous target in humans. In the P001 clinical study, in which MK-1654 was administered both IM and IV, no acute safety reactions to MK-1654 were noted in healthy adult participants up to a dose of 3000 mg IV, as described in Section 2.2.3. Administration of a single IM dose of MK-1654 in this study further reduces the risk of hypersensitivity reactions that were seen with re-exposure to palivizumab after multiple monthly doses.

Nevertheless, given potential safety risks, participants will be closely monitored post-dose with a scheduled onsite safety observation period. Study staff will monitor participants through 2 hours post-dose for local and systemic symptoms of reactogenicity to MK-1654 with VS, plus physical examination as needed.

4.2.1.2 Pharmacokinetic Endpoints

As part of the allocation number assignment and blood sampling groups, participants enrolled prior to Amendment 04 will be assigned by IRT to 1 of 4 different blood sampling schedules (Group 1a, 1b, 2a, or 2b). Participants who enroll in Panels D and E under Amendment 04 will be assigned to a separate blood sampling group (Group 3). Blood sampling groups describe the time points at which participants are to have blood drawn, as scheduled in the SoA and outlined in the operations/laboratory manual, for the following PK/PD assays.

4.2.1.2.1 Serum PK of MK-1654

The PK of MK-1654 will be measured as described in Section 1.3 to define C_{max}, the distribution of the mAb, and the PK profile when administered IM. PK will be measured using a validated bioanalytical assay throughout the entire 1-year study period to determine

the half-life of the molecule, which will support PK projections for subsequent clinical development in the target infant population.

4.2.1.2.2 Blood Microsampling Assay

The blood microsampling PK profile after a single IM dose of MK-1654 will be evaluated. This will support development of a validated whole blood microsampling assay for MK-1654 PK, with the intent that blood volumes required for these tests would be reduced in future studies.

4.2.1.2.3 MK-1654 PK and Infant Body Weight

The PK profile of MK-1654 will be estimated in different segments of the infant population with respect to body weight. This will help to further characterize MK-1654 PK and further inform dose selection in the target infant population. Treatment allocation/randomization of pre-term infants in Panels B, C, and D will be stratified by weight using IRT, as described in Section 6.3.2.

4.2.1.3 Pharmacodynamic Endpoints

The following exploratory endpoints will be evaluated to characterize the pharmacodynamics of a single IM dose of MK-1654.

4.2.1.3.1 Anti-drug Antibodies to MK-1654

The presence and titer of ADAs will be measured. ADAs can develop to biologics like MK-1654 and may be either clinically inconsequential or change the drug PK and/or efficacy. Moreover, ADAs may lead to loss of drug efficacy and/or AEs. Therefore, ADA titers will be analyzed for association with PK and safety events and, as applicable, for associations with RSV SNA titers, as described below.

4.2.1.3.2 RSV SNAs

This study will also evaluate the effect of single ascending doses of MK-1654 on RSV SNA. In this assay, serial dilutions of the participant's serum will be used to inhibit the entry of RSV into target cells in vitro. Total RSV serum neutralizing activity could be influenced by environmental exposure to RSV in addition to the presence of MK-1654. Moreover, the activity of MK-1654 may be inhibited by the presence of ADAs. Therefore, unexpected changes in RSV SNA titers will be examined for associations with respiratory infection and ADA titer.

4.2.1.4 Other Exploratory Endpoints

The following additional exploratory endpoint will be evaluated.

4.2.1.4.1 Acute Respiratory Infection Incidence

The incidence of viral ARI in the study will be explored, as determined by presence of symptoms (as listed in Section 8.8.2) and RT-PCR detection. This will serve to describe the incidence of ARI, including RSV, influenza, and hMPV infection, and help to determine the infectious cause of the ARI and estimate the relative proportion of RSV A and B infections in the target infant population. The procedures for respiratory virus infection determination are detailed in Section 8.8. Note that this study is not powered to show an effect of MK-1654 on the incidence of LRI or hospitalizations caused by RSV.

4.2.1.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research 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 this future biomedical research are presented in Appendix 6: Collection and Management of Specimens for Future Biomedical Research.

4.2.2 Rationale for the Use of Comparator/Placebo

The primary goal of the study is to evaluate the safety and tolerability of MK-1654 in the target infant population. A placebo-controlled study will allow for an unbiased assessment of safety and tolerability of MK-1654. Secondary and exploratory outcomes are also supported by the use of placebo, including the identification of ADAs, which should only be observed in participants receiving MK-1654, and the effect of MK-1654 on RSV serum neutralizing activity, which could be influenced by environmental exposure to RSV, making a placebo arm a key negative control. Lastly, as participants are healthy infants of at least 29 weeks gestational age and not recommended to receive palivizumab (the only approved RSV prophylactic), an active comparator is not possible. Sterile 0.9% saline has been chosen as the placebo as the goal of the study is to test the relative safety and tolerability of the MK-1654 investigational product.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The starting IM dose in this study is 20 mg (refer to the IB for discussion of the starting IM dose and safety margin in humans). The MK-1654 molecule is considered to be of low risk to human participants as a fully human mAb with linear PK in non-human primates and no endogenous target in humans. It is expected to have no biologic effect in the absence of RSV infection. The safety of MK-1654 administration to humans is supported by the results from preclinical toxicology, tissue cross-reactivity, and cytokine release studies (refer to the IB for additional details). It is also supported by preliminary clinical findings from the FIH study in healthy adult participants, in which MK-1654 was tested up to an IM dose of 300 mg and up to an IV dose of 3000 mg, as described in Section 2.2.3.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose of MK-1654 in this study (100 mg) was chosen to meet or exceed the anticipated clinical dose of MK-1654, which will be determined after an analysis of the safety, tolerability, and PK from this study and prior to initiation of subsequent clinical studies in infants. This maximum dose is supported by safety margins provided by both the pre-clinical safety and P001 FIH studies of MK-1654. For comparison of the projected exposures in infants at MK-1654 doses at or exceeding 100 mg with those observed in the rat repeated-dose toxicity study and projected in the P001 FIH study, see the IB.

Prior clinical evaluation in adults and infants of similar mAbs targeting the RSV F protein also supports the maximum dose in this study. The projected exposures for MK-1654 in infants after administration of the proposed doses in this study are based on preclinical studies of MK-1654 as well as extensive modeling with the clinical benchmark, motavizumab-YTE; see the IB for details.

MK-1654 has a similar target, mechanism of action, and safety and PK profile to those of MedImmune's marketed agent, palivizumab, which is indicated for infants at high risk of RSV disease. Both mAbs are directed against a foreign target acting via the established mechanism of binding to the RSV F protein to prevent viral cell entry [American Academy of Pediatrics Committee on Infectious Diseases 2014]. MedImmune has also tested another mAb with a similar mechanism of action, motavizumab, in a Phase 3 randomized, double-blind, placebo-controlled study in infants [O'Brien, K. L., et al 2015]. A version of motavizumab with YTE mutations (similar to MK-1654) tested in a Phase 1 study in healthy adults showed a comparable safety and tolerability profile to that of the parental mAb, motavizumab, along with an extended half-life after IV dosing up to 30 mg/kg [Robbie, G. J., et al 2013]. MedImmune has also recently completed a FIH study of another RSV F protein-specific mAb with YTE mutations, MEDI8897, in healthy adult participants. In this study, MEDI8897 administered up to an IM dose of 300 mg and up to an IV dose of 3000 mg had a safety profile similar to that of placebo [Griffin MP, Khan AA, Esser MT, Jensen K, Takas T, Kankam MK 2016].

4.3.3 Rationale for Dose Interval and Study Design

The dosing regimen was determined based on the known pharmacology of similar mAbs, the dose-linear PK profile and extended half-life of MK-1654 in non-human primates and PK profile of MK-1654 in healthy adults, the preclinical safety margins for MK-1654, and inclusion of extensive safety monitoring in the present study. Safety assessment studies, ancillary pharmacology studies, and the ongoing FIH study with MK-1654 provide no contraindications to the initiation of clinical studies of MK-1654 administered via the IM route in infants. No dose-limiting toxicities were observed in the GLP repeat-dose toxicity study in rats, and substantial preclinical safety margins were obtained over initial human doses.

This study will have up to 5 sequential dose escalation panels and enroll approximately 180 participants (approximately 144 receiving MK-1654 and 36 receiving placebo). The rationale for Panel D in 40 participants (32 active and 8 placebo) is to gain additional experience at MK-1654 100 mg.

4.4 Beginning and End of Study Definition

The overall study begins when written informed consent is provided for the first participant. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, 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 serology assay result.

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, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, and/or procedure-related problems and/or if the number of discontinuations for administrative reasons is too high.

4.4.2 Clinical Criteria for Study Pause

During the study, if any of the following events occur, the study will be paused to further dosing:

- One treatment-related SAE.
- Two or more treatment-related severe AEs (Grade 3 or higher) for 2 days or greater duration, as defined in the diary card, within the same dose panel.

AEs will be assessed for intensity as described in Section 10.3.4.

In the event of any of the above occurrences, a meeting to review available safety data by the investigator and Sponsor will be required for approval of further dosing.

5. STUDY POPULATION

Healthy male and female participants who are pre-term infants (born at 29 to 35 weeks gestational age) or full-term infants (born at over 35 weeks gestational age), all of whom have chronological age of 2 weeks to 8 months, will be enrolled in this study.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Be healthy (based on screening safety laboratory, medical history, and physical examination results) participants.

Demographics

2. Participant is Male or Female.

3. Participant is a pre-term infant (born at 29 weeks to 35 weeks gestational age) or a full-term infant (born at over 35 weeks gestational age), as confirmed in medical records.

4. Participant has chronological age of 2 weeks to 8 months at the time of signing the informed consent.

5. Participant weighs at least 2 kg at the time of screening.

Informed Consent

6. The participant's legally acceptable representative provides written informed consent for the study. The participant's legally acceptable representative may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has been recommended to receive palivizumab per local standard of care.
2. Has one or more documented out-of-range safety laboratory results, adjusted for age, at the time of screening†:
    a. Serum Creatinine >2.0 X upper limit of normal (ULN) for age [Unbound Medicine 2018]
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.0 X ULN [Unbound Medicine 2018]
    c. Hemoglobin <9.0 g/dL
    d. WBC count <4000 cells/mm^3
    e. Platelets <120,000/mm^3

    † Retest is allowed at the discretion of the study investigator.
3. Has a known hypersensitivity to any component of the RSV mAb.
4. Has a history of congenital or acquired immunodeficiency (eg, splenomegaly).
5. Has documented HIV infection.
6. Has documented hepatitis B (HBsAg+) or hepatitis C (HCV RNA+) infection.
7. Has known history of functional or anatomic asplenia.
8. Has a recent (within 14 days prior to screening) diagnosis of failure to thrive.
9. Has known or history of a coagulation disorder contraindicating IM injection.
10. Has received or is expected to receive blood products (except irradiated platelets) within 3 months prior to enrollment.
11. Has prior known documented RSV infection.
12. Has hemodynamically significant congenital heart disease.

    Note: Participants with asymptomatic patent ductus arteriosus, foramen ovale, and atrial septal defect are allowed for enrollment.

13. Has chronic lung disease of prematurity requiring ongoing medical therapy.

14. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that, in the opinion of the investigator, might expose the participant to undue risk by participating in the study, confound the results of the study, or interfere with the participant's participation for the full duration of the study.

15. Has any history of malignancy prior to randomization.

If any of the following Medical Conditions criteria apply, the Day 1 Visit may be rescheduled for a time when these criteria are not met:

16. Has had a recent febrile illness (rectal temperature 38.1°C [100.5°F] or higher or axillary temperature 37.8°C [100.0°F] or higher) within 72 hours pre-dose

17. Is not up-to-date on required vaccinations per local pediatric vaccine schedule at time of screening.

18. Has received inactivated or component vaccines (eg, influenza, hepatitis B) less than 14 days pre-dose.

19. Has received live, attenuated, non-study licensed pediatric vaccines (eg, Bacillus Calmette–Guérin vaccine), except for oral rotavirus and oral polio vaccine, less than 30 days pre-dose.

Prior/Concomitant Therapy

20. Prior administration of any vaccine or mAb for the prevention of RSV.

Prior/Concurrent Clinical Study Experience

21. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device at any time prior to first dose administration or while participating in this current study. Participants enrolled in observational studies may be included and will be reviewed on a case-by-case basis for approval by the Sponsor.

22. Has enrolled previously in the current study and been discontinued.

23. Participant's mother participated in RSV vaccine clinical study while pregnant and participant is 3 months or less in chronological age.

Diagnostic Assessments

Not applicable.

Other Exclusions

24. Is unable to provide blood sample at screening.

25. Cannot be adequately followed for safety according to the protocol plan.

26. Has a parent/legal guardian/legally acceptable representative who is unlikely to adhere to study procedures, keep appointments, or is planning to relocate during the study.

27. Has any other reason that in the opinion of the investigator may interfere with the evaluation required by the study.

28. 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

No restrictions are required.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6. STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Levels	Route of Administration	Regimen	Use	IMP/ NIMP	Sourcing
MK-1654	Experimental	Active	Biological/Vaccine	Vial	100 mg/mL	20 mg 50 mg, 75 mg, 100 mg	IM	Single 0.2 mL, Single 0.5 mL, 0.75 mL (0.5 mL in the right thigh + 0.25 mL in the left thigh), 1 mL (0.5 mL in the right thigh + 0.5 mL in the left thigh)	Experimental	IMP	Sponsor
Placebo	Placebo Comparator	Placebo	Other	Vial	Not applicable	Not applicable	IM	Same as MK-1654 regimen	Placebo	NIMP	Sponsor or site

Placebo=Sterile saline 0.9% sodium chloride injection, USP provided by either the Sponsor or the site. Equivalent volumes of saline will be used to correspond with the respective dose level.
IM=intramuscular; IMP=investigational medicinal product; NIMP=non-investigational medicinal product; USP=United States Pharmacopeia.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Medical Devices

Not applicable for this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed in order 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 provided in Section 4.3.

MK-1654 and placebo (0.9% sodium chloride, USP sterile saline) will be prepared by an unblinded pharmacist or medically qualified study personnel (see Section 6.3.3). The syringe(s) for IM injection(s) should be prepared shortly before administration, whenever possible, per the instructions, including for syringe stability and storage conditions.

The assigned study intervention (MK-1654 or placebo) will be administered via IM (vastus lateralis) injection on Day 1 to all participants as determined by the Panel:

- Panel A: 20-mg dose – 0.2 mL single IM injection
- Panel B: 50-mg dose – 0.5 mL single IM injection
- Panel C: 75-mg dose – 0.75 mL split into 2 IM injections
    - 0.5 mL administered in right thigh
    - 0.25 mL administered in left thigh
- Panels D and E: 100-mg dose - 1 mL split into 2 IM injections
    - 0.5 mL administered in right thigh
    - 0.5 mL administered in left thigh

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an IRT system. There are 6 study intervention arms. Participants will be assigned randomly in a 4:1 ratio to 20 mg MK-1654 or placebo, 50 mg MK-1654 or placebo, 75 mg MK-1654 or placebo, or, 100 mg MK-1654 or placebo in panels A, B, C, and D, respectively, or 100 mg MK-1654 or placebo in panel E. Nested in the randomization to MK-1654 or placebo within Panels A through C, D1, and E1, participants will also be randomized by IRT to 1 of 4 different blood sampling schedules (Group 1a, Group 1b, Group 2a, or Group 2b). All participants in Panels D2 and E2 will follow the same blood sampling schedule (Group 3).

6.3.2 Stratification

Treatment allocation/randomization of pre-term infants in Panels B, C, and D will be stratified by weight.

In Panels B and D, at least 12.5% of participants enrolled will be small pre-term infants (weigh 2 to 5 kg [inclusive] at randomization), and up to 87.5% of participants enrolled will be large pre-term infants (weigh more than 5 kg at randomization).

In Panel C, at least 10% of participants enrolled will be small pre-term infants (weigh 2 to 5 kg [inclusive] at randomization), and up to 90% of participants enrolled will be large pre-term infants (weigh more than 5 kg at randomization).

Treatment allocation/randomization of pre-term infants in Panel A will not be stratified by weight, due to the small number of participants in this lowest-dose panel. Safety and PK evaluation in small infants will be sufficient based on the number of small pre-term infants in

Panels B, C, and D, so stratification of treatment allocation/randomization of full-term infants in Panel E will not be necessary.

6.3.3 Blinding

A double-blinding technique will be used. MK-1654 and placebo will be prepared and administered in a blinded fashion by an unblinded pharmacist or medically qualified study personnel not otherwise involved in the conduct of the study. Unblinded study personnel should not have contact with participants for any study-related procedures/assessments post-dose, including all safety follow-up procedures. The participant's legally acceptable representative and the investigator(s) will be unaware of the study intervention assignments.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.4 Study Intervention Compliance

Study interventions will be prepared and administered as described in Section 6.2.1 and Section 6.3.3 and stored, handled, and documented as described in Section 6.2.2.

Study intervention information, such as Component Identification Number, dose panel, and time of administration, must be recorded on the appropriate electronic case report form (eCRF) as outlined in the Data Entry Guidelines.

6.5 Concomitant Therapy

Administration of non-study licensed pediatric vaccines [eg, influenza, hepatitis B, diphtheria, tetanus, and pertussis vaccine(s)] will be permitted during this study provided the following conditions are met:

1. Inactivated or component vaccines (eg, influenza, hepatitis B) should not be administered less than 14 days pre- or post-dose.

2. Live, attenuated, non-study licensed pediatric vaccines (eg, Bacillus Calmette–Guérin vaccine) should not be administered less than 30 days pre- or post-dose.

3. No prior administration of any vaccine or mAb for the prevention of RSV.

4. Oral rotavirus and oral polio vaccine may be administered without any exclusionary windows around MK-1654.

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

agreement of the investigator, the Sponsor, and the participant's legally acceptable representative.

Any concurrent medication or medical treatment must be recorded on the appropriate eCRF.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

As outlined in the IB and Section 4.2.1.1, the risk of acute systemic or local injection reactions to MK-1654 is considered low. However, acute systemic or local injection reactions may be observed. As the purpose of the study is to characterize the safety profile of MK-1654, no prophylactic pre-medications to reduce the risk of injection reactions will be given prior to MK-1654 administration.

All participants will be observed for 2 hours post-dose for acute reactions to MK-1654 and evaluated for systemic and local injection reactions. Severe injection reactions, including cytokine release syndrome and hypersensitivity reactions, must be promptly treated with medical management, appropriate monitoring, and life-saving measures. Appropriate resuscitation equipment and a physician/designee and/or study staff will be readily available during the period of drug administration through the 2-hour post-dose onsite safety observation period. Less severe injection reactions may respond to medical management. Acetaminophen may be administered per investigator discretion without prior consultation with the Sponsor.

Participants who experience injection reactions, including hypersensitivity reactions, in conjunction with the study intervention should receive appropriate supportive care measures as deemed necessary by the treating physician. Investigators should strongly consider hospitalization for any severe systemic reaction or any life-threatening reactions. Participants should be carefully observed until complete resolution of all signs and symptoms, if a reaction occurs. Any AEs will be reported according to the guidelines in Section 8.4 and Section 10.3 (Appendix 3).

6.6 Dose Modification (Escalation)

Each panel will enroll 4 participants (study-wide, not per site) with review of safety through Day 3 before additional participants can be dosed within the panel, except in Panel D and E if the dose level is not escalated from Panel C. The site lead investigator(s) at the respective site(s) and Sponsor will assess the first 2 participants for safety through Day 3 prior to dosing the next 2 participants. The site lead or sub-investigator(s) at the respective site(s) and Sponsor will then assess the next 2 participants for safety through Day 3 prior to dosing additional participants in the panel. An IRT hold will prevent enrollment/randomization of additional participants study-wide until this is achieved; when this hold is lifted, enrollment/randomization and dosing of the remaining participants in the panel may proceed (study-wide). This is to allow for identification of any potential systemic treatment-related AEs that could be observed with dose escalation. If no clinical criteria for study pause in

Section 4.4.2 are met, further dosing within the panel may proceed. Safety follow-up, as scheduled in the SoA, is detailed in Section 4.2.1.1.

The decision to escalate the dose between Panels A and B and Panels B and C will be made based on review of: 1) available safety data through at least Day 14 for at least 50% of participants in the previous panel(s); and 2) available PK data from the previous panel(s). Ongoing safety monitoring and PK analyses will continue throughout Panels A, B, and C.

The decision to dose escalate between Panels C and D in pre-term infants and between Panel C in pre-term infants and Panel E in full-term infants, and on the dose level(s) in Panels D and E (up to 100 mg), will be made in an siDMC Meeting based on review of: 1) available safety data through at least Day 14 from Panels A, B, and C; 2) PK data through Day 90 for evaluable participants in Panel A and PK data through Day 30 for at least 50% of evaluable participants in Panel B; and 3) available PK data from Panel C. Note that Panels D and E may initiate prior to completion of Panel C.

The siDMC will hold a meeting after Panel C for the decision to escalate the dose in Panels D and E.

If, as judged by the Sponsor, the safety, tolerability, and PK 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,
- Receive the same or lower dose, or
- Dosing may be stopped.

Clinical criteria for study pause are specified in Section 4.4.2.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the 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). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies. See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

Not applicable for this study.

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 prior to completion of the protocol-specified intervention period will still continue to participate in the study as specified in the SoA and Section 8.13.3.

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 8.13.3.

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

- The participant's legally acceptable representative requests to discontinue study intervention.
- For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, 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's legally acceptable representative and reschedule the missed visit. If the participant's legally acceptable representative is contacted, the participant's legally acceptable representative 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's legally acceptable representative at each missed visit (eg, telephone calls and/or a certified letter to the legally acceptable representative'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 utilized 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's legally acceptable representative. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The approximate total blood volume drawn per participant is approximately 9.0 mL, as detailed in the operations/laboratory manual. The maximum amount of blood collected from each participant over the duration of the study, including for any extra assessments that may be required, will be in accordance with regulatory guidelines for pediatric studies and recommended maximum blood draw volumes [Jack, R. 2001]. 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 consent from each potential participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. 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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented on the consent form by the dated signature of the participant's legally acceptable representative along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant's legally acceptable representative before the individual's participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant's legally acceptable representative must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the willingness for the participant 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 dated signature of the participant's legally acceptable representative.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 future biomedical research consent to the participant's legally acceptable representative, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant's legally acceptable representative.

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

The legally acceptable representative for each participant will be given a participant identification card identifying the individual as a participant 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 legally acceptable representative for each participant with a participant identification card immediately after written informed consent is provided. At the time of intervention allocation/randomization, site personnel will add the intervention/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare 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/vaccination use and record prior medication taken by the participant to assess inclusion and exclusion criteria including time windows for medication/vaccination use.

8.1.5.2 Concomitant Medications

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

Any concurrent medication or medical treatment must be recorded on the appropriate eCRF. On the day of dosing, it is important to record the use of any analgesic or antipyretic use on the electronic diary card and appropriate eCRF.

If a medical condition required the use of immunoglobulins, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible and any such use must be documented on the appropriate eCRF.

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 prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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 provided in Section 8.13.1.

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 allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer the study intervention. Study intervention should be prepared by and administered by an unblinded pharmacist or appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance and described in Section 6.2, Section 6.3.3, and the pharmacy manual.

The assigned study intervention (MK-1654 or placebo) will be administered via IM (vastus lateralis) injection on Day 1 to all participants as defined by the Panel:

- Panel A: 20-mg dose – 0.2 mL single IM injection
- Panel B: 50-mg dose – 0.5 mL single IM injection
- Panel C: 75-mg dose – 0.75 mL split into 2 IM injections
    - 0.5 mL administered in right thigh
    - 0.25 mL administered in left thigh
- Panels D and E: 100-mg dose - 1 mL split into 2 IM injections
    - 0.5 mL administered in the right thigh
    - 0.5 mL administered in the left thigh

8.1.8.1 Timing of Dose Administration

Study intervention is given on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

MK-1654 or placebo, as randomly assigned, will be administered to each participant at the study site on Day 1, as set out in the SoA and specified in Section 6.2.1, Section 8.1.8, and the Pharmacy Manual.

See Section 6.5 on the timing of study intervention administration with regard to concomitant therapy.

Participants will be observed for 2 hours immediately post-dose for safety monitoring by the blinded investigator and/or study staff, as described in the SoA and Section 4.2.1.1.

8.1.8.2 Diary Card

Each participant's legally acceptable representative will be provided an electronic diary card on a handheld electronic device to help in identifying any systemic or local injection reactions. The electronic diary card and use of the handheld electronic device will be reviewed with the participant's legally acceptable representative at the study site, as indicated in the SoA.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the intervention period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4. Participants who discontinue ≥2 weeks after last blood draw will complete the Day 365 (Panels A through C, D1, and E1) or Day 545 (Panels D2 and E2) visit blood collection, regardless of their assigned blood sampling schedule group.

8.1.9.1 Withdrawal From Future Biomedical Research

Consent for future biomedical research may be withdrawn by the participant's legally acceptable representative. Consent may be withdrawn by the legally acceptable representative at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research 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's legally acceptable representative of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that 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 should continue to be monitored in the study.

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

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

8.1.11 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 is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study; surrogate markers of efficacy are outlined in Section 8.8.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood to be drawn over the course of the study (from pre-study to post-study visits), including approximate blood volumes drawn by visit and by sample type per participant, are detailed in the operations/laboratory manual.

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) as per institutional standard. Body weight and length will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard based upon any emergent symptoms at the discretion of the investigator.

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

8.3.2 Vital Signs

- Body temperature, heart rate, and respiratory rate will be assessed.

- Temperature and respiratory rate will be measured and recorded as single measurements. The same method must be used for all measurements for each individual participant and should be the same for all participants.

- Rectal or axillary temperature will be taken by study staff pre- and post-dose as set out in the SoA. Participants who have febrile illness (rectal temperature ≥38.1°C [100.5°F] or axillary temperature ≥37.8°C [100.0°F]) within 72 hours pre-dose must be rescheduled.

- Rectal is the preferred method of obtaining participant's temperature. Axillary (underarm) is an acceptable method. Temperature readings must be recorded on the electronic diary card. Temperature readings should be taken at approximately the same time each day. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited.

- The participant's legally acceptable representative will be asked to record a temperature reading on the electronic diary card from Day 1 through Day 5 post-dose. Temperature measurement must be recorded in the electronic diary card if fever is suspected during Day 6 through Day 14 post-dose.

- Heart rate will be measured with a completely automated device. Manual techniques will be used only if an automated device is not available. Heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- All VS measurements, including temperature readings captured on the electronic diary card, will be recorded on the appropriate eCRF.

8.3.3 Systemic and Local Injection Reaction Assessment

Participants will be monitored at the study site during dosing as outlined in the SoA for signs and symptoms of a systemic injection reaction, including urticaria (hives or welts), lip swelling, wheezing, and/or difficulty breathing. If hives or welts occur during the 30 days following MK-1654 administration, the participant's legally acceptable representative should contact the site to schedule an appointment with the study site for an evaluation as soon as possible, where the study investigator will determine whether the rash represents an urticarial-like eruption. The study site will also receive notice if allergic reactions are entered in the electronic diary card and should contact the participant's legally acceptable representative for an evaluation if hives or welts or other allergic reactions occur during the 30 days following MK-1654 administration. If a rash is confirmed by the study investigator as consistent with urticaria, the investigator may obtain a dermatology consult based on the investigator's discretion. Any systemic injection reactions must be assessed and managed promptly, as described in Section 6.5.1.

During the safety follow-up period (30 days post dosing), surveillance for RSV infection, including the common symptoms of difficulty breathing and wheezing, will also be ongoing (beginning on Day 14 post dosing) for both respiratory infection and allergic reaction. During this time (Days 14-30), clinical judgment will be required to assess the symptoms as part of respiratory infection or allergic reaction. Regardless of the diagnosis, the participant should be brought in for clinical assessment and further evaluation.

An examination of the local injection site(s) will also be performed as scheduled in the SoA, including an assessment of any pain, tenderness, erythema/redness, and induration/swelling for each injection site. These events will be evaluated based on the scale outlined in Section 10.3.4.

Any subsequent systemic or local injection reaction symptoms will be captured as AEs/SAEs during safety monitoring visits and follow-up, as scheduled in the SoA, and at home by the participant's legally acceptable representative on the diary card using the handheld electronic device, as described in Section 4.2.1.1.

Any adverse systemic or local injection reaction will be recorded on the appropriate eCRF.

8.3.4 Safety Follow-up Telephone Calls

Safety follow-up telephone calls will be performed at the time points indicated in the SoA. If a participant is hospitalized at the time, a safety follow-up call will be performed. Safety calls must be performed by appropriately trained study site staff. If the initial call is unsuccessful, the study site staff should make a total of 3 attempts for each scheduled safety call. All attempts to contact the participant's legally acceptable representative will be recorded in the source documents. The calls will facilitate the collection of relevant safety information. The participant's legally acceptable representative will be interviewed to obtain information relating to all AEs through Day 14, solicited AEs of allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) through Day 30, respiratory AEs through Day

365, and SAEs through Day 365 (Panels A through C, D1, and E1) or Day 545 (Panels D2 and E2).

In addition, all concomitant medications and vaccinations will be recorded. All safety information described by the participant's legally acceptable representative must be documented in the source documents.

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 must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (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 operations/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 5 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.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), 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, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or

SAE, as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of allocation/randomization through Day 365 (Panels A through C, D1, and E1) or Day 545 (Panels D2 and E2) following the administration of study intervention, all SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph, also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the participant completing the study but outside the time period specified in the previous paragraph.

OR

2. An SAE that is considered by an investigator who is a qualified physician to be study intervention-related.

Investigators are not obligated to actively seek AE or SAE 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 he/she 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 2.

Table 2 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	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion	Report all	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (ECI; require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (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
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

Care will be taken not to introduce bias when detecting AE and/or SAE 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, events of clinical interest (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. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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

Not applicable, as this study is in infants only.

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

Not applicable for this study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

1. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the dose level in the assigned panel.

No specific information is available on the treatment of overdose.

8.6 Pharmacokinetics

The decision as to which serum samples collected will be assayed for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers. See the Pharmacokinetics/Pharmacodynamics/Biomarkers schedule in the SoA for the timing of each of the 4 blood draw schedules, with detailed instructions and blood volumes to be drawn for each PK assay provided in the operations/laboratory manual.

8.6.1 Blood Collection for MK-1654 Pharmacokinetics

Sample collection, storage, and shipment instructions for serum samples are provided in the operations/laboratory manual.

8.6.2 Blood Microsampling for MK-1654 Pharmacokinetics

Microsample collection, storage, and shipment instructions for blood microsamples are provided in the operations/laboratory manual.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamics samples are provided in the operations/laboratory manual. See the Pharmacokinetics/Pharmacodynamics/Biomarkers schedule in the SoA for the timing of each of the blood draw schedules, with detailed instructions and blood volumes to be drawn for each pharmacodynamics assay provided in the operations/laboratory manual.

8.7.1 Blood Collection for ADAs and RSV Neutralizing Assay

Sample collection, storage, and shipment instructions for serum samples are provided in the operations/laboratory manual.

8.8 Acute Respiratory Infection Determination

See the SoA for the timing of respiratory AEs collection and RSV surveillance weekly telephone calls for determining the need for an unscheduled RSV assessment visit and nasal swab for respiratory virus infection detection.

8.8.1 RSV Season Definition

The Sponsor will define the expected start and end of RSV season for each region participating in the study, based on several prior years' RSV seasons, as determined by national surveillance and/or available peer-reviewed literature. Detailed instructions will be provided in the operations manual.

Globally each year, RSV epidemics initiate near the equator, in August and January in the Northern and Southern Hemisphere, respectively, then move toward temperate regions. Global patterns in monthly RSV activity have been observed and annual average percentage of RSV activity calculated for 152 sites globally in an ongoing review of RSV seasonality studies and online datasets by the Respiratory Syncytial Virus Consortium in Europe (RESCEU) [You, Li 2017].

In the United States, RSV season onset has ranged from late October to late January and season offset has ranged from late January to early April in all 10 Department of Health and Human Services (HHS) regions, except in Florida, which has an earlier RSV season onset and longer duration, as reported by the Centers for Disease Control (CDC) National Respiratory and Enteric Virus Surveillance System (NREVSS). During the 2013–14 season, similarly to previous national patterns, RSV began circulating nationally in early November and ended in late March, with circulation peaking at 24% in late December. The RSV season (onset, offset, peak, and duration) is defined nationally, by HHS region, and by state, based on CDC analysis of RSV laboratory detections reported to the NREVSS. The CDC and World Health Organization define the onset of the RSV season as a 10% threshold of RSV-positive specimens during 2 consecutive weeks.

In the European Union, the RSV season is typically November to April with a peak in the mid-winter months *[European Medicines Agency 2017]*. The European influenza surveillance system captures RSV detection through the influenza-like illness (ILI) or ARI surveillance system from 21 European Union countries, as reported for the 2014-15 season by the European Centre for Disease Control (ECDC) [European Center For Disease Prevention And Control 2015].

In the Southern Hemisphere, the RSV season is generally April to August, starting in February in tropical and subtropical regions and then moving south, peaking in July in temperate regions.

8.8.2 RSV Surveillance Weekly Telephone Calls

During the RSV season, as defined in Section 8.8.1, RSV weekly surveillance starts on Day 14 until the Sponsor deems that RSV season is ended. From Day 14, study sites will conduct weekly telephone surveillance calls to the legally acceptable representative to determine if there have been any changes in the participant's health and if any health care visits have occurred in the last week. If the answer is affirmative, then sites will further inquire if any of the following symptoms of ARI have occurred:

- Runny or stuffy nose
- Cough
- Fever/feverishness
- Trouble feeding
- Noisy breathing (respiratory tract congestion)
- Difficulty or labored breathing
- Wheezing
- Chest wall in-drawing

If any 2 or more of these symptoms have occurred for at least 2 days duration and the symptoms are consistent with ARI, or if any of the ARI symptoms are of concern to the investigator, regardless of duration, a site visit for RSV assessment should be arranged as described in Section 8.8.4.

8.8.3 Legally Acceptable Representative-reported Respiratory Symptoms

In addition to the sites conducting weekly RSV surveillance telephone calls, the legally acceptable representatives will be instructed to phone the site to report respiratory symptoms that have occurred for at least 2 days duration. If 2 or more respiratory symptoms have occurred for at least 2 days duration and the symptoms are consistent with ARI, or if any of the ARI symptoms are of concern to the investigator, regardless of duration, a site visit for RSV assessment should be arranged as described in Section 8.8.4.

8.8.4 Unscheduled Visit for RSV Assessment

If ARI is suspected (during surveillance and/or symptoms collection), the participant should be assessed at the study site as soon as is feasible and no later than 8 days after the legally acceptable representative's initial contact. The unscheduled visit for RSV assessment should occur no later than 10 days after symptom onset. ARI is defined as 2 or more of the

symptoms listed in Section 8.8.2 having occurred for at least 2 days duration, or if in the opinion of the investigator, the symptoms are consistent with ARI, regardless of duration.

A physical exam (including heart rate, respiratory rate, O_2%, and temperature) will be performed to confirm if any of the following signs and symptoms of lower respiratory tract infection (LRI) are present:

- Decreased O_2 saturation (<95% on room air at sea level or <92% on room air at ≥1800 meters)
- Wheezing, chest wall in-drawing, or difficulty breathing
- Rales and crackles, rhonchi or coarse breath sounds, or decreased breath sounds on respiratory exam

RSV-associated LRI is defined as the presence of any of these symptoms, with RSV detected by RT-PCR.

RSV-associated outpatient LRI is defined as above, for a participant seen in an outpatient clinic/doctor's office, emergency department, or urgent care center.

Following careful evaluation of signs and symptoms of ARI/LRI, the study investigator should determine if further triage or evaluation is needed, consistent with the standard of care, and in conjunction with the participant's primary physician (if applicable).

RSV-associated hospitalization is defined as hospital admission for RSV or new onset of respiratory illness during a hospital admission with RSV detected by RT-PCR.

Non-serious respiratory AEs confirmed during the unscheduled visit for RSV assessment will be recorded on the AEs eCRF, as outlined in the SoA for Respiratory AEs Collection. Any other AEs/SAEs will continue to be reviewed and recorded as outlined in the SoA for AE/SAE Review. If a participant is unable to attend a study visit due to respiratory-associated hospitalization, study participant's legally acceptable representative should obtain hospitalization medical summary and schedule a visit with the study site as soon as possible after hospital discharge. If respiratory symptoms are suggestive of RSV infection, a nasal swab should be collected for RT-PCR testing if within 4 weeks of infection symptoms.

8.8.5 Nasal Swab for Respiratory Virus Infection Determination

If the investigator confirms that 2 or more of the symptoms listed in Section 8.8.2 have occurred for 2 days or more, or if any of the ARI symptoms are of concern, a nasopharyngeal swab should be obtained for respiratory virus detection by RT-PCR. Nasal swab will be performed at the unscheduled visit for RSV assessment and analyzed regardless of the physical exam findings and regardless of the participant's intervention assignment (MK-1654 or placebo) or panel (A, B, C, D, or E). The purpose is to estimate the incidence of ARI, including RSV, influenza, and hMPV infection, and help to determine the infectious cause of the ARI and the relative proportion of RSV A and B infections in the target infant

population. Sample collection, storage and shipment instructions for nasal mucosal samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant's legally acceptable representative signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover serum from the MK-1654 PK assay
- Leftover serum from the ADA and SNA assays

8.10 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.11 Biomarkers

Biomarkers will be evaluated as part of the Future Biomedical Research.

8.12 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.13 Visit Requirements

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

8.13.1 Screening

Within 14 days prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Potential participants will be screened at the study site.

Screening procedures may be repeated after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review.

8.13.2 Intervention Period

On Day 1, participants will be randomized and dosed at the study site, as set forth in the SoA and Section 6.

After completing all pre-dose procedures, each participant will be assigned a unique treatment/randomization number associated with a specific intervention as defined by IRT.

On the scheduled day of dosing (Day 1) at the time specified by the investigator, participants will have the IM injection(s) administered as described in Section 6. Participants will be

observed at the study site for at least 2 hours post-dose for safety monitoring, including assessment for injection-reaction AEs/SAEs, followed by a safety follow-up telephone call (or onsite follow-up for inpatients) on the evening of Day 1 and Day 2.

Participants who on Day 1 have an acute illness or fever (see Section 5.2 Exclusion #16) prior to the administration of study drug may be rescheduled.

8.13.3 Discontinued Participants Continuing to be Monitored in the Study and Post-study Visit

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant's legally acceptable representative may be asked to bring the participant back to the study site (or be contacted) for a post-study visit (approximately 365 days post-dose for Panels A through C, D1, and E1, and 545 days post-dose for Panels D2 and E2) to have the applicable procedures conducted. However, the investigator may decide to perform the post-study procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-study visit occurs prior to Day 365 (Panels A through C, D1, and E1/ Day 545 (Panels D2 and E2), the investigator should perform a follow-up telephone call on Day 365/545 to determine if any AEs have occurred since the post-study visit.

9. STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to the final database lock, changes are made to the primary or key secondary analyses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental Statistical Analysis Plan and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study; full details are provided in the following sections.

Study Design Overview	A Double-Blind, Placebo-controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-1654 in Pre-Term and Full-Term Infants
Intervention Assignment	Pre-term infant participants will be assigned randomly in a 4:1 ratio to receive one of the following active doses or placebo: • Panel A: 20 mg MK-1654 • Panel B: 50 mg MK-1654 • Panel C: 75 mg MK-1654 • Panel D: 100 mg MK-1654 In Panels B, C and D, the randomization will be stratified by weight. At least 12.5% of participants enrolled in Panels B and D, and at least 10% of participants enrolled in Panel C will be small pre-term infants (weigh 2 to 5 kg [inclusive] at randomization) while the remainder of the participants enrolled in these panels will be large pre-term infants (weigh more than 5 kg at randomization). Full-term infant participants will be assigned randomly in a 4:1 ratio to receive the following active dose or placebo: • Panel E: 100 mg MK-1654 All participants will receive study intervention administered via IM injection(s) on Day 1.
Analysis Populations	Safety: All Participants as Treated (APaT) Pharmacokinetics: Per-Protocol (PP)
Primary Endpoint	Safety: • Solicited injection site AEs Day 1 through Day 5 post-dose • Solicited systemic AEs Day 1 through Day 5 post-dose • SAEs from Day 1 through Day 365 post-dose for Panels A through C, D1, and E1, and from Day 1 through Day 545 post-dose for Panels D2 and E2.
Key Secondary Endpoints	Pharmacokinetics: • The MK-1654 PK variable(s) $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, C7days, C14days, C90days, C150days and C365days (Panels A through C, D1, and E1) • The MK-1654 PK variable(s) $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, C7days, C150days, and C365days (Panels D2 and E2)

Statistical Methods for Key Pharmacokinetic Analyses	Separately for each PK parameter of interest ($AUC_{0\text{-inf}}$, C_{max}, C7days, C14days, C90days, C150days, and C365days), individual values at each dose level will be natural log-transformed and evaluated with a linear effects model containing a fixed effect for dose. Ninety-five percent confidence intervals (CI) for the least squares means for each dose will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these CIs will yield estimates for the population geometric means (GM) and CIs about the GMs on the original scale. The posterior distribution of the natural log mean C150days will be calculated for each dose using the estimated mean and standard deviation from the above model and using a non-informative prior. The PostPr (true GM C150days ≥7.5 µg/mL| data) will be computed for each dose.
Statistical Methods for Key Safety Analyses	Safety parameters will be summarized via descriptive statistics.
Interim Analyses	Interim analyses of safety and available PK data will be performed for making dose escalation decisions between Panels A and B and Panels B and C. The decision to dose escalate between Panels C and D in pre-term infants and between Panel C in pre-term infants and Panel E in full-term infants, and on the dose level(s) in Panels D and E (up to100 mg), will be made in an siDMC meeting based on review of safety and PK data. An interim analysis of safety and PK data will be performed when all evaluable pre-term infant participants in Panels A and B and at least 10 pre-term infant participants in Panel C have completed their Day 150 visit. Available safety and PK data from Panel D and Panel E will be included in this analysis. The purpose of this interim analysis is to make scientific decisions for future studies.
Multiplicity	Since there are no formal hypothesis tests in this study, no adjustment will be made for multiplicity.
Sample Size and Power	Section 9.9 provides information about the ability of this study to estimate the incidence of AEs in recipients of a dose of MK-1654.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study, ie, the investigators and participants will be blinded to the intervention assignments of the participants. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedules for study intervention assignment. Randomization will be implemented using IRT.

The planned interim analyses are described in Section 9.7. The results of the interim analyses will not be shared with the investigators prior to the completion of the study, with the exception of the dose escalation decisions.

9.3 Hypotheses/Estimation

The objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

9.4.1 Safety Endpoints

Refer to Section 4.2.1.1 for the description of the safety measures in this study. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, systemic and local injection reaction assessments, physical examinations, and VS. AEs will be documented on a validated diary card which will be administered electronically via handheld device. All AEs will be assessed for intensity.

Primary Safety Endpoints

1. Solicited systemic AEs (irritability, drowsiness, fever, and appetite lost) from Day 1 through Day 5 post-dose;

2. Solicited local injection reaction AEs (redness/erythema, swelling, and pain/tenderness) from Day 1 through Day 5 post-dose;

3. SAEs throughout the study duration (from the time the consent form is signed through Day 365 post-dose (Panels A through C, D1, and E1) and Day 545 post-dose (Panels D2 and E2) and/or completion of the participant's participation in the study).

Additional Safety Endpoints

1. Elevated temperature (≥102.2°F [39.0°C] rectal or ≥101.7°F [38.7°C] axillary equivalent) from Day 1 through Day 5 post-dose;

2. Solicited AEs of allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) from Day 1 through Day 30 post-dose;

3. Respiratory AEs from Day 1 through Day 365 post-dose

4. Any other unsolicited non-serious AEs occurring from Day 1 through Day 14 post-dose.

9.4.2 Pharmacokinetic Endpoints

Secondary Endpoint

1. For Panels A through C, D1, and E1, the MK-1654 PK variables: $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, and concentration (C7days, C14days, C90days, C150days and C365days).

   For Panels D2 and E2, the MK-1654 PK variables: $AUC_{0\text{-}inf}$, C_{max}, T_{max}, $t_{1/2}$, and concentration (C7days, C150days, and C365days).

9.4.3 Other Endpoints

Secondary Endpoint

1. MK-1654 ADA titer for Panels A through C, D1, and E1 on Days 14, 90, 150, and 365.

   MK-1654 ADA titer for Panels D2 and E2 on Days 150, 365, and 545.

Exploratory Endpoints

1. Associations between ADA titer, PK parameters, safety endpoints, and RSV serum neutralizing antibody titer.

2. RSV serum neutralizing antibody titers (on Days 150 and 365 for Panels A through C, D1, and E1, and Days 150, 365, and 545 for Panels D2 and E2).

3. MK-1654 PK profile in blood microsamples.

4. Associations between PK parameters of MK-1654 and body weight.

5. Incidence of RSV, influenza, and hMPV in nasal swab in infants with symptoms consistent with respiratory infection.

6. Number and proportion of infants with RSV-associated ARI.

7. Number and proportion of infants with RSV-associated LRI.

8. Number and proportion of infants with RSV-associated hospitalization.

9. Number and proportion of infants with medically attended (including office or clinic visit, emergency department, urgent care, or hospitalizations) LRI.

9.5 Analysis Populations

9.5.1 PK Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of PK data in this study. The PP population consists of all randomized participants with exclusions for important deviations from the protocol that may substantially affect the results of the PK endpoints. Deviations that may result in the exclusion of a participant from the PP population for all PK analyses include:

- Failure to receive study intervention at Day 1,
- Receipt of prohibited medication or prohibited vaccine prior to study intervention, and
- Missing PK results.

The final determination on important protocol deviations, and thereby the composition of the PP population, will be made prior to the final unblinding of the database and will be documented in a separate memo. Participants will be included in the intervention group for the treatment actually received for the analysis of PK data using the PP population.

9.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received study intervention. Participants will be included in the group corresponding to the clinical material they actually received for the analysis of safety data using the APaT population. For most participants this will be the group to which they are randomized. Participants who receive incorrect clinical material will be included in the group corresponding to the clinical material actually received.

9.6 Statistical Methods

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; eg, heteroscedasticity, non-normality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

9.6.1 Statistical Methods for Pharmacokinetic Analyses

Due to the sparse PK sampling in this study, population PK modeling will be used to estimate the PK parameters $AUC_{0\text{-inf}}$, C_{max}, T_{max}, and $t_{1/2}$. Population PK modeling may also be used to estimate the concentrations at the time points where all participants are not being sampled. For the summaries of the PK data, PK data from the pre-term infant panels and full-term infant panel will be combined for the analysis if the full-term infant panel receives the

same dose as one of the pre-term infant panels. PK sample analysis will not be conducted in participants who receive placebo.

Model-Based PK Summary

Separately for each PK parameter of interest ($AUC_{0\text{-inf}}$, C_{max}, C7days, C14days, C90days, C150days, and C365days), individual values at each dose level will be natural log-transformed and evaluated with a linear effects model containing a fixed effect for dose. Ninety-five percent CIs for the least squares means for each dose will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these CIs will yield estimates for the population GMs and CIs about the GMs on the original scale.

The posterior distribution of the natural log mean C150days will be calculated for each dose using the estimated mean and standard deviation from the above model and using a non-informative prior. The PostPr (true GM C150days ≥7.5 µg/mL | data) will be computed for each dose.

Additionally, the proportion of participants with C150days >7.5 µg/mL will be summarized for each dose. All PK parameters and the number of participants with C150days >7.5 µg/mL will be summarized by dose and body weight group at time of administration of MK-1654 (ie, 2 to 5 kg and >5 kg). In addition, the relationship between PK parameters and body weight will be assessed graphically.

Dose Proportionality for PK

An exploratory analysis will be conducted to preliminarily assess dose proportionality of MK-1654 for each PK parameter of interest separately ($AUC_{0\text{-inf}}$, C_{max}, C150days, and C365days). Separately for each naturally log-transformed PK parameter, a linear model with ln (dose) as a covariate will be used to estimate the overall slope. A plot of the observed PK data versus dose will be provided along with an overall estimated regression line on the raw scale and a 95% Schéffe confidence band. Dose proportionality of the PK parameters may also be assessed using dose on the linear and ordinal scales as a covariate.

Descriptive Statistics for PK

Individual values will be listed for each PK parameter ($AUC_{0\text{-inf}}$, C_{max}, C7days, C14days, C90days, C150days, C365days, T_{max} and $t_{1/2}$) by dose and panel, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

Anti-drug Antibodies (ADAs

The proportion of patients who develop ADAs and/or the ADA titers will be summarized at each dose level and time point. The distribution of positive titers will be examined graphically for each dose level and time point. The association between ADA positivity and/or titers and PK parameters will be evaluated for each dose at the time points where both results are available.

9.6.2 Statistical Methods for Safety Analyses

Safety data from participants who receive placebo will be pooled across the panels for the safety summaries. If the same dose of MK-1654 is administered in more than one panel, those panels will be pooled for the safety summaries. Summary statistics and plots will be generated for VS as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events. Patient-reported outcomes will include temperature and AEs reported in the electronic diary card.

Descriptive summaries (point estimates) by MK-1654 dose group and placebo will be provided for all safety parameters. In addition, within-group 95% CIs (based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]) will be provided for the following safety endpoints for each MK-1654 dose group and placebo:

- The proportion of participants with elevated temperature (≥102.2°F [39.0°C] rectal or ≥101.7 °F [38.7°C] axillary equivalent) from Day 1 through Day 5 post-dose;
- The proportion of participants with solicited systemic AEs (irritability, drowsiness, fever, and appetite lost) Day 1 to Day 5 post-dose;
- The proportion of participants with solicited injection reaction AEs (redness/erythema, swelling, and pain/tenderness) Day 1 to Day 5 post-dose;
- The proportion of participants with solicited AEs of allergic reactions (hives or welts, lip swelling, wheezing, and difficulty breathing) Day 1 to Day 30 post-dose;
- The proportion of participants with respiratory AEs Day 1 through Day 365 post-dose
- The proportion of participants with any other unsolicited non-serious AEs Day 1 through Day 14 post-dose;

- The proportion of participants with any AE, a drug-related AE, a SAE, a death, an AE which is both drug-related and serious, and an AE which leads to discontinuation.

The proportion of participants with specific AEs or System Organ Classes will be summarized using point estimates only. For Panels C, D, and E where MK-1654 will be administered as 2 divided-dose IM injections, the injection-site AEs will be summarized separately for each injection site and combined across the 2 injection sites.

9.7 Interim Analyses

Interim analyses of safety and PK data will be performed for making dose escalation decisions between the panels. The decision to escalate the dose between Panels A and B and Panels B and C will be made based on review of: 1) available safety data through at least Day 14 for at least 50% of participants in the previous panel(s); and 2) available PK data from the previous panel(s). Ongoing safety monitoring and PK analyses will continue throughout Panels A, B, and C.

The decision to dose escalate between Panels C and D in pre-term infants and between Panel C in pre-term infants and Panel E in full-term infants, and on the dose level(s) in Panels D and E (up to 100 mg), will be made in an siDMC meeting based on review of: 1) available safety data through at least Day 14 from Panels A, B, and C; 2) PK data through Day 90 for evaluable participants in Panel A and PK data through Day 30 for at least 50% of evaluable participants in Panel B; and 3) available PK data from Panel C.

An interim analysis of safety and PK data will be performed when all evaluable pre-term infant participants from Panels A and B and at least 10 pre-term infant participants from Panel C have completed their Day 150 visit. Available safety and PK data from Panels D and E will be included in this analysis. Group-level summaries will be reviewed by the Sponsor study team in order to make scientific decisions for future studies.

9.8 Multiplicity

Since there are no formal hypothesis tests in this study, no adjustment will be made for multiplicity.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Safety Analyses

The probability of observing at least one SAE in this study depends on the number of participants dosed and the underlying percentage of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 144 participants in any MK-1654 dose group if the underlying incidence of a SAE is 1.2% (1 of every 83 participants receiving MK-1654). There is a 50% chance of observing at least one SAE among 144 participants in any MK-1654 dose group if the underlying incidence of a SAE is 0.5% (1 of every 200 participants receiving MK-1654). If no SAEs are observed

among the 144 participants in any MK-1654 dose group, this study will provide 97.5% confidence that the underlying percentage of participants with a SAE is <2.5% (1 in every 40 participants) in any MK-1654 dose group.

9.9.2 Sample Size and Power for Pharmacokinetic Analyses

An estimate of variability was obtained from the available data from Study P001. The largest variability computed for any PK parameter in that study was 0.45 (standard deviation on natural log scale). Since the variability in the PK of pre-term and full-term infants is expected to be larger than the variability in healthy adults, the log scale standard deviation was assumed to be 1 and 1.5 for computing the precision around the estimate of the GM C150days.

Assuming that there are 27 out of 32 evaluable participants (85% evaluability rate) on MK-1654 in each of Panels B, D, and E, at Day 150, the 95% CIs for various hypothetical GM C150days and natural log scale standard deviation estimates are displayed in Table 3.

Table 3 95% CIs for Varying Standard Deviations and GM C150days with 27 Evaluable Participants on MK-1654 in Panels B, D, and E

Standard Deviation on Natural Log Scale	MK-1654 GM C150days			
	5	7	10	15
1.0	(3.37, 7.43)	(4.71, 10.40)	(6.73, 14.85)	(10.10, 22.28)
1.5	(2.76, 9.05)	(3.87, 12.67)	(5.52, 18.10)	(8.29, 27.15)

C150days=concentration in blood at 150 days; CI=Confidence Interval; GM=Geometric Mean.

9.10 Subgroup Analyses

Not applicable for this study.

9.11 Compliance (Medication Adherence)

Not applicable for this study.

9.12 Extent of Exposure

The number of participants receiving MK-1654 and placebo will be summarized by dose group.

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 and Dohme Corp., a subsidiary of Merck & Co., Inc. (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, 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. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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.

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 fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated.

When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees 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. 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, commonly 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

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 report form 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 prior to transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate Standing Internal Data Monitoring Committee (siDMC) will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an

appropriate frequency (Section 9.7 Interim Analyses) for evidence of adverse effects of study intervention and for dose selection (escalation) per Section 6.6 and the Dose Escalation Diagram in Section 1.2, as described in the detailed monitoring guidelines. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

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 International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (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 trial 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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of good clinical practice); 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 Studies.

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 signed ICF, 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. 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 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by your local laboratory.
- 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 4 Protocol-required Screening Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential:[2] Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	Blood Urea Nitrogen (BUN)[1]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine[3]	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	

MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell.
NOTES:

1 Urea is acceptable if BUN is not available as per institutional standard.

2 Absolute or % acceptable per institutional standard.

3 Glomerular Filtration Rate (measured or calculated) or creatinine clearance can be used in place of creatinine.

Investigators must document their review of each laboratory safety report. Only the laboratory assessments outlined in the inclusion/exclusion criteria are considered for study eligibility.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1 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, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- 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."

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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 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 pre-existing condition that has not worsened is not an SAE. A pre-existing 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.

10.3.3 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

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

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

Assessment of intensity

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

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.3. 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 activities of daily living (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

- The investigator will also make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing awareness of symptoms, but easily tolerated.

    - Moderate: An event that causes sufficient discomfort, definitely acting like something is wrong.

- Severe: An event that causes the participant to be extremely distressed or unable to do usual activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

- Injection site redness or swelling from the day of injection through Day 5 post-dose will be evaluated by maximum size.

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 medically qualified assessment of causality was done. This initialled 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 (diary, etc.), seroconversion or identification of vaccine virus 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 vaccine-induced effect?

  - **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?

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the 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 vaccine 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 his/her 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.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to 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 his/her 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.

10.3.5 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 electronic data collection (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 Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Not applicable for this study in infants.

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

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 drugs/vaccines may interact with
- 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

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 the participant's legally acceptable representative, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participant's legally acceptable representative on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant's legally acceptable representative 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

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link the participant's 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 gender, age, medical history and treatment 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

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing 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. 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

Participants and/or a legally acceptable representative may withdraw consent for future biomedical research and ask that the participant's biospecimens not be used for future biomedical research. Participants and/or a legally acceptable representative may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main 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

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

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

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

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@merck.com.

13. References

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

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase (serum glutamic-pyruvic transaminase [SGPT])
APaT	All participants as treated
ARI	Acute respiratory infection
AST	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase [SGOT])
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time 0 extrapolated to infinity
C#days	Concentration in blood at # days
CDC	Centers for Disease Control
CI	Confidence interval
C_{max}	Maximum concentration in blood
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
EDC	Electronic data collection
EMA	European Medicines Agency
F protein	Fusion protein
FDAAA	Food and Drug Administration Amendments Act
FIH	First-In-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM	Geometric mean
HBsAg+	Hepatitis B surface antigen
HCV	Hepatitis C
HHS	Health and Human Services
HIV	Human immunodeficiency virus
hMPV	Human metapneumovirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous(ly)
LRI	Lower respiratory tract infection
mAb	Monoclonal antibody
NCI	National Cancer Institute
NREVSS	National Respiratory and Enteric Virus Surveillance System
PK	Pharmacokinetic(s)
PK/PD	Pharmacokinetic(s)/pharmacodynamic(s)

Abbreviation	Expanded Term
PP	Per protocol
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
siDMC	Standing internal Data Monitoring Committee
SNA	Serum neutralizing antibodies against RSV
SoA	Schedule of Activities
$t_{1/2}$	Half-life
T_{max}	Time to maximum concentration in blood
USP	United States Pharmacopeia
VS	Vital signs
WBC	White blood cell

11. REFERENCES

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