Official Protocol Title:	A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants
NCT number:	NCT04767373
Document Date:	02-Dec-2022

Title Page

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Protocol Title: A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants

Protocol Number: 004-05

Compound Number: MK-1654

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	130097
EudraCT	2020-002405-26
EU CT	2022-500350-42-00

Approval Date: 02 December 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 5	02-DEC-2022	The key reasons for this amendment are to: 1) allow for over enrollment of participants in the study and 2) allow for local sourcing of placebo.
Amendment 4	01-APR-2022	The primary purpose of this amendment is to: 1) Clarify that blood collection for participants with an anaphylaxis or hypersensitivity AESI of Grade 3 or 4 is to assay for potential ADA to MK-1654, and additional ADA characterization, if indicated; 2) Add China-specific protocol requirements for a separate, additional swab collection for COVID-19 testing.
Amendment 3	29-SEP-2021	The primary purpose of this amendment is to: 1) Provide additional guidance on respiratory infection assessment and nasopharyngeal (NP) sample collection; and 2) Add China-specific protocol requirements.
Amendment 2	23-APR-2021	The purpose of this amendment is to address regional Health Authority feedback.
Amendment 1	08-FEB-2021	The primary purpose of this amendment is to add changes that align with the pediatric development plan and changes in severity grading of adverse events, which has been adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.
Original Protocol	28-JUL-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

The key reasons for this amendment are to: 1) allow for over enrollment of participants in the study and 2) allow for local sourcing of placebo.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema Section 4.1 Overall Design Section 6.3.2 Stratification Section 8.13.4 Early Withdrawal Visit Section 9.1 Statistical Analysis Plan Summary Section 9.7 Interim Analyses Section 9.9.1.1 Sample Size and Power for Testing the Primary Efficacy Hypothesis	• Updated content to allow for over enrollment up to 10%. Made updates for these additional participants to be enrolled and followed through Day 365 (RSV Season 1 only). • Adjusted the early and moderate pre-term infant enrollment from *at least 20% of participants* to *at least 600 participants*.	• To ensure that a sufficient number of participants are enrolled to support registration. Additional participants do not need to be followed through Day 515. • Adjusted early and moderate pre-term infant enrollment to align with absolute count originally anticipated to be enrolled.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 6.1 Study Intervention(s) Administered Section 6.2.1 Dose Preparation	• Removed "USP" from placebo description. • Changed dose formulation from vial to sterile solution. • Added local sourcing option for placebo.	Allow for local sourcing of placebo.
Title Page Section 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Title Page	Added EU CT study identifier.	EU CT number now available.
Section 1.1 Synopsis Section 6.1 Study Intervention(s) Administered	Descriptions of Use and NIMP have been updated: • NIMP to NIMP/AxMP • For use, experimental to test product; placebo to comparator The note in Table 2 describing the classification IMP and NIMP/AxMP was edited accordingly.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council

Section # and Name	Description of Change	Brief Rationale
Section 1.3.2 Schedule of Activities – RSV Season 2 (First 1650 Participants)	Removed "Start of RSV Season 2 follow-up" and "End of RSV Season 2 follow-up" from Visits 7 and 8, respectively, and the notes.	The beginning and end of the RSV Season 2 may not align with study Days 365 and 515, respectively, due to the changing epidemiology of RSV disease due to the COVID-19 pandemic.
Section 4.4 Beginning and End of Study Definition	Added text defining the local start of the study for countries in the European Economic Area as First Site Ready in any Member State.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council
Section 5 Study Population	Added text regarding the Code of Conduct for Clinical Trials at the beginning of this section.	To clarify the collection, use, and confidentiality of demographic data provided by the participants.
Section 8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events Section 10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added definitions for medication error, misuse, or abuse and the need for investigator to report instances as an AE or SAE.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council
Section 8.13.3 Delay in Randomization and Study Medication Administration	Text was updated to associate Day 1 with the day study medication is administered, not the day screening procedures are performed.	Clarification to define Day 1 if screening and dosing do not occur the same day.

Section # and Name	Description of Change	Brief Rationale
Section 9.4.1 Efficacy/ Pharmacokinetics/ Pharmacodynamics/ Immunogenicity Endpoints	Tertiary efficacy endpoints were added to evaluate RSV-associated outpatient and inpatient ARI.	To evaluate efficacy endpoints of interest for the study.
Section 10.1.7 Compliance with Law, Audit, and Debarment	Added content to immediately report any serious/suspected serious breaches.	Per Regulation (EU) No 536/2014 of the European Parliament and of the Council
Section 8.1.1.1 General Informed Consent Section 10.7.3 China	Added specifications for informed consent for participants in China.	Align with local regulatory guidelines.
Section 10.7.3 China	Updated timing of COVID-19 swab collection.	Clarification and to align with standard of practice.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants

Short Title: Efficacy and Safety of MK-1654 in Healthy Pre-term and Full-Term Infants

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

The following objectives will be evaluated in healthy pre-term and full-term infants receiving a single IM dose of MK-1654 or placebo.

Primary Objectives	Primary Endpoints
- To evaluate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose. Hypothesis: Administration of MK-1654 reduces the incidence of RSV-associated MALRI from Days 1 through 150 postdose compared to placebo (The statistical criterion for success requires the lower limit of the 95% CI for efficacy to be greater than 25%).	- RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting: - Cough or difficulty breathing; AND - 1 or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms; AND - RSV-positive RT-PCR NP sample

- To evaluate the safety and tolerability of MK-1654 compared to placebo as assessed by the proportion of participants experiencing AEs.	- Solicited injection-site AEs from Days 1 through 5 postdose - Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C), from Days 1 through 5 postdose - Solicited systemic AEs from Days 1 through 5 postdose - Anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose - Rash AESI from Days 1 through 42 postdose - Nonserious AEs from Days 1 through 42 postdose - SAEs through the duration of study participation
Secondary Objectives	Secondary Endpoints
- To evaluate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated hospitalization from Days 1 through 150 postdose. Hypothesis: Administration of MK-1654 reduces the incidence of RSV-associated hospitalization from Days 1 through 150 postdose compared to placebo (The statistical criterion for success requires the lower limit of the 95% CI for efficacy to be greater than 0%).	- RSV-associated hospitalization, defined as the following: - Hospital admission for respiratory illness; AND - RSV-positive RT-PCR NP sample
- To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose.	- RSV-associated MALRI (outpatient and inpatient), defined as above

Overall Design:

Study Phase	Phase 2/Phase 3
Primary Purpose	Prevention
Indication	Respiratory syncytial virus infection
Population	Healthy pre-term and full-term infants
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3.5 years from the time the first participant's legally acceptable representative provides documented informed consent until the last participant's last study-related contact. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 3300 participants will be allocated/randomized in this study as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
MK-1654	MK-1654	105 mg dose (150 mg/mL dose strength)	Single dose	IM	Single dose at Visit 1 (Day 1)	Test product
Placebo	Placebo	0 mg	Single dose	IM	Single dose at Visit 1 (Day 1)	Placebo

Admin.=administration; IM=intramuscular.

Total Number of Intervention Groups/ Arms

2 intervention groups

Duration of Participation

Each participant will be screened, randomized, and receive the assigned study intervention on Day 1 and will be followed for either 365 days or 515 days. The first 1650 participants (300 from the Phase 2b cohort and the first 1350 from the Phase 3 cohort) will participate in the study for approximately 515 days from the time the participant's legally acceptable representative provides documented informed consent through the final contact. The remainder of participants in the Phase 3 cohort will participate in the study for 365 days from the time the participant's legally acceptable representative provides documented informed consent through the final contact.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance and SAC considerations are outlined in Appendix 1 (Section 10.1.4).	

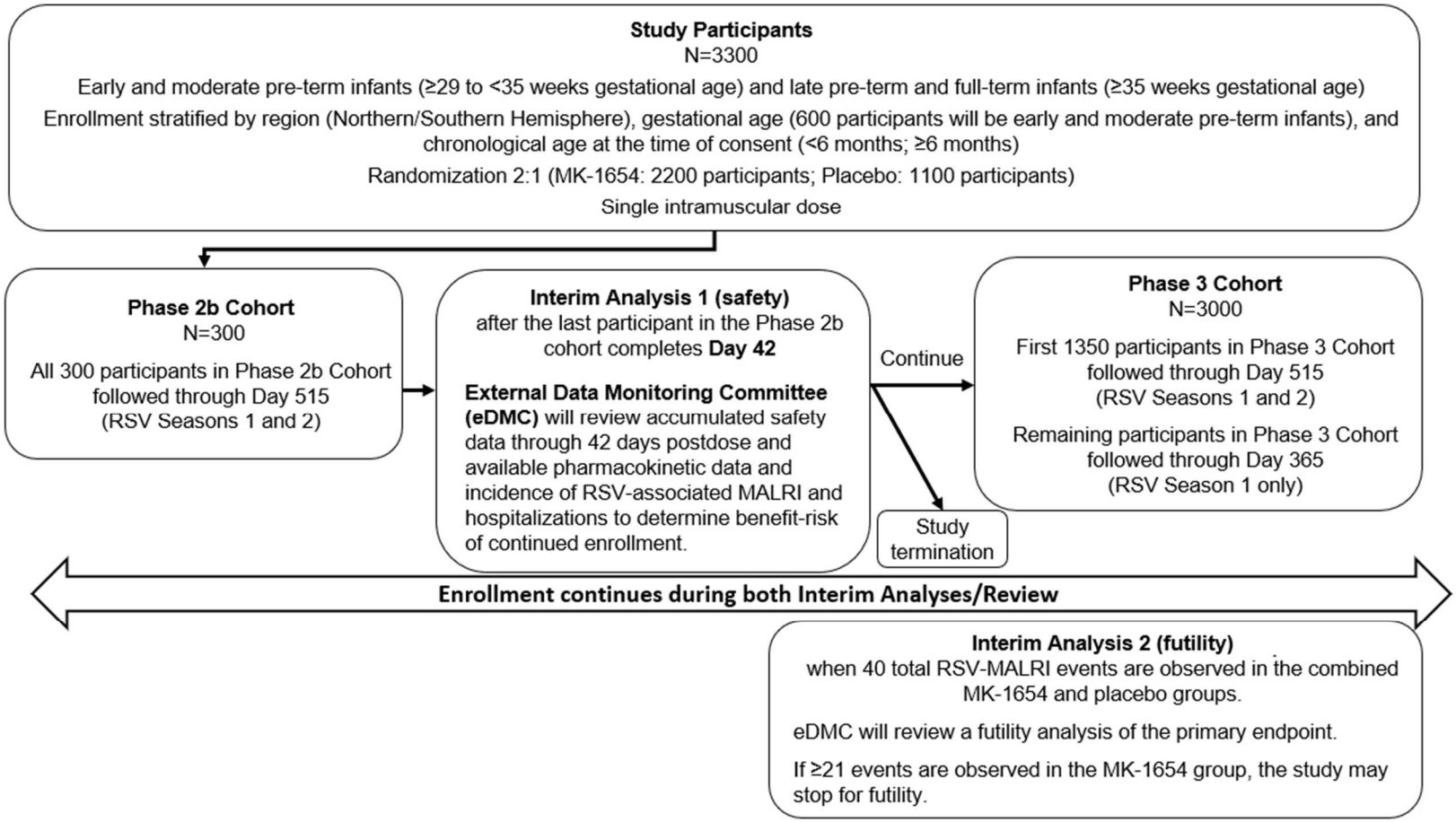
Study Accepts Healthy Volunteers: Yes

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 MK-1654-004 Study Design



1.3 Schedule of Activities

1.3.1 Schedule of Activities – RSV Season 1 (All Participants)

Study Period	Screening, Randomization, and Intervention			Follow-up (through 365 days postdose)											Notes
Visit Number/Title	1			TC	2	Weekly TC start	3	4	5	Weekly TC end	6	TC	7	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment, if indicated.
Scheduled Day and Window (Days):	Day 1			3	7 +2	14 ±2[a]	42 +2	90 ±5	150 ±5	180 ±2[a]	240 ±5	300 ±5	365 +14[b]		[a] Weekly TCs will start at Day 14 and end at Day 180; each weekly TC should occur within 1 week ±2 days of the prior TC. [b] The Visit 7 window (+14 days) applies to participants who complete the study at this visit. For participants who continue on to RSV Season 2, see Section 1.3.2.
	Pre dose	Dose	Post dose												
Administrative Procedures															
Informed Consent	X														
Informed Consent for FBR	X														Participation in FBR is optional and consent must be obtained before collection of buccal swab DNA samples. Not applicable for participants in China (see Appendix 7).
Inclusion/Exclusion Criteria	X														
Participant Identification Card	X														Randomization number will be added to the card.
Medical History	X														
Prior/Concomitant Medication Review	X		X	X	X	X	X	X	X	X	X	X	X	X	After Day 42, only record concomitant medications associated with an SAE.
Predose NP Sample Collection for RT-PCR Testing	X (if indicated)														Collect if respiratory infection symptoms are present within 7 days before Visit 1. See Section 8.13.1.1 and Section 8.2.3.
Assignment of Randomization Number	X														

Study Period	Screening, Randomization, and Intervention			Follow-up (through 365 days postdose)											Notes
Visit Number/Title	1			TC	2	Weekly TC start	3	4	5	Weekly TC end	6	TC	7	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment, if indicated.
Scheduled Day and Window (Days):	Day 1			3	7 +2	14 ±2[a]	42 +2	90 ±5	150 ±5	180 ±2[a]	240 ±5	300 ±5	365 +14[b]		[a] Weekly TCs will start at Day 14 and end at Day 180; each weekly TC should occur within 1 week ±2 days of the prior TC. [b] The Visit 7 window (+14 days) applies to participants who complete the study at this visit. For participants who continue on to RSV Season 2, see Section 1.3.2.
	Pre dose	Dose	Post dose												
MK-1654 or Placebo Administration		X													
Provide or Configure Device for eDiary Data Collection and Provide LAR Training			X												Review instructions for daily eDiary use with LAR (see Section 8.3.5). Instruct LAR on how to detect AESI (see Section 8.4.8 and AESI guidance document).
Review eDiary Data with LAR				X	X	X	X								
Collect eDiary Device from LAR							X								For participants using a study-provided device, collect after the 42-day period.
Safety Procedures															
Full Physical Examination including Weight and Length	X														
Brief Directed Physical Examination including Weight and Length					X		X	X	X		X		X	X[c]	Measure weight and length at all visits. [c] Perform brief directed examination at an unscheduled visit if necessary.
Vital Signs	X		X		X		X	X	X		X		X	X	See Section 8.3.2.
30-minute Postdose Safety Observation			X												Performed by blinded site staff only. Postdose vital signs should be repeated after the observation period.

Study Period	Screening, Randomization, and Intervention			Follow-up (through 365 days postdose)											Notes
Visit Number/Title	1			TC	2	Weekly TC start	3	4	5	Weekly TC end	6	TC	7	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment, if indicated.
Scheduled Day and Window (Days):	Day 1			3	7 +2	14 ±2[a]	42 +2	90 ±5	150 ±5	180 ±2[a]	240 ±5	300 ±5	365 +14[b]		[a] Weekly TCs will start at Day 14 and end at Day 180; each weekly TC should occur within 1 week ±2 days of the prior TC. [b] The Visit 7 window (+14 days) applies to participants who complete the study at this visit. For participants who continue on to RSV Season 2, see Section 1.3.2.
	Pre dose	Dose	Post dose												
AE/SAE Review	X			X	X	X	X	X	X	X	X	X	X	X	
Venous Blood for ADA and Additional ADA Characterization				X (if indicated)										X	Collect if participant experiences a Grade 3 or 4 anaphylaxis/ hypersensitivity AESI on Day 2-42. See Section 8.4.8.1 and Appendix 2.
Respiratory Pathogen Assessments															
Surveillance for Respiratory Infection Symptoms				X	X	←Weekly TC→									Determine if participant had respiratory symptoms or was seen in a clinical setting. Weekly TC after the Day 7 visit through Day 180. See Section 8.2.1.
Respiratory Infection Assessment				X (if indicated)										X	Required if respiratory infection symptoms require further assessment. See Section 8.2.2.
NP Sample Collection for RT-PCR Testing				X (if indicated)										X	Collect if respiratory infection symptoms are observed. See Section 8.2.2.2 and Section 8.2.3. See Appendix 7 for China-specific requirements.

Study Period	Screening, Randomization, and Intervention			Follow-up (through 365 days postdose)											Notes
Visit Number/Title	1			TC	2	Weekly TC start	3	4	5	Weekly TC end	6	TC	7	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment, if indicated.
Scheduled Day and Window (Days):	Day 1			3	7 +2	14 ±2[a]	42 +2	90 ±5	150 ±5	180 ±2[a]	240 ±5	300 ±5	365 +14[b]		[a] Weekly TCs will start at Day 14 and end at Day 180; each weekly TC should occur within 1 week ±2 days of the prior TC. [b] The Visit 7 window (+14 days) applies to participants who complete the study at this visit. For participants who continue on to RSV Season 2, see Section 1.3.2.
	Pre dose	Dose	Post dose												
Pharmacokinetics/Immunogenicity/Pharmacodynamics															All participants will be randomly assigned by IRT to 1 of the 2 blood sampling groups (Group 1 or Group 2), then assigned to 1 of the 2 testing subgroups (a or b). Collect predose from randomized participants only.
Group 1															
Group 1a:															
Group 1a Venous Blood for MK-1654 PK	X				X				X						
Group 1a Venous Blood for ADA	X								X						See Section 4.2.1.4.1.
Group 1a Venous Blood for SNA	X				X				X						Not applicable for participants in China (see Appendix 7).
Group 1b:															
Group 1b Venous Blood for MK-1654 PK	X				X				X						
Group 1b Venous Blood for ADA	X								X						See Section 4.2.1.4.1.

Study Period	Screening, Randomization, and Intervention			Follow-up (through 365 days postdose)											Notes
Visit Number/Title	1			TC	2	Weekly TC start	3	4	5	Weekly TC end	6	TC	7	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment, if indicated.
Scheduled Day and Window (Days):	Day 1			3	7 +2	14 ±2[a]	42 +2	90 ±5	150 ±5	180 ±2[a]	240 ±5	300 ±5	365 +14[b]		[a] Weekly TCs will start at Day 14 and end at Day 180; each weekly TC should occur within 1 week ±2 days of the prior TC. [b] The Visit 7 window (+14 days) applies to participants who complete the study at this visit. For participants who continue on to RSV Season 2, see Section 1.3.2.
	Pre dose	Dose	Post dose												
Group 2															
Group 2a:															
Group 2a Venous Blood for MK-1654 PK	X								X		X				
Group 2a Venous Blood for ADA	X								X		X				See Section 4.2.1.4.1.
Group 2a Venous Blood for SNA	X								X		X				Not applicable for participants in China (see Appendix 7).
Group 2b:															
Group 2b Venous Blood for MK-1654 PK	X								X		X				
Group 2b Venous Blood for ADA	X								X		X				See Section 4.2.1.4.1.
Future Biomedical Research															
Buccal Swabs (DNA) for FBR	X														Should be obtained predose on randomized and FBR-consented participants only. However, it can be collected at any later study visit after randomization. Not applicable for participants in China (see Appendix 7).

ADA=antidrug antibodies; AE=adverse event; AESI=adverse event of special interest; DNA=deoxyribonucleic acid; eDiary=electronic diary; FBR=future biomedical research; IRT=interactive response technology; LAR=legally acceptable representative; NP=nasopharyngeal; PK=pharmacokinetics; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase-polymerase chain reaction; SAE=serious adverse event; SNA=serum neutralizing antibodies against RSV; TC=telephone call; UNSCH=unscheduled visit.

1.3.2 Schedule of Activities – RSV Season 2 (First 1650 Participants)

Study Period:	Follow-up (365 through 515 days postdose)				Notes
Visit Number/Title:	7	Weekly TC start	8	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection assessment, if indicated.
Scheduled Day and Window (Days):	365 ±5	372 ±2[a]	515 +14	If indicated	RSV Season 2 Visit 7 (Day 365) is the same visit as RSV Season 1 Visit 7 (Day 365). Follow-up will be Days 365 through 515 postdose. [a] Weekly TCs will start at Day 372 and continue until 1 week before the day Visit 8 is scheduled; each weekly TC should occur within 1 week ±2 days of the prior TC.
Administrative Procedures					
Concomitant Medication Review	X	X	X	X	Only record concomitant medications associated with an SAE.
Safety Procedures					
Brief Directed Physical Examination including Weight and Length	X		X	X[b]	Measure weight and length at all visits. [b] Perform brief directed examination at an unscheduled visit if necessary.
Vital Signs	X		X	X	See Section 8.3.2.
SAE Review	X	X	X	X	Only record SAEs.
Respiratory Pathogen Assessments					
Surveillance for Respiratory Infection Symptoms		←Weekly TC→			Determine if participant had respiratory symptoms or was seen in a clinical setting. Weekly TC after Visit 7 through RSV Season 2 follow-up.
Respiratory Infection Assessment	X (if indicated)			X	Required if respiratory infection symptoms require further assessment. See Section 8.2.2.
NP Sample Collection for RT-PCR Testing	X (if indicated)				Collect if respiratory infection symptoms are observed. See Section 8.2.2.2 and Section 8.2.3. See Appendix 7 for China-specific requirements.
Immunogenicity/Pharmacodynamics					
Venous Blood for ADA	X		X		Collected only in the first 750 participants continuing in RSV Season 2. These participants will be from Season 1 Group 1a and Group 2a. For ADA, see Section 4.2.1.4.1.
Venous Blood for SNA	X		X		

ADA=antidrug antibodies; LAR=legally acceptable representative; NP=nasopharyngeal; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase-polymerase chain reaction; SAE=serious adverse event; SNA=serum neutralizing antibodies against RSV; TC=telephone call; UNSCH=unscheduled visit.

2 INTRODUCTION

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 immunization approaches (eg, palivizumab) [American Academy of Pediatrics Committee on Infectious Diseases 2014] [Graham, B. S., et al 2015]. MK-1654 has an extended half-life, and 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.

RSV remains a major health problem in infants (see Section 2.2) as well as adults. Vaccine development has been a longstanding challenge. Passive immunization with a neutralizing mAb against the RSV F protein is a proven prophylaxis approach in infants. Palivizumab (Synagis™, MedImmune) is a prophylactic mAb targeting the RSV F protein 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]. 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] [Graham, B. S., et al 2015]. 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 and Section 2.2.

2.1 Study Rationale

MK-1654 is being developed to prevent RSV infection in infants. Very premature infants, and those with chronic heart and lung disease, are at highest risk for complications of RSV infection, and palivizumab is available for this narrow population. However, the vast majority of RSV infections occur among otherwise healthy pre-term and full-term infants. An efficacious prophylactic agent has the potential to make a substantial positive impact on infant health, caregivers, and the healthcare system. To have the greatest impact on the pediatric RSV disease burden, prophylaxis must be active nearly immediately after birth for infants born in the RSV season. MK-1654 is a fully human anti-RSV mAb being developed to prevent MALRI in infants with a single dose administered before the onset of the RSV season or, for those infants born during the RSV season, soon after birth.

The MK-1654-004 study is being conducted to assess the efficacy and safety, along with PK, of MK-1654 for the prevention of RSV-associated MALRI in healthy pre-term and full-term infants. The study will enroll participants with a chronological age from birth up to 1 year and entering their first RSV season at the time that documented informed consent is provided (see Inclusion Criteria 3 and 4 in Section 5.1); infants 0 through 8 months (ie, up to 8 months and 29 days) of age at the time of consent will comprise at least 90% of the participants (see Section 4.2.1.1.1).

2.2 Background

Burden of RSV Infection in Infants

RSV is the most common cause of bronchiolitis, LRI, and hospitalization in infants. An estimated 74,000 to 126,000 infant hospitalizations in the US 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]. Globally, RSV is estimated to cause 22% of all acute LRI among children <5 years old and 3.4 million episodes of severe acute LRI [Garcia, C. G., et al 2010]. Moreover, mortality from RSV infection is significant, with an estimated 94,600 to 149,400 childhood deaths reported annually worldwide [Shi, T., et al 2015]. The overwhelming majority of these deaths occur in developing countries. In contrast, in the US, 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 healthcare 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.

A prophylactic to prevent RSV infection in the majority of healthy infants remains an unmet medical need.

Pre-term infants, and those with underlying medical conditions, are at risk for severe RSV infection, due to comorbidities, relative immunodeficiency, paucity of maternal RSV-specific antibodies, and/or incomplete airway development or damage [van Drunen Littel-van den Hurk, S. 2012]. A prophylactic mAb targeting the RSV 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 and with medical conditions that place them at risk of complications from this disease [U.S. Prescribing Information 2009] [American Academy of Pediatrics Committee on Infectious Diseases 2014]. In the published controlled study of the IMPact-RSV Study Group, palivizumab reduced RSV hospitalization by approximately 55% compared to placebo in premature and high-risk infants (≤35 weeks gestation and ≤6 months of age; or ≤24 months with a clinical diagnosis of CLD (also referred to as bronchopulmonary dysplasia) requiring ongoing medical treatment within the past 6 months) [Joffe, S., et al 1999] [The IMpact-RSV Study Group. 1998]. The safety and

efficacy of palivizumab were assessed in 2 randomized, double-blind, placebo-controlled studies of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization in participants ≤24 months of age with CLD and infants with premature birth (≤35 weeks gestational age who were ≤6 months of age at study entry) (Trial 1) or hemodynamically significant congenital heart disease (Trial 2). Fever and rash were each reported more frequently in participants who received palivizumab compared to placebo (27% vs. 25% and 12% vs. 10%, respectively). The clinical studies do not suggest that RSV infection was less severe among children hospitalized with RSV infection who received palivizumab for RSV prophylaxis compared to those who received placebo. 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.

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

2.2.1 Pharmaceutical and Therapeutic Background

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, P. R., et al 1995]. Compared to palivizumab, MK-1654 exhibits greater potency both in vitro and in the preclinical cotton-rat model. Substitutions 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. Refer to the IB for additional details.

2.2.2 Preclinical and Clinical Studies

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

In a completed Phase 1a randomized, placebo-controlled, double-blind, single-rising dose study evaluating MK-1654 in healthy adult participants (MK-1654-001, also known as PN001), MK-1654 was generally well tolerated at doses up to 300 mg IM and 3000 mg IV and had an extended half-life as predicted.

In a completed Phase 1 randomized, placebo-controlled, double-blind study evaluating MK-1654 in healthy Japanese male adult participants (MK-1654-003, also known as PN003), single doses of MK-1654 (100 and 300 mg IM, and 300 and 1000 mg IV) were generally well tolerated. No apparent differences in PK parameters were observed between healthy non-Japanese (PN001) and Japanese (PN003) adult participants.

Refer to the IB for additional details on the completed clinical studies of MK-1654.

2.2.3 Ongoing Clinical Studies

A Phase 1b/2a randomized, placebo-controlled, double-blind, single-ascending dose study to evaluate the safety and serum PK of MK-1654 in healthy pre-term and full-term infants (MK-1654-002, also known as PN002) was initiated on 31-AUG-2018 and is fully enrolled. An important objective of PN002 is to characterize the PK and quantify the SNA titer of MK-1654 in this population. Information on the safety and PK of MK-1654 in pre-term and full-term infants will further facilitate clinical development in the target infant population. Administration of MK-1654 has been generally well tolerated in healthy pre-term and full-term infant participants in PN002. No deaths or drug-related SAEs have been reported, and no participants have discontinued from the study due to an AE. Safety-related study pause rules have not been triggered.

A Phase 3 randomized, partially blinded, palivizumab-controlled study (MK-1654-007, also known as PN007) to evaluate the safety, tolerability, and efficacy of MK-1654 versus palivizumab in infants and children at increased risk of severe RSV disease began enrollment on 30-NOV-2021. MK-1654 will be evaluated in infants who are eligible and recommended to receive palivizumab (in accordance with national or local guidelines or professional society recommendations) in their first RSV season. The PK of MK-1654 will also be evaluated in this study population. A secondary purpose of the study is to evaluate the safety, efficacy, and PK of a dose of MK-1654 administered at the start of the second RSV season (RSV Season 2) for eligible participants who continue to be at risk of severe RSV who are entering their second RSV season, regardless of RSV Season 1 treatment assignment group.

Refer to the IB for additional details on the ongoing clinical studies of MK-1654.

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 treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

A total of 2200 healthy infants will receive MK-1654 and 1100 healthy infants will receive placebo in this study. MK-1654 is expected to provide lower incidences of RSV-associated MALRI and RSV-associated hospitalization through the RSV season and a comparable safety profile compared to placebo in the target population (healthy early and moderate pre-term and late pre-term and full-term infants with a chronological age from birth up to 1 year and entering their first RSV season at the time that documented informed consent is provided [see Inclusion Criteria 3 and 4 in Section 5.1]). As stated in Section 2.1 and Section 5.2, the population enrolled in this study is not eligible or recommended to receive palivizumab. The lack of an available RSV prophylaxis for this study population provides the justification for inclusion of the placebo control group.

MK-1654 is a fully human, neutralizing mAb targeting the RSV F protein (see Section 2.2). The currently approved palivizumab is a humanized mAb and also targets the RSV F protein.

A fully human mAb administered only once, like MK-1654, should display a relatively lower risk of hypersensitivity events compared to a humanized mAb like palivizumab that must be dosed multiple times. As with all biologic medications, MK-1654 carries a risk of acute systemic events on exposure, as detailed in the IB. These events can be categorized as common acute systemic injection events, acute hypersensitivity events, and high cytokine release events. The risk of any of these acute systemic injection events after administration of the MK-1654 antibody is considered very low because MK-1654 is a fully human mAb, with modifications at the YTE substitutions in the Fc domain only, and has no endogenous target in humans (refer to the IB for additional details). Administration of MK-1654 as a single injection or 2 divided-dose injections on the same day in ongoing and planned clinical studies further reduces the risk of hypersensitivity events, which were largely seen with re-exposure to palivizumab or motavizumab after multiple monthly doses. Administration of MK-1654 has been generally well tolerated in ongoing clinical studies in healthy infant participants to date (PN002) and in healthy Japanese adult male participants at doses up to 300 mg IM and 1000 mg IV (PN003), with no study pause rules triggered at any point in either study (see Section 2.2.3).

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

The following objectives will be evaluated in healthy pre-term and full-term infants receiving a single IM dose of MK-1654 or placebo.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 postdose. • **Hypothesis**: Administration of MK-1654 reduces the incidence of RSV-associated MALRI from Days 1 through 150 postdose compared to placebo (*The statistical criterion for success requires the lower limit of the 95% CI for efficacy to be greater than 25%*).	• RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting: ▪ Cough or difficulty breathing; AND ▪ 1 or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms; AND ▪ RSV-positive RT-PCR NP sample
• To evaluate the safety and tolerability of MK-1654 compared to placebo as assessed by the proportion of participants experiencing AEs.	• Solicited injection-site AEs from Days 1 through 5 postdose • Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C), from Days 1 through 5 postdose • Solicited systemic AEs from Days 1 through 5 postdose • Anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose • Rash AESI from Days 1 through 42 postdose • Nonserious AEs from Days 1 through 42 postdose • SAEs through the duration of study participation

Objectives	Endpoints
Secondary	
• To evaluate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated hospitalization from Days 1 through 150 postdose. • **Hypothesis**: Administration of MK-1654 reduces the incidence of RSV-associated hospitalization from Days 1 through 150 postdose compared to placebo (*The statistical criterion for success requires the lower limit of the 95% CI for efficacy to be greater than 0%*).	• RSV-associated hospitalization, defined as the following: ▪ Hospital admission for respiratory illness; AND ▪ RSV-positive RT-PCR NP sample
• To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose.	• RSV-associated MALRI (outpatient and inpatient), defined as above
Tertiary/Exploratory	
• To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated severe MALRI (outpatient and inpatient) from Days 1 through 150 postdose.	• RSV-associated severe MALRI, defined as the following seen in an outpatient or inpatient clinical setting: ▪ Cough or difficulty breathing; AND ▪ 1 or more of the following: wheezing, chest wall in-drawing/ retractions, rales/crackles, tachypnea, dehydration due to respiratory symptoms; AND ▪ Severe hypoxemia or the need for high flow nasal cannula, oxygen mask, or mechanical ventilatory support; AND ▪ RSV-positive RT-PCR NP sample

Objectives	Endpoints
• To estimate the efficacy of MK-1654 compared to placebo as assessed by the incidence of RSV-associated hospitalization from Days 1 through 180 postdose.	• RSV-associated hospitalization, defined as above
• To estimate the incidence of MALRI (outpatient and inpatient) due to any cause from Days 1 through 150 postdose for the MK-1654 and placebo groups.	• MALRI (outpatient and inpatient) due to any cause, defined as above
• To describe the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 365 through 515 postdose for the MK-1654 and placebo groups.	• RSV-associated MALRI (outpatient and inpatient), defined as above
• To describe the incidence of RSV-associated hospitalization from Days 365 through 515 postdose for the MK-1654 and placebo groups.	• RSV-associated hospitalization, defined as above
• To describe the serum PK concentration of MK-1654 at Days 7, 150, and 240 postdose.	• MK-1654 PK concentration
• To estimate the incidence and magnitude of ADA to MK-1654 on Day 1 (predose) and Days 150, 240, 365, and 515 postdose.	• Incidence and magnitude (titer) of ADA to MK-1654
• To estimate the level of SNA to RSV A on Day 1 (predose) and Days 7, 150, 240, 365, and 515 postdose.	• Level (titer) of SNA to RSV A
• To determine RSV F gene sequence in NP samples from infants infected with RSV who received MK-1654 or placebo.	• RSV F gene sequence determined by deep sequencing in NP samples from infants infected with RSV

4 STUDY DESIGN

4.1 Overall Design

This is a double-blind with in-house blinding, randomized, placebo-controlled, multi-site study to evaluate the efficacy and safety of MK-1654 for the prevention of RSV-associated MALRI in healthy pre-term and full-term infants. The Sponsor estimates that the study will require approximately 3.5 years from the time that documented informed consent is provided for the first participant until the last participant's last study-related telephone call or visit.

Approximately 3300 healthy male and female infants, from birth up to 1 year of age (see Inclusion Criteria 3 and 4 in Section 5.1) and entering their first RSV season at the time that documented informed consent is provided, will be randomized in a 2:1 ratio to receive a single dose of MK-1654 or placebo. The sample size was selected to ensure collection of adequate safety information on the use of MK-1654 in this otherwise healthy population of pre-term and full-term infants. If sites in China have not met their participant allocation targets after enrollment of the global study is closed, these sites may continue to enroll participants until their allocation targets are met to meet local regulatory requirements (see Appendix 7). Up to an additional 10% of participants may be enrolled to ensure an adequate sample size for the safety evaluation for the program.

Randomization will be stratified according to the following factors:

1. Region:
    - Northern Hemisphere
    - Southern Hemisphere
2. Gestational age:
    - Early and moderate pre-term infants* (≥29 to <35 weeks gestational age)
    - Late pre-term and full-term infants (≥35 weeks gestational age)

    ***Note:** Early and moderate pre-term infants will comprise at least 600 participants.
3. Chronological age at the time of consent**:
    - <6 months of age
    - ≥6 months of age

    ****Note:** Infants 0 through 8 months of age (ie, up to 8 months and 29 days) will comprise at least 90% of the participants.

IRT will be used to meet the enrollment target of at least 90% of participants having a chronological age of 0 through 8 months (ie, up to 8 months and 29 days) at the time of

consent. Infants who are eligible or recommended to receive palivizumab, per national or local guidelines or professional society recommendations, must not be enrolled.

Enrollment will begin during the 4 weeks before the estimated onset of the RSV season and will end before the estimated peak of the RSV season (approximately a 17-week duration in temperate regions during a routine RSV season; see Section 4.2.1.1.1). Infants born before the RSV season should be enrolled before the onset of the RSV season. Infants born during the RSV season should be enrolled as soon as possible after birth. Special considerations for RSV season determination in tropical and subtropical regions, as well as disrupted RSV seasonality (eg, due to COVID-19), are in the regional RSV seasonality guidance document (or equivalent).

This study will include 2 cohorts of participants:

- **Phase 2b cohort:** This is the lead-in portion of the study and will include 300 healthy pre-term and full-term infants. Infants enrolled in this cohort must be >2 weeks of age and up to 1 year of age (see Inclusion Criterion 3 in Section 5.1). Data from this cohort will be reviewed by the eDMC (see IA#1 below).

- **Phase 3 cohort:** Approximately 3000 healthy pre-term and full-term infants from birth to 1 year of age (see Inclusion Criterion 4 in Section 5.1) will be enrolled.

After randomization to MK-1654 or placebo, all participants will also be randomized by IRT to 1 of the 2 different blood sampling groups (Group 1 or Group 2) that differ in the schedule of serum PK, ADA, and SNA sampling (see Section 1.3.1). Participants will then be assigned to 1 of the 2 testing subgroups (a or b) that differ in the types of tests to be performed, as follows:

- Group 1a and Group 2a will have PK, ADA, and SNA in Season 1 (see Section 1.3.1) and ADA and SNA in RSV Season 2 (see Section 1.3.2).

- Group 1b and Group 2b will have PK and ADA only in Season 1 (see Section 1.3.1).

In RSV Season 1, samples for SNA will be collected only in the first 1650 participants randomized. In RSV Season 2, samples for ADA and SNA will be collected only in the first 750 participants (from the 1650 participants continuing to RSV Season 2; these participants will be from Season 1 Group 1a and Group 2a).

This approach provides sufficient safety, PK, ADA, and SNA data to meet study objectives, while minimizing the number of blood draws and total blood volume drawn from each participant during the study. Each participant will have a maximum of 3 planned blood draws during RSV Season 1 and the first 750 participants continuing in RSV Season 2 will have an additional 2 planned blood draws during RSV Season 2.

In the event a participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI postdose, as confirmed by the investigator, an additional blood draw is required for

evaluation for potential ADA to MK-1654, and additional ADA characterization, if indicated (see Section 1.3.1 and Appendix 2).

The approximate maximum blood volume drawn per participant ≥3 kg at each visit is 2.4 mL. Further requirements for the maximum blood draw volume, based on participant weight, are provided in Appendix 2.

All participants will receive the assigned study intervention (MK-1654 or placebo [0.9% sodium chloride, sterile saline]) administered via IM injection on Day 1.

All participants will be followed for 365 days after receiving study intervention (see Section 1.3.1). Efficacy surveillance for respiratory infection symptoms will be conducted for 180 days postdose. All AEs will be collected for 42 days postdose, and SAEs will be collected for the duration of study participation.

A subset of participants (the first 1650 participants enrolled) will continue to be followed throughout the second RSV season, from Days 365 through 515 postdose, in order to have at least 1500 participants complete the follow-up through Day 515 (see Section 1.3.2). No additional study intervention will be administered in RSV Season 2. Weekly surveillance will continue to monitor the incidence of RSV-associated MALRI and hospitalization.

Two IAs (IA#1 and IA#2) are planned for this study and will be conducted by an external unblinded statistician and reviewed by an eDMC (see Section 10.1.4.3).

IA#1: IA#1 will be conducted after the last participant randomized in the Phase 2b cohort completes the Day 42 visit and the safety data are available. The eDMC will review safety data and all available PK data as well as efficacy estimates for the endpoints of RSV-associated MALRI and RSV-associated hospitalization to determine the benefit-risk of continued enrollment (see Section 9.7). During the eDMC review, participant screening and randomization will continue.

IA#2: If the study continues after IA#1, IA#2 for futility evaluation will be conducted when 40 total RSV-associated MALRI cases in the combined MK-1654 and placebo groups have been observed in the study. If ≥21 cases are observed in the MK-1654 group (observed efficacy <50%), the study may stop for futility. Available safety, PK, SNA, and ADA data will also be summarized and reviewed by the eDMC.

If the study does not stop at IA#2, the study will continue as planned. After all participants in the global study (see Appendix 7 regarding enrollment in China) have completed 180 days postdose follow-up, a database lock will be executed, and the Sponsor study team will be unblinded. A separate blinded study team will be appointed to continue assessments for the remainder of the study.

If the study stops after either IA, no further participants will be enrolled; however, participants already enrolled in the study will continue to be monitored for safety for 365 days postdose.

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.

4.2 Scientific Rationale for Study Design

This study will collect efficacy and safety data to evaluate the efficacy and safety of MK-1654 compared to placebo for the prevention of RSV-associated MALRI in the target population (healthy pre-term and full-term infants), in accordance with the 2017 draft FDA Guidance for Industry: *Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment [Food and Drug Administration 2017]*. The study is designed to have a high level of statistical significance for the primary endpoint with >90% statistical power to show the efficacy of MK-1654 compared to placebo for the prevention of RSV-associated MALRI with a lower bound of the 95% CI exceeding 25%.

This study will also assess the PK of MK-1654 for up to 240 days after administration of the single dose of MK-1654 to obtain PK data in this population. A subset of participants (the first 1650 participants randomized) will continue to be followed during RSV Season 2 from 365 to 515 days after administration of the single dose of MK-1654 or placebo in order to have at least 1500 participants complete the follow-up through Day 515. The purpose of this additional follow-up is to monitor the incidence of RSV-associated MALRI and hospitalization in the absence of additional RSV prophylaxis and to collect safety data (SAEs only).

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint for this study is RSV-associated outpatient and inpatient MALRI diagnosed as in Table 1. The diagnostic criteria are based on published literature and information from clinical studies, RSV expert panels, and WHO and CDC guidelines [Manoha, C., et al 2007] [Nair, H., et al 2010] [Simoes, E. A. F., et al 2015]. Cough or difficulty breathing are included based on the case definition for severe and very severe LRI by the expert panel on RSV vaccine development convened by the WHO [Simoes, E. A. F., et al 2015].

RSV-associated MALRI represents most of the RSV disease burden, and is a clinically important and well-defined RSV disease endpoint across geographies and healthcare settings [Nair, H., et al 2010] that has been recommended by RSV prophylaxis trial expert committees [Simoes, E. A. F., et al 2015]. The primary time point for evaluation of efficacy against RSV-associated MALRI will be from Days 1 through 150 postdose (the length of a typical RSV season in a temperate climate).

A secondary time point for evaluation of efficacy against RSV-associated MALRI will be from Days 1 through 180 postdose, as an additional month of efficacy would allow flexibility in healthcare practitioners' timing of dosing MK-1654 and additional coverage for regions with longer RSV seasons (see Section 4.2.1.1.1). An assessment of efficacy against

RSV-associated hospitalization from Days 1 through 150 postdose is also planned as a secondary efficacy endpoint as this is an outcome of clinical importance to healthcare practitioners and healthcare systems.

Table 1 Respiratory Syncytial Virus (RSV)-associated Medically Attended Lower Respiratory Infection (MALRI) Diagnostic Criteria

Signs/Symptoms	Indicators of LRI/Severity	RSV
Endpoint definition requires at least 1 from each column seen in an outpatient or inpatient clinical setting (outpatient clinic, clinical study visit, Emergency Department, urgent care center, or hospital) and confirmed or observed by the investigator.		
• Cough • Difficulty breathing	• Wheezing • Chest wall in-drawing/Retractions • Rales/Crackles • Hypoxemia (SpO_2 <95% on room air at sea level, <92% on room air at altitude ≥1800 m)[a] • Tachypnea (RR ≥60 breaths per minute for <2 months of age; ≥50 breaths per minute for 2 to 12 months of age; or ≥40 breaths per minute for >12 to 24 months of age) • Dehydration due to respiratory symptoms	• RSV-positive RT-PCR NP sample (collected within 12 days of symptom onset or worsening)

LRI=lower respiratory infection; MALRI=medically attended lower respiratory infection; NP=nasopharyngeal; RR=respiratory rate; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase-polymerase chain reaction; SpO_2=oxygen saturation as measured by pulse oximetry.

[a] For severe MALRI: Severe hypoxemia (SpO_2 <90% on room air at sea level; <87% on room air at altitude ≥1800 m) or the need for high flow nasal cannula, oxygen mask, or mechanical ventilatory support.

In addition, RSV-associated hospitalization through 180 days postdose, RSV-associated severe MALRI through 150 days postdose, and RSV-associated MALRI and hospitalization in RSV Season 2 (Days 365 through 515 postdose) are planned as tertiary endpoints. The burden of RSV-associated hospitalizations is described in Section 2.2, and a decrease in hospitalization rate represents a benefit to public health.

An RSV expert panel convened for design of clinical endpoints for RSV prophylaxis studies in 2014 suggested that cough or difficulty breathing be a required component of the LRI clinical endpoint definition [Simoes, E. A. F., et al 2015]. This panel also proposed that the definition of LRI include the presence of lower chest wall in-drawing, or wheezing or crackles, or hypoxemia (SpO_2 <95% on room air at sea level, <92% on room air at altitude ≥1800 m) in a child <5 years of age with cough, tachypnea, or difficulty breathing. Typically, RSV infection starts with several days of mild upper respiratory tract signs, cough, and low-grade fever, followed by lower respiratory tract involvement and a worsening cough, with the infant becoming tachypneic and possibly having progressively more labored breathing, with dyspnea and retractions of the chest wall; crackles and wheezes are the most common

auscultatory signs. Dehydration due to respiratory symptoms encompasses dehydration secondary to inability to feed.

The terms “difficulty breathing” or “labored breathing” are conventional in describing the signs and symptoms of pediatric RSV in the published literature; several recent active surveillance studies have reported a high frequency of difficult or labored breathing in infants and young children with RSV. Among hospitalized infants, it was reported that 81%, 75%, and 73% of infants age 0 to 2 months, 3 to 5 months, and 6 to 11 months had difficulty breathing on admission [Rha, B., et al 2018]. A CDC active surveillance study in children <5 years of age with RSV found that 73%, 85%, and 95% of children presenting to the pediatrician’s office, Emergency Department, and hospital for admission, respectively, had labored breathing [Hall, C. B., et al 2013]. Clinical signs of difficulty breathing or labored breathing may include tachypnea, grunting, nasal flaring, retractions, cyanosis, and/or apnea.

4.2.1.1.1 RSV Season Definition

RSV epidemics begin each year near the equator and 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 RESCEU [You, Li 2017].

In the US, 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 DHHS regions, except in Florida, which has an earlier RSV season onset and longer duration, as reported by the CDC NREVSS [Haynes, A. K., et al 2014]. During the 2013–2014 RSV season, similarly to previous national patterns, RSV began circulating nationally in early November and ended in late March, with circulation peaking at 24% (the number of RSV-positive specimens among all respiratory specimens tested) in late December. The RSV season (onset, offset, peak, and duration) is defined nationally, by DHHS region, and by state, based on CDC analysis of RSV laboratory detections reported to the NREVSS. The CDC and WHO 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 midwinter months [European Medicines Agency 2017]. The European influenza surveillance system captures RSV detection through the ILI or ARI surveillance system from 21 European Union countries, as reported for the 2014-2015 RSV season by the ECDC [European Center For Disease Prevention And Control 2015].

In the Southern Hemisphere, the RSV season is typically April to August, peaking in July in temperate regions. Tropical and subtropical regions have different RSV season profiles, as detailed in the regional RSV seasonality guidance document (or equivalent).

Infants entering their first RSV season are typically under 9 months of age. For example:

- An infant born in the Northern Hemisphere in January during their first RSV season may be enrolled during this RSV season. When the infant is 9 months old, they will be entering their second RSV season.

- An infant born in a temperate region of the Southern Hemisphere in June during their first RSV season may be enrolled during this RSV season. When the infant is 9 months old, they will be entering their second RSV season.

These considerations support enrollment of at least 90% of participants who are 0 through 8 months of age (ie, up to 8 months and 29 days), with up to 10% of the remaining participants ≥9 months of age to allow for potential moves between hemispheres in infancy (ie, where an infant may be 9 to 12 months of age and still in their first RSV season).

The Sponsor will define the expected start and end of the 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 regional RSV seasonality guidance document (or equivalent).

4.2.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the MK-1654 safety profile observed in previous studies, published data from palivizumab, and guidance from regulatory agencies during product development. An eDiary will be used to record AEs during the postdose period as recommended in the 2009 FDA Guidance for Industry: *Patient-Reported Outcome Measures: Use In Medical Product Development To Support Labeling Claims* [U.S. Food and Drug Administration 2009]. See Section 8.3.5 for details on the AEs to be collected on the eDiary.

Certain hypersensitivity and rash AEs are of special interest (AESI) in this study. MK-1654 is a fully human mAb; prior humanized mAbs in this class have had associated hypersensitivity and rash AEs. See Section 8.4.8 for details on the AESI to be collected, further evaluated, and reported. In the event of a Grade 3 or 4 anaphylaxis or hypersensitivity AESI, a blood sample for ADA and additional ADA characterization, if indicated, is also to be collected (see Section 1.3.1 and Section 10.2). Details on the safety endpoints evaluated in this study are provided in Section 8.3 and Section 9.4.2. Details on AEs, including definitions and reporting requirements, are provided in Appendix 3.

4.2.1.3 Pharmacokinetic Endpoints

4.2.1.3.1 MK-1654 Serum Concentration

A sparse PK collection of no more than 3 samples per participant is planned for the pediatric participants in this study. The PK serum collection time points have been developed based on known information from preclinical and clinical studies evaluating MK-1654. MK-1654 concentrations will be measured using a validated bioanalytical assay on samples collected at several time points from Day 1 to Day 240 to determine the PK profile of the molecule, which will provide information regarding the MK-1654 PK profile in the target pediatric population.

Samples for PK will be collected in all participants in RSV Season 1 (see Section 1.3.1).

4.2.1.4 Immunogenicity Endpoints

4.2.1.4.1 Antidrug Antibodies (ADA)

The presence and titer of ADA will be measured in this study. ADA to biologics like MK-1654 may develop and be either clinically inconsequential or change the drug PK. Therefore, ADA incidence and magnitude may be analyzed for association with PK and safety events and, as applicable, for associations with changes in RSV serum neutralizing activity, as described below. In RSV Season 1, samples for ADA will be collected in all participants (see Section 1.3.1). In RSV Season 2, samples for ADA will be collected only in the first 750 participants (from the first 1650 participants continuing to RSV Season 2; these participants will be from RSV Season 1 Group 1a and Group 2a) (see Section 1.3.2). The collected samples will yield a sufficient amount of serum to be used for further characterization of immunogenicity, if needed.

4.2.1.5 Pharmacodynamic Endpoints

4.2.1.5.1 Serum Neutralizing Activity Against RSV

This study will also evaluate the effect of a single dose of MK-1654 on RSV serum neutralizing activity to model the relationship between SNA and efficacy. (**Note:** SNA will not be tested in participants enrolled at sites in China; see Appendix 7.) 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 may 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 ADA. Therefore, unexpected changes in RSV serum neutralizing activity will be examined for associations with respiratory infection and ADA titer.

In RSV Season 1, samples for SNA will be collected only in the first 1650 participants randomized (see Section 1.3.1). In RSV Season 2, samples for SNA will be collected only in the first 750 participants (from the first 1650 participants continuing to RSV Season 2; these participants will be from RSV Season 1 Group 1a and Group 2a) (see Section 1.3.2).

4.2.1.6 Additional Tertiary Endpoints

4.2.1.6.1 RSV F Gene Sequencing and MK-1654 Sensitivity Testing

This study will also evaluate RSV F gene sequence in NP samples from cases of infants infected with RSV who received MK-1654 or placebo. To assess for the potential emergence or selection of MK-1654 resistance, the entire F protein coding region will be sequenced and variants with substitutions in the MK-1654 binding site/highly conserved sites/unusual substitutions at polymorphic sites will be tested for sensitivity to MK-1654.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA),

proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

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

4.2.2 Rationale for the Use of Placebo

The primary goals of the study are to evaluate the efficacy of MK-1654 compared to placebo (sterile 0.9% saline) in preventing RSV-associated outpatient and inpatient MALRI and to evaluate the safety and tolerability of MK-1654 in the target infant population. There is no agent currently approved for RSV prophylaxis in healthy full-term infants, and pre-term enrollment in this study is restricted to infants not eligible or recommended for palivizumab; therefore, there is no approved agent suitable for use as a comparator in this study.

A placebo-controlled study is needed to establish baseline RSV disease and will allow for an unbiased assessment of the efficacy, safety, and tolerability of MK-1654. Secondary and tertiary outcomes are also supported by the use of placebo, including 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.

4.3 Justification for Dose

The dose of MK-1654 (105 mg) in this study was determined based on the results of robust modeling analyses, which included data from the Phase 1b/2a dose-finding study in the target pediatric population (PN002) (see Section 2.2.3). The dose was selected based on the totality of information, including preclinical data, published clinical data for anti-RSV mAbs, and PK/pharmacodynamic modeling based on data in adults (PN001, up to 300 mg IM and 3000 mg IV) and the target pediatric population (PN002, up to 100 mg IM). Modeling results indicated that a dose of 105 mg in an infant's first year of life has a high likelihood of providing high efficacy for the prevention of RSV-MALRI in the target population.

Data from the ongoing Phase 1b/2a study in the target population (PN002) has provided no evidence for contraindications to the administration of MK-1654 via the IM route in infants in this study. Doses up to 100 mg have been administered to pre-term infants in PN002. No deaths, treatment-related SAEs, hypersensitivity AEs, discontinuations due to AEs, or dose-dependent pattern of treatment-related AEs have been reported in PN002. PK modeling predicts that exposures (C_{max} and $AUC_{0-\infty}$) after a 105-mg dose in infants in their first RSV season will be 8- and 5-fold lower, respectively, than the highest well-tolerated exposures observed in healthy adults (PN001).

Refer to the IB for additional information.

4.4 Beginning and End of Study Definition

The overall study begins when documented informed consent is provided for the first participant. For the purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant's legally acceptable representative is unable to be contacted by the investigator), whichever comes last.

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

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Healthy male and female infants who have a chronological age from birth up to 1 year and are entering their first RSV season at the time of consent will be enrolled in this study.

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

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is healthy (based on medical history and physical examination results). Healthy is defined as the absence of medical conditions or acute illnesses (beyond mild symptoms requiring no more than minimal medical intervention). Any congenital or chronic medical conditions should be stable.

Demographics

2. Is male or female and is an early or moderate pre-term infant (≥29 to 34 weeks and 6 days gestational age) or a late pre-term or full-term infant (≥35 weeks gestational age).

3. For the **Phase 2b cohort only**: Has a chronological age >2 weeks of age up to 1 year and is entering their first RSV season at the time that documented informed consent is provided. (See Appendix 7 for age requirements specific for participants who are enrolled at sites in countries from the European Union or the United Kingdom.)

4. For the **Phase 3 cohort only**: Has a chronological age from birth up to 1 year and is entering their first RSV season at the time that documented informed consent is provided. (See Appendix 7 for age requirements specific for participants who are enrolled at sites in countries from the European Union or the United Kingdom.)

5. **For South Korea only:** Participant weighs ≥2 kg. (See Appendix 7 for weight requirements specific for participants who are enrolled at sites in South Korea.)

Informed Consent

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

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

1. Is eligible or recommended to receive palivizumab per national or local (eg, state or provincial) guidelines or professional society recommendations.

Medical Conditions

2. Has known hypersensitivity to any component of MK-1654 (refer to the IB for a list of components).

3. Has a bleeding disorder contraindicating intramuscular administration.

4. Has had a recent illness with rectal temperature ≥100.5°F (≥38.1°C) or axillary temperature ≥100.0°F (≥37.8°C) within 72 hours predose.
   Note: If the participant meets this exclusion criterion, the participant may be rescreened when this criterion is not met.

Prior/Concomitant Therapy

5. Has received any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy.

Prior/Concurrent Clinical Study Experience

6. Is currently participating in or has participated in an interventional clinical study with an investigational compound or device at any time before 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.

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

Diagnostic Assessments

Not applicable.

Other Exclusions

8. 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.

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

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

Table 2 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Type	Dose Formu-lation	Unit Dose Strength	Dosage Level	Route of Admini-stration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
MK-1654	Experimental	MK-1654	Biological/ Vaccine	Vial	150 mg/mL	105 mg	IM	Single administration	Test Product	IMP	Sponsor
Placebo	Placebo Comparator	Placebo	Other	Sterile Solution	0 mg/mL	0 mg	IM	Single administration	Placebo	IMP	Sponsor or local

EEA=European Economic Area; IM=intramuscular; IMP=investigational medicinal product; NIMP/AxMP-noninvestigational/auxiliary medicinal product.

Placebo=Sterile saline 0.9% sodium chloride injection. Equivalent volumes of saline will be used to correspond with the respective dose level.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. 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, sterile saline) will be prepared by an unblinded pharmacist or medically qualified study personnel (see Section 6.3.3).

Study intervention should be equilibrated to room temperature prior to dose administration, and the syringes for IM injection should be prepared shortly before administration, per the instructions provided in the pharmacy manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to MK-1654 or placebo.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Region:
    - Northern Hemisphere
    - Southern Hemisphere
2. Gestational age:
    - Early and moderate pre-term infants* (≥29 to <35 weeks gestational age)
    - Late pre-term and full-term infants (≥35 weeks gestational age).

    ***Note:** Early and moderate pre-term infants will comprise at least 600 participants.
3. Chronological age at the time of consent**:
    - <6 months of age
    - ≥6 months of age

    ****Note:** Infants 0 through 8 months of age (ie, up to 8 months and 29 days) will comprise at least 90% of the participants.

6.3.3 Blinding

A double-blinding technique will be used. MK-1654 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel otherwise not 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, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Participant study intervention compliance is defined in this study as a participant who receives the protocol-specified single dose of MK-1654 or placebo. Any changes in the protocol-specified study intervention plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

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 and time of administration, must be recorded on the appropriate eCRF as outlined in the data entry guidelines.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from the study 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.

Specifically, if a participant receives palivizumab after randomization, discontinuation from the study may be required after discussion with the Sponsor Clinical Director.

Participants should receive recommended childhood vaccines in alignment with local/national immunization guidelines. The site staff should follow their local/national immunization recommendations for administering multiple injectable vaccines at the same visit. Any licensed COVID-19 vaccine (including for emergency use) in a particular country is allowed to be used in the study as recommended per local and national immunization guidelines, as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. Investigational vaccines (ie, those not licensed or approved for emergency use) are not allowed.

If any injectable vaccine(s), including recommended childhood vaccines or licensed COVID-19 vaccines, are given at Visit 1 (when study intervention is given), they should be administered in the contralateral (opposite) thigh from that used for study intervention to avoid confounding results. If possible, multiple injection sites on the same limb should be separated by 1 inch or more.

On the day that study intervention is administered, any concomitant vaccinations should be administered **AFTER** the 30-minute postdose observation period of the study intervention.

Also, the participant must wait at the site for an additional 15 minutes postconcomitant vaccination to observe for any AEs (see Section 8.3.4).

Any concurrent medications, vaccines, or medical treatments must be recorded on the appropriate eCRF as described in Section 8.1.5.2.

Allowed rescue medications and supportive care are discussed in Section 6.5.1.

6.5.1 Rescue Medications and Supportive Care

As the purpose of the study is to characterize the safety and efficacy profile of MK-1654, prophylactic premedications to reduce the risk of injection reactions should not be given to participants before administration of study intervention. However, medications such as paracetamol and acetaminophen may be administered postadministration of study intervention for minor ailments without prior consultation with the Sponsor.

Participants should receive appropriate supportive care measures as deemed necessary by the treating physician.

As a precaution, study sites should have medications and support to treat hypersensitivity reactions available at the time of study intervention administration.

Any AEs will be reported according to the guidelines in Section 8.4 and Appendix 3. All concomitant medications and medical interventions will be reported in the appropriate eCRFs.

6.6 Dose Modification

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur prior to the intervention and generally represents withdrawal from the study.

Participants who receive a single-dose intervention cannot discontinue 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 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's legally acceptable representative 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's legally acceptable representative, 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 participant's 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 pre-specified 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.

- 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.

Blood Collection and Maximum Blood Volumes

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 volume [European Commission 2017]. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Each participant should have a maximum of 3 planned blood draws during RSV Season 1 and the first 750 participants continuing in RSV Season 2 should have an additional 2 planned blood draws during RSV Season 2 (see Section 1.3.2 and Table 11).

The maximum amount of blood obtained from each participant is dependent upon the participant's weight at the visit. If the participant does not meet the weight requirement of ≥3 kg, then the maximum blood draw volume should be reduced according to criteria in Table 12. The approximate maximum blood volume drawn per participant ≥3 kg at each visit is 2.4 mL (Table 11). The approximate total maximum blood volume drawn per participant ≥3 kg in RSV Season 1 is 7.2 mL and for those participants continuing into RSV Season 2, the approximate total maximum blood volume drawn is 12.0 mL (combined RSV Season 1 and RSV Season 2, Table 11). In the event a participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI postdose, an additional blood draw of 1.2 mL is required for evaluation for potential ADA to MK-1654, and additional ADA characterization, if indicated (see Section 1.3.1 and Appendix 2).

Study sites should follow infection control and prevention practices, per local guidelines, for encounters with legally acceptable representatives and/or participants, including practices pertaining to control and prevention of COVID-19.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant's legally acceptable representative prior to participating in this 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant's legally acceptable representative must be documented on a consent form (see Appendix 7 for China-specific requirements). The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant's legally acceptable representative and of the person conducting the consent discussion.

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

The initial ICF, any subsequent revised ICF, and any written information provided to the participant's legally acceptable representative must receive the 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 participant's legally acceptable representative's dated signature.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant's legally acceptable representative, answer all of his/her questions, and obtain documented 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 before performing any procedure related to future biomedical research.

8.1.2 Inclusion/Exclusion Criteria

Before randomization, 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 utilized 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 documented informed consent is provided. At the time of treatment randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a 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 predose at Visit 1 (Day 1). All medical history, including risk factors for RSV, any respiratory conditions, prior RSV infections, low birth weight, and any relevant history of the mother, will be obtained and recorded on the appropriate eCRFs. Risk factors for RSV may include, for example, gestational age, gender, maternal smoking status, breastfeeding status, and number and age of siblings.

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 medications/vaccinations 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 medications/vaccinations, if any, taken by the participant during the study. In addition, the participant's legally acceptable representative will record new and/or concomitant medications/vaccinations taken after Visit 1 (Day 1) up to Day 42 in the eDiary. Palivizumab taken after randomization (see Section 6.5) at any time during the study will also be recorded on the appropriate eCRF.

After Day 42, only concomitant medications associated with an SAE will be recorded 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 individual 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. Pre-trial participant screening logs may be collected for review by the Sponsor. If applicable, participant names or any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after treatment randomization. Once a 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 randomization number.

8.1.8 Study Intervention Administration

Study intervention should be prepared and administered by 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.

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.

8.1.8.1 Timing of Dose Administration

Study intervention (MK-1654 or placebo) will be administered at Visit 1 (Day 1), after the participant is deemed eligible for the study. MK-1654 or placebo will be administered via IM injection into the side of the participant's thigh (vastus lateralis). Study staff administering study intervention will be unblinded and not otherwise involved in any study-related procedures/assessments, as described in Section 6.3.3.

See Section 8.13.3 for required procedures if study intervention cannot be administered on the same day as the screening procedures due to unanticipated circumstances.

Study intervention may be administered at any time of day, and without regard to timing of meals. See Section 6.5 on the timing of study intervention administration with regard to concomitant therapy.

Rectal or axillary temperature will be taken by study staff predose and after the 30-minute postdose safety observation period as indicated in the SoA (see Section 1.3.1). Participants who have had a recent illness with rectal temperature ≥100.5°F (≥38.1°C) or axillary temperature ≥100.0°F (≥37.8°C) within 72 hours predose should not be administered study intervention and may be rescreened (see Section 8.13.1).

Participants will be observed for 30 minutes postdose for any immediate reactions; this observation must be performed by the blinded investigator and/or study staff, as described in Section 8.3.4.

8.1.9 Discontinuation and Withdrawal

Participants in this study will receive a single dose intervention and cannot discontinue study intervention.

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

8.1.9.1 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@MSD.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 severity 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.

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.

8.1.11 Domiciling

Not applicable for this study.

8.1.12 Calibration of Equipment

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

8.2 Efficacy (Respiratory Pathogen) Assessments

See the SoA (Section 1.3) for the timing of respiratory pathogen assessments.

8.2.1 Surveillance for Respiratory Infection Symptoms

To facilitate the collection of relevant efficacy data, sites will conduct weekly active surveillance during the time periods defined in the SoA (Section 1.3).

Weekly surveillance will be conducted via phone call. Phone calls must be performed by appropriately trained site staff. The Sponsor will provide each site with a guidance document outlining the questions to be asked at the weekly surveillance call. If the initial call is unsuccessful, the site staff should make a total of 3 additional attempts for each scheduled call. All attempts to call the participant's legally acceptable representative will be recorded in the call log (or equivalent). In addition, site staff will review the eDiary data with the legally acceptable representative (see Section 8.3.5).

In addition to site-conducted weekly active surveillance, the legally acceptable representative will be instructed at Visit 1 (and reminded during the weekly phone calls) to proactively call the site as soon as possible to report respiratory infection symptoms, symptoms of concern, or any outpatient or inpatient visits. If any of these are reported, the procedures in Section 8.2.2 and Section 8.2.3 should be followed.

The purpose of this surveillance is to:

1) **Identify if the following respiratory infection symptoms have occurred or worsened:**

    - Signs/symptoms of ARI and indicators of ARI severity (at least 2 of the following for at least 2 days):
        - Cough
        - Congestion (stuffy or runny nose)
        - Fever (see Section 8.3.3)
        - Trouble feeding
    - Signs/symptoms of LRI and indicators of LRI severity, as follows:
        - Cough or difficulty breathing for at least 1 day; AND
        - At least 1 of the following:
            - Wheezing
            - Chest wall in-drawing/Retractions

- Tachypnea (rapid breathing)

If respiratory infection symptoms are reported (as defined above), the participant should be assessed at the site by the investigator or medically qualified designee (see Section 8.2.2).

2) **Identify if the participant was assessed or is being assessed for respiratory infection symptoms in an outpatient or inpatient clinical setting** (outpatient clinic, Emergency Department, urgent care center, or hospital), and if this is the case, the participant should also be assessed at the site by the investigator or medically qualified designee (see Section 8.2.2).

   Medical records from the outpatient facility or hospital (if available) should be obtained and relevant information (respiratory infection symptoms, PCR results, etc.) should be recorded on the appropriate eCRF(s).

8.2.1.1 Definition of Distinct Episodes of Respiratory Infection

Multiple respiratory infections may occur for some participants during a single RSV season and multiple respiratory assessment visits may be needed to assess a respiratory infection episode. A respiratory infection episode is defined as the onset of respiratory symptoms after a period of at least 48 hours free of respiratory infection symptoms (except mild runny nose) and feeding well.

The start and stop dates of each respiratory infection episode should be documented in the participant's source record and appropriate eCRF.

8.2.2 Respiratory Infection Assessment

8.2.2.1 Requirements for Scheduling a Respiratory Infection Assessment

To identify potential cases of RSV-associated LRI, participants with any respiratory infection symptoms should be assessed at the site by the investigator or medically qualified designee. RSV-associated MALRI is defined in Section 4.2.1.1.

A respiratory infection assessment is required when:

- Respiratory infection symptoms are reported (see Section 8.2.1).
- New respiratory infection symptoms arise or symptoms worsen during an existing episode.
- The participant is seen in an outpatient or inpatient clinical setting for respiratory infection symptoms.

The respiratory infection assessment should be performed within 3 days of symptom onset or worsening.* If this is not possible or the visit for the assessment is missed, it can be performed within 12 days of symptom onset or worsening.*

***Note**: Symptom onset or worsening may refer to the symptom onset or worsening that led to the outpatient visit or hospital admission.

A respiratory infection assessment may occur during an unscheduled visit or at a scheduled study visit (ie, Visits 2, 3, 4, or 5) if that visit occurs within the time requirements noted above.

Every attempt should be made to assess the participant at the study site. If this is not possible, a home visit or visit to an alternate study site may be used, where available and when permitted by local regulations and IRB/IEC. In the case of a home visit or visit to an alternate study site, all indicated study procedures should be performed, including NP swab collection for RT-PCR testing at the central laboratory (see Appendix 7 for specific requirements for sites in China).

8.2.2.2 Procedures at a Respiratory Infection Assessment

The respiratory infection assessment must be performed by the investigator or medically qualified designee.

The following procedures are to be performed to assess the participant for respiratory infection:

1. A brief directed physical examination and vital signs measurement (including heart rate, RR, SpO_2, and body temperature) to assess the participant's symptoms.

2. Confirm if any signs or symptoms of respiratory infection are present:

    - Cough
    - Congestion (stuffy or runny nose)
    - Fever
    - Trouble feeding
    - Difficulty breathing (clinical signs of difficulty breathing or labored breathing may include tachypnea, grunting, nasal flaring, retractions, cyanosis, and/or apnea)
    - Wheezing
    - Chest wall in-drawing/Retractions
    - Rales/Crackles
    - Hypoxemia (SpO_2 <95% on room air at sea level, <92% on room air at altitude ≥1800 m); severe hypoxemia is defined in Table 1.

- Tachypnea (RR ≥60 breaths per minute for <2 months of age, ≥50 breaths per minute for 2 to 12 months of age, or ≥40 breaths per minute for >12 to 24 months of age)
- Dehydration due to respiratory symptoms

All respiratory infection signs/symptoms observed during the visit will be recorded on the appropriate eCRF(s).

3. If any signs or symptoms of respiratory infection are present, then an NP sample will be collected from the participant for RT-PCR testing (see Section 8.2.3).

   Collect an NP sample:

   - If any of the signs/symptoms listed above are observed or confirmed during the initial assessment for a new respiratory infection episode;

     OR

   - If there are new or worsening **LRI** signs/symptoms observed or confirmed at a subsequent assessment for an existing respiratory infection episode

4. Determine if further triage or clinical evaluation is needed, consistent with the standard of care, and in conjunction with the participant's primary physician (if applicable).

5. Review medical records (if available) for participants assessed for respiratory infection symptoms in an outpatient or inpatient clinical setting and record relevant information (respiratory infection symptoms, PCR results, etc.) on the appropriate eCRF.

8.2.3 Nasopharyngeal Sample Collection for RT-PCR Testing for Respiratory Pathogen Identification

NP samples should be collected within the time requirements for the respiratory infection assessment in Section 8.2.2.1.

The swabs for collecting NP samples for RT-PCR testing are provided by the central laboratory. Sample collection, storage, and shipment instructions for the NP sample are provided in the laboratory manual (see Appendix 7 for specific requirements for sites in China).

All swabs collected for NP sampling by a qualified designee will be sent to the central laboratory for analysis. The analysis will determine the presence or absence of RSV, including the strain of RSV (ie, RSV A or B) if RSV is detected, as well as other respiratory pathogens included in the RT-PCR assay panel and COVID-19 (see Appendix 7 for specific requirements for sites in China). Additional details are available in the laboratory manual.

An NP sample should be collected for RT-PCR testing for respiratory pathogen identification if any respiratory symptoms are observed during a respiratory infection assessment (see Section 8.2.2). If a participant requires collection of another sample(s) (at the same visit or

any subsequent visits), the subsequent sample(s) should be taken from the same nostril as the first sample.

The following procedures should be followed for obtaining RT-PCR results for respiratory pathogen identification during a nonstudy visit to an outpatient clinic, Emergency Department, urgent care center, or hospital visit (ie, other than during a scheduled or unscheduled visit to the study site), under each of the following circumstances:

1) Site staff can collect NP sample at a nonstudy visit

If a participant first visits an outpatient facility or hospital (ie, a nonstudy visit) and is confirmed to have respiratory symptoms, the study staff should make every effort to obtain an NP sample using the study-supplied swab, as permitted, and the site should send this sample to the central laboratory for analysis.

2) Site staff cannot collect NP sample at a nonstudy visit

If an NP sample using the study-supplied swab cannot be collected by site staff during an outpatient visit or hospitalization, the sample should be collected using the study-supplied swab as soon as possible postvisit or postdischarge. The medical records (if available) should also be obtained from the outpatient facility or hospital.

Note: Collection of the NP sample using the study-supplied swab during either of the above circumstances should be within the time requirements in Section 8.2.2.1.

3) PCR results from a local laboratory

If an NP sample using the study-supplied swab cannot be collected, but nonstudy staff at an outpatient facility or hospital collected a sample and PCR results for respiratory pathogen identification are available from a local laboratory, medical records (if available) should be obtained to collect the:

- Name of the local laboratory
- Pathogens identified (details will be provided in the data entry guidelines)

Note: Only PCR diagnostic test results are acceptable.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided in this section. Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations Including Length and Weight

A complete physical examination and brief directed physical examinations will be conducted by an investigator or medically qualified designee and consistent with local requirements. Length and weight will also be measured and recorded.

The complete physical examination should include an assessment of the head, eyes, ears, nose and throat, skin, lymph nodes, neurological system, and musculoskeletal system as well as auscultation of the heart and lungs, and an examination of the abdomen.

The brief directed physical examination should include a general assessment for respiratory distress, auscultation of the heart and lungs, and examination of the abdomen.

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

8.3.2 Vital Signs

- Body temperature, heart rate, RR, and SpO_2 will be assessed at the specified visits (see Section 1.3) including predose and at the end of the 30-minute postdose safety observation period (see Section 8.3.4) and at any respiratory infection assessments (see Section 8.2.2.2) and any AESI assessments (see Section 8.4.8).

- Body temperature and RR will be measured and recorded as single measurements. The same method should be used for all measurements for each individual participant and should be the same for all participants, where possible (see Section 8.3.3 for body temperature measurement procedures).

8.3.3 Body Temperature Measurement

Rectal or axillary temperature will be taken by study staff predose and after the 30-minute postdose safety observation period at Visit 1 and at all scheduled and unscheduled visits postdose, as indicated in the SoA (Section 1.3).

Rectal is the preferred method of obtaining participant's temperature and should be performed unless prohibited by local authorities or local pediatric guidelines. Axillary (underarm) is an acceptable method. Use of oral, temporal, or tympanic thermometers to collect temperature for this study is **not** permitted.

Additionally, the participant's legally acceptable representative will be asked to record a temperature reading and method of measurement (rectal* or axillary) in the eDiary on Days 1 through 5 postdose. Temperature readings should be taken at approximately the same time each day with the thermometer provided by the study.

***Note:** For legally acceptable representatives unfamiliar with how to take a rectal temperature, site staff should provide training.

If an elevated temperature is detected using the axillary method (≥100.0°F [≥37.8°C]), the temperature should be confirmed by rectal measurement (unless prohibited by local authorities or local pediatric guidelines). If rectal measurement is prohibited, a repeat axillary temperature measurement should be obtained.

Fever is defined as any rectal temperature ≥102.2ºF (≥39.0ºC) or axillary temperature ≥101.7ºF (≥38.7ºC). All fevers must be reported for Days 1 through 42 unless the fever is a symptom of another reported AE. If a temperature is recorded in the eDiary that meets this definition of fever, the site should call the legally acceptable representative to inquire about respiratory symptoms or any other symptoms. If no other symptoms are present, the fever should be reported as an AE.

8.3.4 30-minute Postdose Safety Observation

Participants will be monitored at the study site during a 30-minute postdose observation period for any signs/symptoms of:

- An immediate anaphylaxis/hypersensitivity AE (see Section 8.4.8.1);
- An immediate rash AE (see Section 8.4.8.2);
- Injection-site AEs (including redness/erythema, swelling, and tenderness/pain); and
- Any other AEs.

This observation period may be extended if deemed necessary.

If any AEs are observed during this period, the type of event, the time at which the event started, any concomitant medications that were administered, any medical intervention provided, and resolution of the event (if applicable), must be recorded on the appropriate eCRFs.

Vital signs should be repeated after the observation period (see Section 8.3.2).

If concomitant vaccinations are given at Visit 1 after administration of study intervention, the participant must undergo an additional 15-minute postconcomitant vaccination observation period at the study site for any AEs.

8.3.5 Electronic Diary

Each participant's legally acceptable representative will be provided an eDiary device or have their own device configured, if compatible, to complete the eDiary. At Visit 1, the participant's legally acceptable representative will be instructed by the investigator or delegate on how to complete the eDiary and how to identify suspected AESI.

The investigator or delegate will review the data captured in the eDiary throughout the 42-day period, and with the participant's legally acceptable representative at the time points

indicated in the SoA (see Section 1.3.1). Noncompliance with the eDiary will require retraining by the site as soon as possible to ensure accurate and complete data capture.

The study-provided eDiary device will be collected from the participant's legally acceptable representative after the 42-day period to ensure safety data is completed for all 42 days, as indicated in the SoA (see Section 1.3.1).

Legally acceptable representatives will use the eDiary from Days 1 through 42 postdose to record the following information:

1. Solicited daily body temperature to identify fever* Days 1 through 5 postdose (see Section 8.3.3);

   ***Note:** Fever is defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C).

2. Solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain)** Days 1 through 5 postdose;

   ****Note:** Injection-site AEs of redness/erythema and swelling will be measured by the legally acceptable representative using a study-supplied ruler.

3. Solicited systemic AEs (irritability, drowsiness, and appetite lost) Days 1 through 5 postdose;

4. Anaphylaxis/hypersensitivity AESI Days 1 through 42 postdose (see Section 8.4.8.1);

5. Rash AESI Days 1 through 42 postdose (see Section 8.4.8.2);

6. Any other AEs Days 1 through 42 postdose; and

7. Concomitant medications and nonstudy vaccinations on Days 1 through 42 postdose.

If any respiratory infection symptoms are reported that might require further assessment, the site staff should call the legally acceptable representative to ascertain additional information and arrange a site visit if needed (see Section 8.2.1 and Section 8.2.2).

The investigator will use the information provided by the participant's legally acceptable representative, both from the eDiary and verbally at the time of eDiary review, to provide an assessment for severity of AEs (see Section 10.3.5).

8.3.6 Day 3 Safety Phone Call

Site staff are required to call the legally acceptable representative of each participant on Day 3 postdose to inquire about the participant's safety, in particular, if any AESI (anaphylaxis/hypersensitivity events and rash events) and SAEs have occurred since Day 1, in addition to reviewing any data entered into the eDiary, including information pertaining to potential injection-site AEs (redness, swelling, or tenderness). The Sponsor will provide each

site with a guidance document (or equivalent) outlining the questions to be asked during this phone call.

If the first attempt on Day 3 is unsuccessful, site staff should try to call the legally acceptable representative an additional 2 times that same day. If the legally acceptable representative is unreachable on Day 3, site staff should continue to try to call at least 3 additional times within the following 7 days. Each attempt should be recorded on the log provided by the Sponsor (or equivalent).

If any respiratory infection symptoms (see Section 8.2.1) or suspected AESI (see Section 8.4.8) are reported, the participant should be brought to the site for further assessment, if applicable.

8.3.7 Clinical 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.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or after the 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, Serious Adverse Events, and Other Reportable Safety Events

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

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, severity, and causality.

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

All AEs, SAEs, and other reportable safety events that occur after the participant's legally acceptable representative provides documented informed consent but before intervention randomization must be reported by the investigator if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention.

From the time of intervention randomization through 42 days following cessation of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious 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 all	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Not applicable since participants are infants.			
Event of Clinical Interest (require regulatory reporting)	There are no events of clinical interest for this study.			
Event of Clinical Interest (do not require regulatory reporting)	There are no events of clinical interest for this study.			
Adverse Event of Special Interest (AESI)	Report if: - due to intervention - causes exclusion	Report all	Report Serious AESI in the same manner as SAE	Within 5 calendar days of learning of event (unless serious)
Cancer	Report if: - due to intervention - causes exclusion	Report all	Report Serious Cancer in the same manner as SAE	Within 5 calendar days of learning of event (unless serious)
Overdose	Not applicable	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 AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable, as participants are infants.

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

Not applicable; there are no ECIs defined for this study.

8.4.8 Adverse Events of Special Interest

All AESI occurring through Day 42 postdose will be reported to the Sponsor. After Day 42, only AESI that meet the serious AE criteria (see Section 10.3.3) should be reported to the Sponsor.

The investigator will provide an assessment of severity for AESI according to the grading scales provided in both Section 10.3.5 and the Severity Grading for Adverse Events document, which are based on an adaption of the NCI CTCAE, version 5.

8.4.8.1 Anaphylaxis/Hypersensitivity Events

The following anaphylaxis/hypersensitivity events (Table 4) are defined as AESI in this study. The Sponsor will provide each site with an AESI guidance document (or equivalent). Refer to the AESI guidance document for the most updated list of terms, definitions, and additional details.

Table 4 Terms for Anaphylaxis/Hypersensitivity Events

Term	Definition
Anaphylaxis	A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.
Angioedema	Localized, non-pitting, and transient swelling of submucosal or subcutaneous region.
Bronchospasm	A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.
Drug hypersensitivity (drug-related allergic reaction)	Adverse effects of drugs that clinically resemble allergic reactions. Immediate clinical manifestations may include urticaria, angioedema, rhinitis, conjunctivitis bronchospasm, and anaphylaxis. Delayed clinical manifestations may include urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).
Dyspnea (difficulty breathing)	A disorder characterized by an uncomfortable sensation of difficulty breathing.
Hypersensitivity	Excessive immune response. Clinically, manifestations may include allergic manifestations such as urticaria, anaphylaxis, angioedema, allergic rhinitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), serum sickness, and vasculitis.

Term	Definition
Dysphonia	A disorder characterized by an inflammation involving the larynx.
Wheezing	A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.

Before study start, the investigator or medically qualified designee will receive support from the Sponsor to assist in identifying the anaphylaxis/hypersensitivity AESI terms listed above in addition to instructions on the process from identification to data entry. At Visit 1, the investigator will provide anticipatory guidance to the legally acceptable representative for a suspected anaphylaxis or hypersensitivity event.

If any anaphylaxis/hypersensitivity event is reported in the eDiary (through Day 42) or during weekly surveillance calls, further assessment by the site may be required. The site must call the legally acceptable representative for additional information; if it is determined that an onsite assessment is required, a site visit should be conducted as soon as possible after becoming aware of the anaphylaxis/hypersensitivity event or within 3 days.

In addition, the legally acceptable representative should call the site as soon as possible if they suspect an anaphylaxis/hypersensitivity event or within 3 days of event onset.

In the event a participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI postdose, as confirmed by the investigator, an additional blood draw is required for evaluation for potential ADA to MK-1654, and additional ADA characterization, if indicated (see Section 1.3.1 and Appendix 2).

8.4.8.2 Rash Events

The following rash events (Table 5) are defined as AESI in this study. Refer to the AESI guidance document (or equivalent) for the most updated list of terms, definitions, and additional details.

Table 5 Terms for Rash Events

Term	Definition
Acute generalized exanthematous pustulosis (AGEP)	A disorder characterized by fever and sterile pustules, circumscribed and elevated skin lesions filled with pus.
Drug eruption	An adverse skin reaction to a drug, not otherwise included in this table of rash terms.
Drug reaction with eosinophilia and systemic symptoms (DRESS)	A disorder characterized by fever, influenza-like symptoms, skin rash, eosinophilia, with or without atypical lymphocytes, elevated transaminase concentration, and/or impaired renal function.

Term	Definition
Erythema multiforme	A disorder characterized by target lesions (a pink-red ring around a pale center).
Generalized rash of exfoliative nature (including dermatitis exfoliative and exfoliative rash)	A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves >90% of the body surface area.
Stevens-Johnson syndrome (SJS)	A disorder characterized by ≤30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
Toxic epidermal necrolysis (TEN)	A disorder characterized by >30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
Urticaria	A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.

The investigator or medically qualified designee will receive support from the Sponsor to assist in identifying the rash AESI terms listed above (eg, representative photographic images) in addition to detailed instructions on the process from identification to photographic image submission. At Visit 1, the investigator will provide anticipatory guidance to the legally acceptable representative for suspected rash events.

If any rash event is reported in the eDiary (through Day 42) or during weekly surveillance calls, further assessment for AESI by the site may be required. The site must call the legally acceptable representative for additional information; if it is determined that an onsite assessment for AESI is required, a site visit should be conducted as soon as possible after becoming aware of the rash event or within 3 days. Photographs (see Section 8.4.8.2.1) and a dermatology consultation (see Section 8.4.8.2.2) may also be required.

In addition, the legally acceptable representative should call the site as soon as possible if they suspect a rash AESI or within 3 days of event onset.

8.4.8.2.1 Photography

If a participant has a suspected or confirmed rash AESI on evaluation, photographs must be taken. For all other rashes (non-AESI), photographs are not required.

Photographs will be taken to document the visual appearance and scope of dermal involvement. Whenever possible, photographs of participant's faces or any other identifying features should be avoided or redacted. Sites should follow local policies for maintaining participant confidentiality and privacy.

Before the end of the visit, the photographs should be reviewed by site staff to ensure they meet the imaging vendor requirements; additional photographs should be taken if needed. All photographs will be uploaded to the central vendor repository.

The imaging vendor will provide the following to each site:

- Training
- Details and requirements for the photographs (eg, number of photos, lighting)
- Instructions for uploading photographs to the vendor repository
- All imaging equipment

8.4.8.2.2 Dermatology Consultation

Severe rash AESI (Grade 3 and Grade 4) are unusual in general pediatric practice and therefore require evaluation by dermatologic specialists.

If the investigator determines that the suspected rash is indeed a Grade 3 or 4 AESI, every effort should be made to schedule a consultation with a local dermatologist (pediatric dermatologist is preferred where possible). This consultation with the local dermatologist should occur as soon as possible or within 3 days from the time the site diagnoses the Grade 3 or Grade 4 AESI.

The purpose of the dermatology consultation is to gain confirmation of the rash diagnosis. This consultation should be conducted per local standards of care. The dermatologist should be provided access to the photos taken at the site visit and copies of relevant source documents collected for the purpose of this study.

After the dermatology consultation, the local dermatologist's assessment and recommendations should be obtained. The diagnosis from the local dermatologist as well as any procedures or other intervention should be recorded on the appropriate eCRFs and added to the source documents.

See the AESI guidance document (or equivalent) for additional details.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the protocol-defined dose.

No specific information is available on the treatment of overdose.

8.6 Pharmacokinetics

The decision as to which serum samples collected will be tested to evaluate PK will be determined by the Sponsor. If indicated, these samples may also be tested and/or pooled for testing in an exploratory manner for metabolites and/or additional markers.

See the Pharmacokinetics/Immunogenicity/Pharmacodynamics schedule in the SoA for the timing of each blood draw. Detailed instructions including blood volumes to be drawn are provided in the laboratory manual.

8.7 Immunogenicity

8.7.1 Blood Collection for Antidrug Antibodies (ADA) Assay

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

See the Pharmacokinetics/Immunogenicity/Pharmacodynamics schedule in the SoA for the timing of each blood draw.

8.8 Pharmacodynamics

8.8.1 Blood Collection for Serum Neutralizing Antibodies Against RSV (SNA) Assay

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

See the Pharmacokinetics/Immunogenicity/Pharmacodynamics schedule in the SoA for the timing of each blood draw.

8.9 Gene Sequencing and Sensitivity Testing

8.9.1 Nasopharyngeal Sample Collection for RT-PCR Testing and RSV F Gene Sequencing for Sensitivity to MK-1654

See the SoA (Section 1.3) and Section 8.2.3 for the timing of collection of the NP sample for RT-PCR testing for respiratory pathogen identification.

RSV F gene sequencing will only be performed if the NP specimen tests positive for RSV.

Detailed instructions are provided in the laboratory manual.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Future Biomedical Research Sample Collection

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

- DNA for future research

- Leftover serum from the PK assay will be stored for future research.
- Leftover serum from the ADA, SNA, and additional ADA characterization assays will be stored for future research.
- Leftover NP swabs from RT-PCR testing will be stored for future 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 8.1 through Section 8.11. Additional specific requirements are detailed below.

8.13.1 Screening (Visit 1 Predose)

At Visit 1, potential participants will be evaluated to determine whether they meet entry requirements as set forth in Section 5. Potential participants will be screened at the study site.

Infants with a recent illness with fever (rectal temperature ≥100.5°F [≥38.1°C] or axillary temperature ≥100.0°F [≥37.8°C]) within 72 hours predose at Visit 1 before administration of study intervention are not eligible, but may be rescreened (see Section 5.2 Exclusion Criterion 4).

Participants may be rescreened up to 4 times. Screening procedures listed in the SoA (including consent review; see Section 1.3.1) should be repeated at each rescreen visit.

8.13.1.1 Predose Nasopharyngeal Sample Collection for RT-PCR Testing

If symptoms of respiratory infection have been present within 7 days before Visit 1, an NP sample should be collected. Collecting an NP sample at Visit 1 does not exclude an infant from participating in the study.

8.13.2 Randomization/Dose Administration/Observation (Visit 1)

If a participant is deemed eligible for the study, and completes all other predose procedures, the participant will be assigned a unique treatment/randomization number by the IRT system.

All participants will also be randomized by IRT to 1 of the 2 different blood sampling groups (Group 1 or Group 2) that differ in the schedule of serum PK, ADA, and SNA sampling (see Section 1.3.1). Participants will then be assigned by IRT to 1 of the 2 subgroups (a or b) that differ in the tests to be performed.

Predose samples should be collected from randomized participants only. Samples should be collected after randomization in the IRT system but before dose administration. If the predose blood sample cannot be collected after 3 attempts, the dose should be administered.

After randomization in the IRT system, participants will receive study intervention administered as a single IM injection at the study site as described in Section 6.1 and Section 8.

Participants will be observed at the study site for at least 30 minutes postdose for any immediate AEs (see Section 8.3.4). This observation must be performed by the blinded investigator and/or study staff.

Vital sign measurements should be repeated at the end of the 30-minute postdose safety observation period.

8.13.3 Delay in Randomization and Study Medication Administration

All efforts should be made to randomize participants and administer study medication on Day 1 after predose screening procedures as per protocol. However, if randomization and study medication administration cannot be conducted on the same day as screening, they may be conducted within 5 days of the predose screening procedures.

Prior to randomization in the IRT system and administration of study medication (Day 1), the site should confirm participant's eligibility by repeating vital signs measurements, the full physical examination (including weight), and review the eligibility criteria and the informed consent.

8.13.4 Early Withdrawal Visit

If the legally acceptable representative withdraws consent prior to the last study visit, the participant should be brought in for a final visit (at the study site, at home, or at an alternate study site location; see Section 8.13.5) as follows:

- First 1650 participants: Complete all assessments and procedures indicated for Visit 8 in the SoA (Section 1.3.2).
- Remaining participants: Complete all assessments and procedures indicated for Visit 7 in the SoA (Section 1.3.1).

If the participant withdraws consent while attending a scheduled visit, any additional assessments and procedures needed for the final study visit should be conducted in addition to the assessments and procedures for the scheduled visit.

8.13.5 Visits at the Study Site, at Home, or at an Alternate Study Site Location

Every attempt should be made to assess the participant at the study site for all scheduled study visits (see Section 1.3.1 and Section 1.3.2) and for any unscheduled visit to assess possible respiratory infection symptoms or a suspected AESI (see Section 8.2.2 and Section 8.4.8). However, if this is not possible, additional efforts should be made to ensure the per-protocol assessments are conducted for these visits.

A visit at the study site is required at Visit 1 (Day 1). Study site visits are preferred for Visits 2 through 8 to ensure the participants are seen in person by the investigator and site staff in the event respiratory infection symptoms or a suspected AESI are present. See Section 1.3.1 and Section 1.3.2 for the visit schedules.

If circumstances do not support a visit at the study site, a home visit by the site personnel or a healthcare service provider (eg, home healthcare vendor) or a visit to an alternate study site location may be appropriate to perform study assessments and procedures per the SoA, where available and when permitted by local regulations and IRB/IEC. All indicated study procedures should be completed, including blood draws. The documentation from the visit should be provided to the investigator or medically qualified designee (consistent with local requirements) for review and assessment per institutional standard. Also, this documentation should be provided to site staff for data entry purposes.

Refer to the home visit manual (or equivalent) for details.

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 any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to tertiary or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc tertiary analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants
Treatment Assignment	Participants will be assigned randomly in a 2:1 ratio to receive a single dose of MK-1654 or placebo. Randomization will be stratified by region (Southern Hemisphere and Northern Hemisphere), gestational age (≥29 to <35 weeks; ≥35 weeks), and chronological age at the time of consent (<6 months; ≥6 months).
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)

Primary Endpoint(s)	• Efficacy: Number of participants with RSV-MALRI in the MK-1654 and placebo groups from Days 1 through 150 postdose. • Safety: Number of participants experiencing solicited injection-site AEs from Days 1 through 5 postdose, solicited daily body temperature to identify fever from Days 1 through 5 postdose, solicited systemic AEs from Days 1 through 5 postdose, anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose, rash AESI from Days 1 through 42 postdose, nonserious AEs from Days 1 through 42 postdose, and SAEs through the duration of study participation.
Key Secondary Endpoints	• Efficacy: Number of participants with RSV hospitalization in the MK-1654 and placebo groups from Days 1 through 150 postdose. • Efficacy: Number of participants with RSV-MALRI in the MK-1654 and placebo groups from Days 1 through 180 postdose.
Statistical Methods for Key Efficacy Analyses	The primary efficacy hypothesis will be evaluated by calculating the efficacy of MK-1654 compared to placebo with respect to the RSV-MALRI endpoint. The p-value for testing the primary hypothesis that efficacy>25% as well as estimation of the 95% CI of efficacy will be based on the modified Poisson regression with robust variance proposed by Zou [Zou, G. 2004].
Statistical Methods for Key Safety Analyses	There are no a priori clinical events identified in this trial as Tier 1 events. Tier 2 events identified in this trial include solicited injection-site AEs; solicited daily body temperature to identify fever; solicited systemic AEs; drug-related AEs; any serious AEs; discontinuations due to AEs; anaphylaxis/hypersensitivity AESI; rash AESI; nonserious AEs; and AEs by system organ class observed in ≥1% of participants in at least one group. Estimates of 95% CIs for between-treatment differences in the percentage of participants with events will be calculated using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	Two IAs are planned in this study. The first IA (IA#1) will be conducted after the last participant in the Phase 2b cohort completes the Day 42 visit. Summaries of the safety, available PK, and efficacy for the endpoints of RSV-associated MALRI and hospitalization will be assessed at the IA#1 to evaluate the benefit versus risk for continued enrollment. The second IA (IA#2) will be conducted when 40 total cases of RSV-associated MALRI have accrued across the MK-1654 and placebo groups. Futility of the primary hypothesis will be assessed at IA#2. The IAs will be performed by an unblinded statistician and results will be reviewed by an eDMC. Details are provided in Section 9.7.
Multiplicity	The overall 1-sided Type 1 error in testing the efficacy hypotheses is controlled at 2.5% based on gatekeeping procedure. The primary efficacy hypothesis will be tested at an overall 1-sided Type 1 error of 2.5%, as discussed in Section 9.9.1.1. The secondary efficacy hypothesis regarding RSV hospitalization from Days 1 through 150 postdose will be tested at 1-sided Type 1 error of 2.5% only if the primary efficacy hypothesis is successfully demonstrated, as discussed in Section 9.9.1.2.

Sample Size and Power	This study will randomize approximately 3300 healthy infants in a 2:1 allocation ratio into the MK-1654 group and the placebo group. Approximately 167 total cases of RSV-MALRI in the MK-1654 and placebo groups are expected to accrue by the end of the study. For RSV-MALRI, the study has >95% power to demonstrate that the efficacy of MK-1654 compared to placebo to prevent RSV-MALRI is >25% if the underlying efficacy is 70% at an overall 1-sided Type 1 error of 2.5%. A total of approximately 33 cases of RSV hospitalization in the MK-1654 and placebo groups are expected to accrue by the end of the study. For RSV hospitalization, the study has 93.6% power to demonstrate that the efficacy of MK-1654 compared to placebo to prevent RSV hospitalization is >0% if the underlying efficacy is 70% at an overall 1-sided Type 1 error of 2.5%.

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 under in-house blinding procedures. 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 schedule(s) for study treatment assignment. Randomization will be implemented using IRT.

Blinding issues related to the planned IAs are described in Section 9.7.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

The efficacy, PK, pharmacodynamics, immunogenicity, and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy/Pharmacokinetics/Pharmacodynamics/Immunogenicity Endpoints

Efficacy Endpoints

The primary efficacy endpoint that will be used to evaluate and test the primary efficacy hypothesis is the number of participants with RSV-associated outpatient and inpatient MALRI occurring from Days 1 through 150 postdose, as described in Section 4.2.1.1. RSV-associated outpatient and inpatient MALRI is defined by the presence of the following seen in an outpatient or inpatient clinical setting: cough or difficulty breathing; AND 1 or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia,

tachypnea, dehydration due to respiratory symptoms; AND RSV-positive RT-PCR NP sample. The secondary efficacy endpoints are:

- Number of participants with RSV-associated hospitalization from Days 1 through 150 postdose, defined as hospital admission for respiratory illness; AND RSV-positive RT-PCR NP sample
- Number of participants with RSV-associated outpatient and inpatient MALRI from Days 1 through 180 postdose

The following are the tertiary efficacy endpoints for this study:

- Number of participants with RSV-associated outpatient and inpatient severe MALRI from Days 1 through 150 postdose
- Number of participants with RSV-associated outpatient and inpatient severe MALRI from Days 1 through 180 postdose
- Number of participants with RSV-associated hospitalization from Days 1 through 180 postdose
- Number of participants with outpatient and inpatient MALRI due to any cause from Days 1 through 150 postdose
- Number of participants with RSV-associated outpatient and inpatient MALRI from Days 365 through 515 postdose
- Number of participants with RSV-associated hospitalization from Days 365 through 515 postdose
- Number of participants hospitalized with RSV-associated LRI from Days 1 through 150 postdose
- Number of participants hospitalized with RSV-associated LRI from Days 1 through 180 postdose
- Number of participants hospitalized with LRI due to any cause from Days 1 through 150 postdose
- Number of participants with non-RSV-associated outpatient and inpatient MALRI from Days 1 through 150 postdose
- Number of participants with RSV-associated outpatient and inpatient MALRI excluding cases where other pathogens are found from Days 1 through 150 postdose
- Number of participants with RSV-associated outpatient and inpatient ARI from Days 1 through 150 postdose

- Number of participants with RSV-associated outpatient and inpatient ARI from Days 1 through 180 postdose
- Number of participants with physician-assessed wheezing from Days 1 through 180 postdose
- Number of participants with physician-assessed wheezing from Days 365 through 515 postdose

Pharmacokinetics Endpoints

The tertiary PK endpoints are the serum PK concentration of MK-1654 at Days 7, 150, and 240 postdose.

Pharmacodynamics Endpoints

The tertiary pharmacodynamics endpoints are SNA titers against RSV A at Day 1 (predose) and Days 7, 150, 240, 365, and 515 postdose.

Immunogenicity Endpoints

The tertiary immunogenicity endpoints are ADA to MK-1654 at Day 1 (predose) and Days 150, 240, 365, and 515 postdose.

Additional Tertiary Endpoints

The additional tertiary endpoint is RSV F gene sequence determined by deep sequencing in NP samples from infants infected with RSV.

9.4.2 Safety Endpoints

Safety and tolerability of MK-1654 in this study will be assessed by clinical review of all relevant parameters including AEs and laboratory values. The endpoints that will be used to assess the safety and tolerability of MK-1654 include the following:

- Number of participants experiencing solicited injection-site AEs (redness/erythema, swelling, and pain/tenderness) from Days 1 through 5 postdose
- Number of participants experiencing solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C), from Days 1 through 5 postdose
- Number of participants experiencing solicited systemic AEs (irritability, drowsiness, and appetite lost) from Days 1 through 5 postdose
- Number of participants with anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose

- Number of participants with rash AESI from Days 1 through 42 postdose
- Number of participants experiencing nonserious AEs occurring from Days 1 through 42 postdose
- Number of participants experiencing SAEs through the duration of study participation (from the time the consent form is signed through completion of the participant's participation in the study; for complete details on SAE data collection, see Section 10.3.5).

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

Full Analysis Set (FAS) Population

The FAS population will serve as the primary population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. The FAS population consists of all randomized participants who receive 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they were randomized to for the analysis using the FAS population.

For an episode of respiratory infection to be considered for evaluation of an efficacy endpoint for the analysis in the FAS population, a PCR result from the study central laboratory must be available for an NP sample that is collected no more than 12 days after symptom onset or symptom worsening, or after symptom onset and no more than 7 days before symptom worsening. A sensitivity analysis will be conducted, which will include PCR results from NP samples collected within the timeframe mentioned above, but not tested at the study central laboratory.

Per-Protocol Efficacy (PPE) Population

The PPE population will serve as a supportive analysis population for the evaluation of efficacy and for the estimation of incidence of RSV-associated disease. To be eligible for inclusion in the PPE population, study participants must satisfy the following criteria:

- Receive 1 dose of the correct clinical material corresponding to the treatment group the participants were randomized into,
- Have at least 1 follow-up visit/phone call for assessment of RSV disease, and
- At any time during dosing or efficacy follow-up, do not experience a protocol deviation that may interfere with the assessment of protection against RSV infection conferred by MK-1654.

The final determination on important protocol deviations, and thereby the composition of the PPE population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

For an episode of respiratory infection to be considered for evaluation of an efficacy endpoint for the analysis in the PPE population, a PCR result from the study central laboratory must be available for an NP sample that is collected no more than 12 days after symptom onset or symptom worsening, or after symptom onset and no more than 7 days before symptom worsening.

For both analysis populations, if a participant with symptoms of respiratory infection prior to dosing has an NP sample collected predose on Day 1 or any subsequent NP samples collected for this episode that are PCR positive for RSV, this episode will not be counted as a case toward the efficacy endpoints.

9.5.2 Immunogenicity and Pharmacodynamic Analysis Populations

The immunogenicity and pharmacodynamic analysis populations that will be used in tertiary analyses of immunogenicity and pharmacodynamic endpoints will be described in the sSAP that will be written for this study.

9.5.3 Pharmacokinetic Analysis Populations

The PK analysis populations that will be used in tertiary analyses of PK will be described in the sSAP that will be written for this study.

9.5.4 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received a dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population.

9.6 Statistical Methods

Statistical testing and inference relating to efficacy are described in Section 9.6.1. Statistical methods relating to safety analyses are described in Section 9.6.2. Demographic and baseline characteristics are described in Section 9.6.3. Statistical methods relating to immunogenicity and PK analyses are described in the sSAP. Efficacy results that will be deemed to be statistically significant after consideration of the Type 1 error control strategy are described in Section 9.8. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analyses

To address the primary efficacy hypothesis, a 1-sided test of the null hypothesis that the efficacy is ≤25% versus the alternative that efficacy is >25% will be conducted. The primary efficacy hypothesis will be tested at 1-sided α=0.025 level (ie, 2.5% Type 1 error). Efficacy is defined as:

$$E\% = 100*\{1-(Rt/Rp)\}$$

where Rt and Rp are the incidence rates of RSV-associated MALRI in the MK-1654 and placebo groups, respectively. The incidence rate Rt is defined as Rt=Ct/Tt, where Ct=the count of RSV-associated MALRI cases in the MK-1654 group and Tt=total person-time of follow-up for efficacy in the MK-1654 group. The incidence rate Rp is defined similarly. The 95% CI for E is denoted as (EL, EU), and the statistical criterion for success with respect to the primary efficacy hypothesis will be met if EL >25%.

A modified Poisson regression approach with robust variance [Zou, G. 2004] will be used for the efficacy analyses. The mean and 95% CI of relative risk, Rt/Rp, will be obtained from the model, and will be used to estimate the mean and 95% CI of E. The modified Poisson regression model will include treatment group, and stratification variables of region (Southern Hemisphere and Northern Hemisphere), gestational age (early and moderate pre-term infants [≥29 to <35 weeks gestational age] and late pre-term and full-term infants [≥35 weeks gestational age]), and chronological age at the time of consent (<6 months; ≥6 months) as covariates. To allow for differences in follow-up times among the participants, log (follow-up time) as the offset term will be added in the modified Poisson regression.

If the number of participants in any stratum is too small and/or convergence cannot be achieved for either of the primary and secondary efficacy endpoints, the covariate will be excluded from the model for the final analysis of all primary and secondary efficacy endpoints. If convergence issues persist, additional covariates will be excluded from the model in the following order: region, chronological age, and gestational age, until the model converges for all primary and secondary efficacy endpoints. Therefore, the same set of covariates will be used in the models for all of the primary and secondary efficacy endpoints in the final analyses.

For the primary analyses of efficacy, cases of RSV-associated outpatient and inpatient MALRI will be counted starting at Day 1 postdose and through 150 days postdose. For the primary efficacy hypothesis, cases of both RSV A and RSV B associated MALRI will be counted as endpoints. The efficacy of MK-1654 against RSV A and RSV B associated MALRI will also be estimated separately.

For the secondary efficacy hypothesis of RSV-associated hospitalization from Days 1 through 150 postdose, the statistical criterion for success will be met if EL >0%. For the secondary efficacy endpoint of RSV-associated outpatient and inpatient MALRI occurring from Days 1 through 180 postdose, the estimate of efficacy and corresponding 95% CI will be provided. The analysis strategy for key efficacy variables is summarized in Table 6.

Table 6 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Endpoint				
Incidence of RSV-associated outpatient and inpatient MALRI from Days 1 through 150 postdose	P/S	Modified Poisson regression (estimate, 95% CI, P-value)	FAS/PPE	Missing data will not be imputed
Secondary Endpoints				
Incidence of RSV-associated hospitalization from Days 1 through 150 postdose	P/S	Modified Poisson regression (estimate, 95% CI, P-value)	FAS/PPE	Missing data will not be imputed
Incidence of RSV-associated outpatient and inpatient MALRI from Days 1 through 180 postdose	P/S	Modified Poisson regression (estimate, 95% CI)	FAS/PPE	Missing data will not be imputed

CI=confidence interval; FAS=Full Analysis Set; MALRI=medically attended lower respiratory infection; P=primary approach; PPE=per-protocol efficacy; S=supportive approach; RSV=respiratory syncytial virus.

[a] The statistical methods are described in Section 9.6.1.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs. All safety summaries will be provided separately for the first and second RSV seasons.

The analysis of safety results will follow a tiered approach (Table 7). AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory and vital signs parameters are either pre-specified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AESI that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as no treatment-related SAEs have been observed in the Phase 1 studies of MK-1654.

Tier 2 Events

Membership in Tier 2 requires that at least 1% participants in any treatment group exhibit the event; OR AEs listed in Table 7. All other AEs will belong to Tier 3. Maximum body temperature will be summarized using Brighton Collaboration cutoffs.

The threshold of at least 1% was chosen to draw clinical meaningful inference. When less than 1% of participants report AEs in both groups, the 95% CI for the between-group difference may exclude zero. However, the clinical significance of these differences is unknown given the small number of participants who report AEs. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Comparison of MK-1654 and Placebo	Descriptive Statistics
Tier 2	Any AE[a]	X	X
	Any Serious AE	X	X
	Any Drug-related AE	X	X
	Any Serious and Drug-related AE	X	X
	Discontinuation due to AE	X	X
	Solicited Injection-site AEs Days 1-5 Postdose	X	X
	Solicited Daily Body Temperature Days 1-5 Postdose	X	X
	Solicited Systemic AEs Days 1-5 Postdose	X	X
	Anaphylaxis/hypersensitivity AESI Days 1-42 Postdose	X	X
	Rash AESI Days 1-42 Postdose	X	X
	Nonserious AEs Days 1-42 Postdose	X	X
	AEs by SOC (incidence ≥1% of participants in 1 of the treatment groups)	X	X
Tier 3	AEs by SOC (incidence <1% of participants in all of the treatment groups)		X

AE=adverse event; AESI=adverse event(s) of special interest; SAE=serious adverse event; CI=confidence interval; SOC=System Organ Class; X=results will be provided.

[a] Indicates broad AE category of the number of participants reporting any AE.

9.6.3 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants

screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, gender, race, and ethnicity), baseline characteristics (including medical history as outlined in Section 8.1.4), primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment group either by descriptive statistics or categorical tables.

9.6.3.1 Population Pharmacokinetic Analyses

Based on PK data obtained within this study, a separate population PK analysis will be performed and reported separately. The prospective details of this analysis will be specified in a separate population PK analysis plan.

9.7 Interim Analyses

A total of 2 IAs are planned for this study. All IAs will be conducted by an external unblinded statistician. Enrollment will not be paused during IAs/review of results by eDMC. All available safety, PK, and RSV disease incidence data will be summarized for each IA. Ongoing PK bioanalysis and PK modeling will be conducted by a separate, unblinded modeling group and external bioanalysts. In addition to these planned IAs, the eDMC will review available safety and RSV disease incidence data from this study at least once every 6 months while the study is still enrolling or as outlined in the eDMC charter.

Treatment-level results and/or participant-level data from the IA will be provided by the unblinded statistician to the eDMC. The extent to which individuals are unblinded with respect to results of the IAs will be documented by the unblinded statistician. The results of the IAs will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to the external unblinded statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study.

IA#1: After the last participant randomized in the Phase 2b cohort completes the Day 42 visit and the safety data are available, the first IA will be conducted. Summaries of the safety data will be reviewed by the eDMC. Additionally, the eDMC will review a summary of the available PK data, and estimates of efficacy along with the 95% CIs for the endpoints of RSV-associated MALRI and RSV-associated hospitalization (based on the exact binomial method proposed by Chan and Bohidar [Chan, I. S. F. and Bohidar, N. R. 1998]). Futility of the primary efficacy endpoint will not be assessed at this IA. The eDMC will assess the benefit versus risk for continued enrollment and a recommendation on whether the study should continue will be made by the eDMC. The study will not stop for success of the primary efficacy hypothesis at the IA. If the study stops at the IA, no further participants will be enrolled. However, participants that have already been enrolled in the study will continue to be monitored for safety for 365 days postdose.

IA#2: If the study continues, the second IA for futility evaluation will be conducted when 40 total RSV-MALRI cases in the combined MK-1654 and placebo groups have been observed in the study. If ≥21 cases are observed in the MK-1654 group (observed efficacy <50%), the study may stop for futility. If the study stops at this IA due to futility, no further

participants will be enrolled. However, participants that have already been enrolled in the study will continue to be monitored for safety for 365 days postdose. The study will not stop for success of the primary efficacy hypothesis at the IA. The operating characteristics of the futility criterion are shown in Table 8. Summaries of the available safety and PK data will be summarized and reviewed at the second IA.

Table 8 Futility Evaluation Operating Characteristics (Interim Analysis #2)

Analysis Time Point	Total Cases to Accrue	Stop for Futility (MK-1654 Cases)	Observed Efficacy (%) (95% CI)	True Efficacy	Probability of Stopping for Futility at IA#2 (%)[a]	Probability of NOT Stopping for Futility at IA#2 (%)[a,b]
IA 2	40	≥21	45 (-9, 72)	25% (Null)	87.0	13.0
				50%	43.7	56.3
				60%	19.3	80.7
				70%	3.8	96.2
				80%	0.1	99.9
				90%	0.0	100.0

CI=confidence interval; IA=interim analysis.

[a] Probability is based on the exact binomial method proposed by Chan and Bohidar [Chan, I. S. F. and Bohidar, N. R. 1998].

[b] =100 − probability of stopping for futility at IA#2.

If the study does not stop at the second IA, the study will continue as planned. After all participants in the global study (see Appendix 7 regarding enrollment in China) have completed 180 days postdose follow-up, a database lock will be executed, and the Sponsor study team will be unblinded. All analyses to evaluate the primary, secondary, and tertiary objectives of the study will be conducted, and a CSR will be written. A separate blinded Sponsor study team will be appointed to conduct the remainder of the study. All participants will continue in the study until all follow-up assessments per the protocol have occurred. When all participants have completed all follow-up assessments per the protocol 365 days postdose, a database lock will be executed, and the supplemental CSR will be written. If the first 1650 participants enrolled finish the follow-up through RSV Season 2 by the time all participants finish the follow-up through 365 days postdose, all analyses will be written in 1 supplemental CSR; otherwise, another supplemental CSR will be written at the end of RSV Season 2 follow-up. Investigators, study participants, and their legally accepted representatives will remain blinded to individual treatment assignments throughout the duration of the entire study and will be unblinded upon completion of the end-of-study CSR.

The details for the reports of data reviewed by the eDMC and processes by which recommendations and decisions are reached and communicated by the eDMC will be documented in the eDMC charter for the Sponsor. The eDMC charter will be referenced in the CSR. Prior to final study unblinding, Sponsor individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol,

statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

9.8 Multiplicity

The overall 1-sided Type 1 error in testing the efficacy hypotheses is controlled at 2.5% based on a gatekeeping procedure.

The primary efficacy hypothesis will be tested at an overall 1-sided Type 1 error equal to 2.5% (see Section 9.9.1.1). The secondary efficacy hypothesis regarding RSV hospitalization from Days 1 through 150 postdose will be tested at 1-sided Type 1 error of 2.5% only if the primary efficacy hypothesis is successfully demonstrated (see Section 9.9.1.2).

A futility analysis of the primary endpoint will be conducted when 40 total RSV-MALRI cases in the combined MK-1654 and placebo groups have been observed. No Type 1 error adjustment is needed for the futility analysis because there is no possibility to stop the study and conclude efficacy.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

9.9.1.1 Sample Size and Power for Testing the Primary Efficacy Hypothesis

The sample size of approximately 3300 was selected to ensure collection of adequate safety information on the use of MK-1654 in this otherwise healthy population of pre-term and full-term infants. This study will randomize approximately 2200 healthy infants into the MK-1654 group and approximately 1100 healthy infants into the placebo group. A total of approximately 167 cases of RSV-associated MALRI in the MK-1654 and placebo groups are expected to accrue by the end of the study, under the following assumptions: 1) incidence of RSV-associated MALRI in the placebo group is 10% per season; 2) efficacy=70%, so that the incidence of RSV-associated MALRI in the MK-1654 group is 3% per season; and 3) attrition rate is 5%. Under these assumptions, there is >95% power to demonstrate that the efficacy of MK-1654 compared to placebo to prevent RSV-associated MALRI is >25% if the underlying efficacy is 70% at an overall 1-sided Type 1 error of 2.5%. The calculations are based on a simulation study for the modified Poisson regression and carried out using the SAS software.

9.9.1.2 Sample Size and Power for Testing the Secondary Efficacy Hypothesis

RSV-associated hospitalization is the secondary efficacy endpoint. A total of approximately 33 cases of RSV-associated hospitalization in the MK-1654 and placebo groups are expected to accrue by the end of the study, under the following assumptions: 1) incidence of RSV-associated hospitalization in the placebo group is 2% per season; 2) efficacy=70%, so that the incidence of RSV-associated hospitalization in the MK-1654 group is 0.6% per season; and 3) attrition rate is 5%. Under these assumptions, there is 93.6% power to demonstrate that the efficacy of MK-1654 compared to placebo to prevent RSV-associated hospitalization is >0%

if the underlying efficacy is 70% at an overall 1-sided Type 1 error of 2.5%. The calculations are based on a simulation study for the modified Poisson regression and carried out using the SAS software.

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants treated 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. If the underlying incidence of an SAE is 0.069% (1 of every 1456 participants receiving the MK-1654), there is an 80% chance of observing at least 1 SAE among 2200 participants in the MK-1654 group. If the underlying incidence of an SAE is 0.033% (1 of every 3039 participants receiving the MK-1654), there is a 50% chance of observing at least 1 SAE among 2200 participants in the MK-1654 group. If no SAEs are observed among the 2200 participants in the MK-1654 group, this study will provide 97.5% confidence that the underlying percentage of participants with an SAE is <0.139% (1 in every 720 participants) in the MK-1654 group.

The percentage point differences between the 2 groups that could be detected with 80% probability for a variety of hypothetical underlying incidences of an AE are summarized in Table 9. These calculations assume 2200 participants in the MK-1654 group and 1100 participants in the placebo group and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 9 Differences in Incidence of Adverse Event Rates Between the 2 Groups That can be Detected With an ~80% Probability (Assuming 2-sided 5% Alpha Level With 2200 Participants in the MK-1654 Group and 1100 Participants in the Placebo Group)

Incidence of Adverse Event		Risk Difference
Placebo (%)	MK-1654 (%)	Percentage Points
0.1	0.8	0.7
2.0	3.8	1.8
5.0	7.5	2.5
10.0	13.3	3.3
15.0	18.9	3.9
20.0	24.3	4.3
30.0	34.9	4.9
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Based on an asymptotic method [Farrington, C. P. 1990].		

9.10 Subgroup Analyses

The consistency of the treatment effect will be assessed descriptively by category for the classification variables listed below. Efficacy of MK-1654 against RSV-associated MALRI will be estimated separately in (1) Southern Hemisphere and Northern Hemisphere regions; (2) the early and moderate pre-term infants (≥29 to <35 weeks gestational age) and late pre-term and full-term infants (≥35 weeks gestational age) subgroups; (3) age groups at the time of consent (<6 months; ≥6 months); (4) weight groups at the time of consent. In addition to the 2 age groups, efficacy will also be summarized in infants ≤2 weeks of age. The incidence of RSV-associated MALRI in each treatment group, the estimate of efficacy, and the nominal 95% CI will be reported for each subgroup.

Subgroup analyses of safety and PK profiles will be summarized descriptively by age groups at randomization. The descriptive statistics will be reported for each subgroup.

9.11 Compliance (Medication Adherence)

Given that participants will receive just a single dose of MK-1654 or a single dose of placebo, compliance will not be calculated. However, the number and proportion of randomized participants receiving each treatment will be summarized (see Section 9.12).

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered MK-1654 and the number and proportion of randomized participants administered placebo.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection 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

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

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

10.1.5 Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical 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 Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests described in Table 10 will be performed by the central laboratory.
- The overall blood draw schedule, the approximate total blood sample volume at each visit, and the total blood volume for RSV Seasons 1 and 2 for participants in the study are provided in Table 11. The maximum amount of blood drawn from each participant is dependent upon weight at each study visit. For participants who weigh <3 kg at the time of the blood draw, the maximum blood sample volume must be adjusted according to the participant weight cutoffs provided in Table 12.
- Collect a blood sample (1.2 mL) if participant has a Grade 3 or 4 anaphylaxis/hypersensitivity AESI postdose, as confirmed by the investigator, for evaluation for potential ADA to MK-1654, and additional ADA characterization, if indicated (see Section 1.3.1, Section 8.4.8.1, and Table 10).
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- The participant/participant's legally acceptable representative, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants will be blinded to the data. Only unblinded study team members will have access to the data.
- 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.
- Unblinding may be appropriate for safety issues (see Section 8.1.10).

Table 10 Laboratory Assessments in the MK-1654-004 Study

Laboratory Assessments	Parameters
Protocol-required Laboratory Assessments	
Virology	• RT-PCR assay for RSV and other respiratory pathogens included in the RT-PCR assay panel • Assay for COVID-19 • RSV F gene sequencing will only be performed if RT-PCR test is positive for RSV
Pharmacokinetics	• Assay to measure serum PK concentration of MK-1654
Immunogenicity[a]	• Assay for ADA to MK-1654, and additional ADA characterization, if indicated
Pharmacodynamics	• Assay for SNA
Safety (if indicated)	• Assay for ADA to MK-1654, and additional ADA characterization, if indicated, in the event a participant experiences a Grade 3 or 4 anaphylaxis or hypersensitivity AESI

ADA=antidrug antibodies; PK=pharmacokinetics; RSV=respiratory syncytial virus; RT-PCR=reverse transcriptase-polymerase chain reactions; SNA=serum neutralizing antibodies against RSV.
[a] A sufficient amount of serum will be stored for further characterization of immunogenicity, if needed.

Table 11 Blood Draw Schedule and Approximate Blood Sample Volumes Drawn Per Study Visit for Participants who Weigh ≥3kg

	RSV Season 1					RSV Season 2			
Study Period	**Screening, Randomization, and Intervention**	**Follow-up (through 365 days postdose)**			**Total Blood Volume[a] for RSV Season 1**	**Follow-up (365 through 515 days postdose)**		**Total Blood Volume[a] for RSV Season 2**	**Total Blood Volume[a] for RSV Seasons 1 and 2**
Visit Number/Title	**1**	**2[b]**	**5**	**6**		**7**	**8**		
Scheduled Day and Window (Days):	**Day 1 Predose**	**7 +2**	**150 ±5**	**240 ±5**		**365 ±5**	**515 +14**		
Group 1a:									
Blood Volume[a]	2.4 mL	1.2 mL	2.4 mL	-	6.0 mL	2.4 mL	2.4 mL	4.8 mL	10.8 mL
Group 1b:									
Blood Volume[a]	2.4 mL	1.2 mL	2.4 mL	-	6.0 mL	-	-	-	6.0 mL
Group 2a:									
Blood Volume[a]	2.4 mL	-	2.4 mL	2.4 mL	7.2 mL	2.4 mL	2.4 mL	4.8 mL	12.0 mL
Group 2b:									
Blood Volume[a]	2.4 mL	-	2.4 mL	2.4 mL	7.2 mL	-	-	-	7.2 mL

RSV=respiratory syncytial virus.

[a] The blood sample volume at each visit and total blood sample volume for RSV Seasons 1 and 2 are provided for participants who weigh ≥3 kg at the time of the visit. For participants who weigh <3 kg at a visit, the maximum blood sample volume at the visit must be adjusted according to the participant weight cutoffs provided in Table 12.

[b] In the event a participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI postdose (see Section 1.3.1 and Section 8.4.8.1), an additional blood sample (1.2 mL) is required.

Table 12 Maximum Blood Sample Volume Drawn Per Study Visit by Participant Weight

Participant Weight[a]	**Maximum Blood Sample Volume Per Study Visit**
≥3 kg	2.4 mL
≥1.5 to <3 kg	1.2 mL
<1.5 kg	No sampling

[a] Indicates participant weight at the time of the visit.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent 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."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of 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.

- Congenital disorder (eg, present from birth) that is detected/diagnosed in an infant participant.

10.3.3 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, following dosing:

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.

10.3.4 Additional Events Reported

Additional events that require reporting

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

1. Is a cancer

2. Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

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

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

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

Assessment of severity

- 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 assess the severity for each AE, SAE, and AESI (and other reportable safety event) reported during the study. Severity will be graded according to an adaption of NCI CTCAE version 5.0 as applicable for pediatric assessments. Where necessary, the NCI CTCAE scale has been adapted to conform to AE assessment for infant participants. Once the assessment has been made, the severity grade should be recorded in the "overall toxicity grade" section of the AE eCRF.

- The severity of solicited injection-site AEs, solicited systemic AEs, elevated temperature, and AESI will be assessed according to the grading criteria (for Grade 1 through Grade 4) provided in Table 13 through Table 17. Additional grading definitions for AEs are provided in the separate study document: Severity Grading for Adverse Events.

- The severity for all other types of AEs that are not in the adapted NCI CTCAE will be determined by the investigator based upon clinical judgment and by using the following severity grading criteria (for Grade 1 through Grade 4):

  - **Grade 1**: Mild; mild symptoms; clinical or diagnostic observations only; intervention not indicated; awareness of symptoms, but easily tolerated.

  - **Grade 2**: Moderate; minimal, local, or noninvasive intervention indicated. Infant is definitely acting like something is wrong.

  - **Grade 3**: Severe or medically significant but not immediately life-threatening; intensive intervention indicated; disabling. Infant is extremely irritable or unable to do usual activities.

  - **Grade 4**: Life-threatening consequences; urgent intervention indicated.

  - **Any AE that results in death will be assigned a severity grade of Grade 5.**

It is important to distinguish between seriousness criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.3.3. A Grade 3 AE is not necessarily considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Grading Scales for the Assessment of Severity for Solicited Injection-Site AEs, Solicited Systemic AEs, Elevated Temperature, and AESI

Note: Injection-site redness/erythema and injection-site swelling reported from Days 1 through 5 postdose will be evaluated by maximum size.

Table 13 Solicited Injection-site AE Severity Grading Scale

Solicited Injection-Site AE[a]	**Severity Grade**			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pain/Tenderness	Mild pain or tenderness with or without associated symptoms; does not interfere with normal activity	Moderate pain or tenderness. Interferes with normal activity	Severe pain or tenderness; prevents normal activity	Life-threatening consequences; urgent intervention indicated
Erythema/Redness	Size measured as >0 and ≤1	Size measured as >1 and ≤2	Size measured as >2	Necrosis or exfoliative dermatitis OR results in ER visit or hospitalization
Swelling	Size measured as >0 and ≤1	Size measured as >1 and ≤2	Size measured as >2	Necrosis or exfoliative dermatitis OR results in ER visit or hospitalization

AE=adverse event; eDiary=electronic diary; ER=emergency room.

[a] Based upon information provided by the legally acceptable representative in the eDiary and verbally during the eDiary review. Erythema/redness and swelling are specific injection-site AEs with size designations of numbers 1 through 8, as indicated on the study-supplied ruler. If the participant has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned a grade of 4, regardless of the size measured.

Table 14 Solicited Systemic AE Severity Grading Scale

Solicited Systemic AE[a]	**Severity Grade**			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Irritability	Mild; mild symptoms; clinical or diagnostic observations only; intervention not indicated; awareness of symptoms but easily tolerated.	Moderate; minimal local or noninvasive intervention indicated. Infant is definitely acting like something is wrong.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling. Infant is extremely irritable or unable to do usual activities.	Life-threatening consequences; urgent intervention indicated.
Drowsiness	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; awareness of symptoms but easily tolerated.	Moderate; minimal local or noninvasive intervention indicated. Infant is definitely acting like something is wrong.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling. Infant is extremely distressed or unable to do usual activities.	Life-threatening consequences; urgent intervention indicated.

Solicited Systemic AE[a]	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Irritability	Mild; mild symptoms; clinical or diagnostic observations only; intervention not indicated; awareness of symptoms but easily tolerated.	Moderate; minimal local or noninvasive intervention indicated. Infant is definitely acting like something is wrong.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling. Infant is extremely irritable or unable to do usual activities.	Life-threatening consequences; urgent intervention indicated.
Appetite lost	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; awareness of symptoms but easily tolerated.	Moderate; minimal local or noninvasive intervention indicated. Infant is definitely acting like something is wrong.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling. Infant is extremely distressed or unable to do usual activities.	Life-threatening consequences; urgent intervention indicated.

AE=adverse event; eDiary=electronic diary.
[a] Based upon information provided by the legally acceptable representative in the eDiary and verbally during the eDiary review.

Table 15 Elevated Temperature (Rectal) Severity Grading Scale

	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Elevated Temperature				
(°C) [a]	≥38.0 to <39.0	≥39.0 to <40.0	≥40.0	≥40.0
(°F) [a]	≥100.4 to <102.2	≥102.2 to <104.0	≥104.0 for ≤24 hours	≥104.0 for >24 hours

[a] Rectal temperature. Correction factors to adjust axillary temperatures for an equivalent rectal temperature are axillary temperature +2 degrees in Fahrenheit OR axillary temperature +1.1 degrees in Celsius.

Table 16 AESI: Anaphylaxis/Hypersensitivity Severity Grading Scale

AESI Term	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anaphylaxis	Not applicable	Not applicable	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated
Angioedema	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; awareness of symptoms, but easily tolerated	Moderate; minimal, local or noninvasive intervention indicated. Infant is definitely acting like something is wrong	Severe or medically significant but not immediately life-threatening; intensive intervention indicated; disabling. Infant is extremely distressed or unable to do usual activities	Life-threatening consequences; urgent intervention indicated
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting routine activities such as feeding	Limiting routine activities such as feeding; supplemental oxygen indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
Drug hypersensitivity (drug-related allergic reaction)	Allergic reaction; systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; IV intervention indicated	Life-threatening consequences; urgent intervention indicated
Hypersensitivity	Allergic reaction; systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; IV intervention indicated	Life-threatening consequences; urgent intervention indicated
Dyspnea (difficulty breathing)	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting routine activities such as feeding	Shortness of breath at rest; limiting routine activities such as feeding	Life-threatening consequences; urgent intervention indicated
Dysphonia	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	Not applicable
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting routine activities such as feeding	Severe respiratory symptoms limiting routine activities such as feeding; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated
AESI=adverse event(s) of special interest.				

Table 17 AESI: Rash Severity Grading Scale

AESI Term	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute generalized exanthematous pustulosis (AGEP)	Not applicable	Not applicable	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting routine activities such as feeding	Life-threatening consequences; urgent intervention indicated
Drug eruption	Lesions covering <10% BSA; topical intervention indicated	Lesions covering 10–30% BSA; oral intervention indicated	Lesions covering >30% BSA; IV intervention indicated	Not applicable
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not applicable	Not applicable	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting routine activities such as feeding	Life-threatening consequences; urgent intervention indicated
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10-30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated
Generalized rash of exfoliative nature (including dermatitis exfoliative and exfoliative rash)	Not applicable	Erythema covering >90% BSA without associated symptoms	Erythema covering >90% BSA with associated symptoms (eg, pruritus or tenderness); limiting routine activities such as feeding	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated
Stevens-Johnson syndrome	Not applicable	Not applicable	Skin sloughing covering <10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10–30% BSA with associated signs (ie, erythema, purpura, epidermal detachment, and mucous membrane detachment)

AESI Term	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Toxic epidermal necrolysis	Not applicable	Not applicable	Not applicable	Skin sloughing covering ≥30% BSA with associated symptoms (eg, erythema, purpura, or epidermal detachment)
Urticaria (hives or welts)	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10-30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	Not applicable
AESI=adverse event(s) of special interest; BSA=body surface area; ICU=intensive care unit; IV=intravenous.				

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a 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 study intervention 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 intervention study; or (3) study intervention(s) is/are used only 1 time.)

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

- Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to 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 study intervention relationship).

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

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

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

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

- 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

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 8.11 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legally acceptable representatives, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants or legally acceptable representatives on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant or 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 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 intervention outcomes are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage

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 outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants or legally acceptable representatives may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants or legally acceptable representatives may withdraw consent at any time by contacting the 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@MSD.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 or legally acceptable representative 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@MSD.com.

13. References

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

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

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

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Countries in the European Union Region and the United Kingdom

A potential participant from an investigator site located in a country in the European Union or the United Kingdom must be assessed for eligibility for enrollment in the study according to the inclusion and exclusion criteria in Section 5 1 and Section 5.2, respectively, with the exception of the age criteria below. For age criteria, a potential participant from an investigator site located in a country in the European Union or the United Kingdom must meet the following age criteria for eligibility for enrollment in the study:

Inclusion Criteria

Demographics

- For the **Phase 2b cohort only**: Has a chronological age >2 weeks of age up to 8 months and 29 days and is entering their first RSV season at the time that documented informed consent is provided.
- For the **Phase 3 cohort only**: Has a chronological age from birth up to 8 months and 29 days and is entering their first RSV season at the time that documented informed consent is provided.

The European Union countries participating in this study include the following:

- Belgium
- Denmark
- Finland
- France
- Italy
- Poland
- Romania
- United Kingdom (no longer in the European Union, but following these age criteria)

10.7.2 South Korea

A potential participant from an investigator site located in South Korea must be assessed for eligibility for enrollment in the study according to the inclusion and exclusion criteria in Section 5.1 and Section 5.2, respectively. As an additional inclusion criteria requirement (included in Section 5.1), participants must weigh ≥2 kg at Visit 1.

10.7.3 China

Enrollment of Participants in China

If sites in China have not met their participant allocation targets after enrollment of the global study is closed, these sites may continue to enroll participants until their allocation targets are met.

Future Biomedical Research (FBR)

No samples collected from participants enrolled at sites located in China will be used for FBR.

Informed Consent

To be consistent with local requirements, the investigator or medically qualified designee must obtain documented informed consent from each potential participant's legally acceptable representative prior to participating in this clinical study. Informed consent given by at least one of the participant's legally acceptable representatives is acceptable. A participant cannot be enrolled in this study under emergencies without the documented informed consent of the legally acceptable representative.

Serum Neutralizing Antibodies Against RSV (SNA)

SNA will not be tested in participants enrolled at sites in China.

Sample Collection for RT-PCR Testing for Respiratory Pathogen Identification and Testing for COVID-19

Within 24 hours after the NP sample collection for RT-PCR testing for identification of respiratory pathogens (included in the RT-PCR assay panel), a separate, additional swab will be collected for COVID-19 testing for participants enrolled at sites in China. If a COVID-19 test was performed within 24 hours before the site visit and the results are provided to the site, then the COVID-19 test does not need to be performed at the site visit.

Sample collection, storage, shipment, and laboratory testing for COVID-19 should follow local site requirements. Specimen information and local COVID-19 testing results will be entered into the database by site staff, as detailed in the data entry guidelines.

If 2 separate NP samples are required to be collected in the same respiratory infection assessment per local site requirements, the first NP sample should be collected for RT-PCR testing for identification of respiratory pathogens (included in the RT-PCR assay panel), and the second NP sample should be collected for COVID-19 testing.

If a participant requires collection of another NP sample(s) for RT-PCR testing for identification of respiratory pathogens (included in the RT-PCR assay panel), at the same visit or any subsequent visits, the subsequent sample(s) should be taken from the same nostril as the first sample. This requirement does not apply for separate, additional sample(s) for COVID-19 testing.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADA	Antidrug antibodies
AE	Adverse event
AESI	Adverse event(s) of special interest
APaT	All Participants as Treated
ARI	Acute respiratory infection
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
BSA	Body surface area
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CLD	Chronic lung disease
C_{max}	Maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
Cp	The count of RSV-associated MALRI cases in the placebo group
CRF	Case Report Form
CSR	Clinical Study Report
Ct	The count of RSV-associated MALRI cases in the MK-1654 group
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
E	Efficacy
ECDC	European Centre for Disease Control
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic case report form
EDC	Electronic data collection
eDiary	Electronic diary
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EL	Lower bound of the confidence interval of efficacy
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ER	Emergency room
EU	Upper bound of the confidence interval of efficacy
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
FAS	Full Analysis Set
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSR	First Site Ready
GCP	Good Clinical Practice
hMPV	Human metapneumovirus
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee

Abbreviation	Expanded Term
ILI	Influenza-like illness
IM	Intramuscular(ly)
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous(ly)
LRI	Lower respiratory infection
mAb	Monoclonal antibody
MALRI	Medically attended lower respiratory infection
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NP	Nasopharyngeal
NREVSS	National Respiratory and Enteric Virus Surveillance System
PCR	Polymerase chain reaction
PDLC	Predefined limit of change
PK	Pharmacokinetic(s)
PPE	Per-protocol efficacy
RESCEU	Respiratory Syncytial Virus Consortium in Europe
RNA	Ribonucleic acid
Rp	Incidence rate of RSV-associated MALRI in the placebo group
RR	Respiratory rate
RSV	Respiratory syncytial virus
Rt	Incidence rate of RSV-associated MALRI in the MK-1654 group
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SNA	Serum neutralizing antibodies against RSV
SoA	Schedule of Activities
SOC	System Organ Class
SpO_2	Oxygen saturation as measured by pulse oximetry
sSAP	Supplemental Statistical Analysis Plan
SUSAR	Suspected unexpected serious adverse reaction
TC	Telephone call
Tp	Total person-time of follow-up for efficacy in the placebo group
Tt	Total person-time of follow-up for efficacy in the MK-1654 group
UNSCH	Unscheduled visit
US	United States
WHO	World Health Organization

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