Official Protocol Title:	A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease
NCT number:	NCT04938830
Document Date:	25-Sep-2024

TITLE PAGE

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Protocol Title: A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease

Protocol Number: 007-03

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):

NCT	NCT04938830
EU CT	2022-500752-39-00
EudraCT	Not applicable
JRCT	jRCT2031210664
WHO	Not Applicable
UTN	Not Applicable
IND	130097

Approval Date: 25 September 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	25-SEP-2024	The primary purpose of this amendment is to update collection of SAEs after the protocol-specified follow-up period.
Amendment 2	18-MAY-2022	The primary purpose of this amendment is to add requirements specific to the Czech Republic.
Amendment 1	23-FEB-2022	The primary purpose of this amendment is to: 1) Specify enrollment targets for different age groups and 2) provide clarification on respiratory infection assessment and nasopharyngeal (NP) sample collection.
Original Protocol	17-MAY-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update collection of SAEs after the protocol-specified follow-up period.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Update collection of SAEs after the protocol-specified follow-up period to include only those that are related to study intervention.	This change was made to address incorrect non-standard text to align with company standard operating procedures and ICH guidelines.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Throughout	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other changes and their reasons are included for completeness.
Throughout	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.
Title Page	New study identifiers (NCT and jRCT) were added.	Update study identifiers.
	Remove EudraCT study identifier.	Refer to Title Page rationale on study identifiers.
Section 1.1, Synopsis	Intervention Groups and Duration: Terminology in the Use column was revised (Experimental was revised to Test Product).	To align with ISO standards and comply with EU CTR.
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.	To comply with EU CTR.
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 6.1, Study Intervention(s) Administered	Table 2: Terminology in the Dose Formulation column was revised (Vial revised to Solution).	Refer to Section 1.1 rationale.
	Table 2: Terminology in the Use column was revised (Experimental revised to Test Product).	Refer to Section 1.1 rationale.
Section 8.4, Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added statement to document if an SAE was associated with a medication error, misuse, or abuse.	Refer to Section 4.4 rationale.
Section 10.1.6, Compliance with Study Registration and Results Posting Requirements	Updated specified EU regulation.	Refer to Section 4.4 rationale.
Section 10.1.7, Compliance with Law, Audit, and Debarment	Added content to immediately report any serious/suspected serious breaches.	Refer to Section 4.4 rationale.
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.	Refer to Section 4.4 rationale.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease

Short Title: Palivizumab-Controlled Evaluation of Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

This is an estimation study without hypotheses. The following objectives will be evaluated in the study population. The RSV Season 1 42-day safety follow-up period consists of safety data collected from Day 1 post Dose 1 through 14 days post Dose 2.

Primary Objectives	Primary Endpoints
- RSV Season 1: To evaluate the safety and tolerability of MK-1654 compared to palivizumab in RSV Season 1 as assessed by the proportion of participants experiencing AEs.	- Solicited injection-site AEs from Days 1 through 5 after each dose - 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 after each dose - Solicited systemic AEs from Days 1 through 5 after each dose - Anaphylaxis/hypersensitivity AESI from Days 1 through 42 post Dose 1 - Rash AESI from Days 1 through 42 post Dose 1 - Nonserious AEs from Days 1 through 42 post Dose 1 and 14 days after each subsequent dose - SAEs through the duration of participation in RSV Season 1

Secondary Objectives	Secondary Endpoints
- RSV Season 1: To estimate the efficacy of MK-1654 compared to palivizumab as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 post Dose 1 in RSV Season 1.	- 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
- RSV Season 1: To estimate the incidence of RSV-associated hospitalizations from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.	- RSV-associated hospitalization, defined as the following: ▪ Hospital admission for respiratory illness; AND ▪ RSV-positive RT-PCR NP sample
- RSV Season 1: To describe the serum PK concentration of MK-1654 at Days 7, 150, and 240 after the dose of MK-1654 in RSV Season 1.	- MK-1654 PK concentration
- RSV Season 2: To describe the safety of MK-1654 administered in RSV Season 2 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 from Days 1 through 180 postdose
- RSV Season 2: To describe the serum PK concentration of MK-1654 at Days 7 and 150 postdose in RSV Season 2.	- MK-1654 PK concentration

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Respiratory syncytial virus infection
Population	Infants and children at increased risk for severe RSV disease
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control
Study Blinding	Part 1 - Double-blind with in-house blinding Part 2 - Unblinded, open-label
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 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 1000 participants will be randomized in this study as described in Section 9.9.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
MK-1654	MK-1654	150 mg/mL	105 mg	IM	Single dose in RSV Season 1[a] (Day 1 visit)	Test Product
MK-1654	Placebo	0 mg/mL	0 mg	IM	Single dose in RSV Season 1 (Day 28 visit)	Placebo
MK-1654	MK-1654	150 mg/mL	210 mg	IM	Single dose in RSV Season 2[a] (Day 1 visit)	Test Product
Palivizumab	Palivizumab	100 mg/mL	15 mg/kg body weight	IM	3 to 5 monthly doses in RSV Season 1[a] (starting at Day 1 visit)	Comparator
Palivizumab	MK-1654	150 mg/mL	210 mg	IM	Single dose in RSV Season 2[a] (Day 1 visit)	Test Product

IM=intramuscular; RSV=respiratory syncytial virus
[a] If during the RSV season a participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the surgical procedure, additional study intervention may be administered post-surgery based on the Sponsor consultation.

Palivizumab is registered/marketed under the brand name Synagis™ in several countries globally.

Total Number of Intervention Groups/ Arms	2 intervention groups

Duration of Participation	Each participant will be screened, enrolled to participate in either 1 or 2 RSV seasons, randomized, and receive the first dose of assigned study intervention on RSV Season 1 Day 1. All participants enrolled will be administered subsequent doses as scheduled and be followed for 365 days. Participants enrolled for 2 RSV seasons will also receive a dose of MK 1654 in RSV Season 2 and will be followed for an additional 180 days postdose. Most participants will participate in the study for 365 days (1 RSV season) from the time the participant's legally acceptable representative provides documented informed consent through the final contact. Participants who enroll, consent, and remain eligible for 2 RSV seasons will participate in the study for up to 575 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 Section 10.1.4 (Appendix 1).

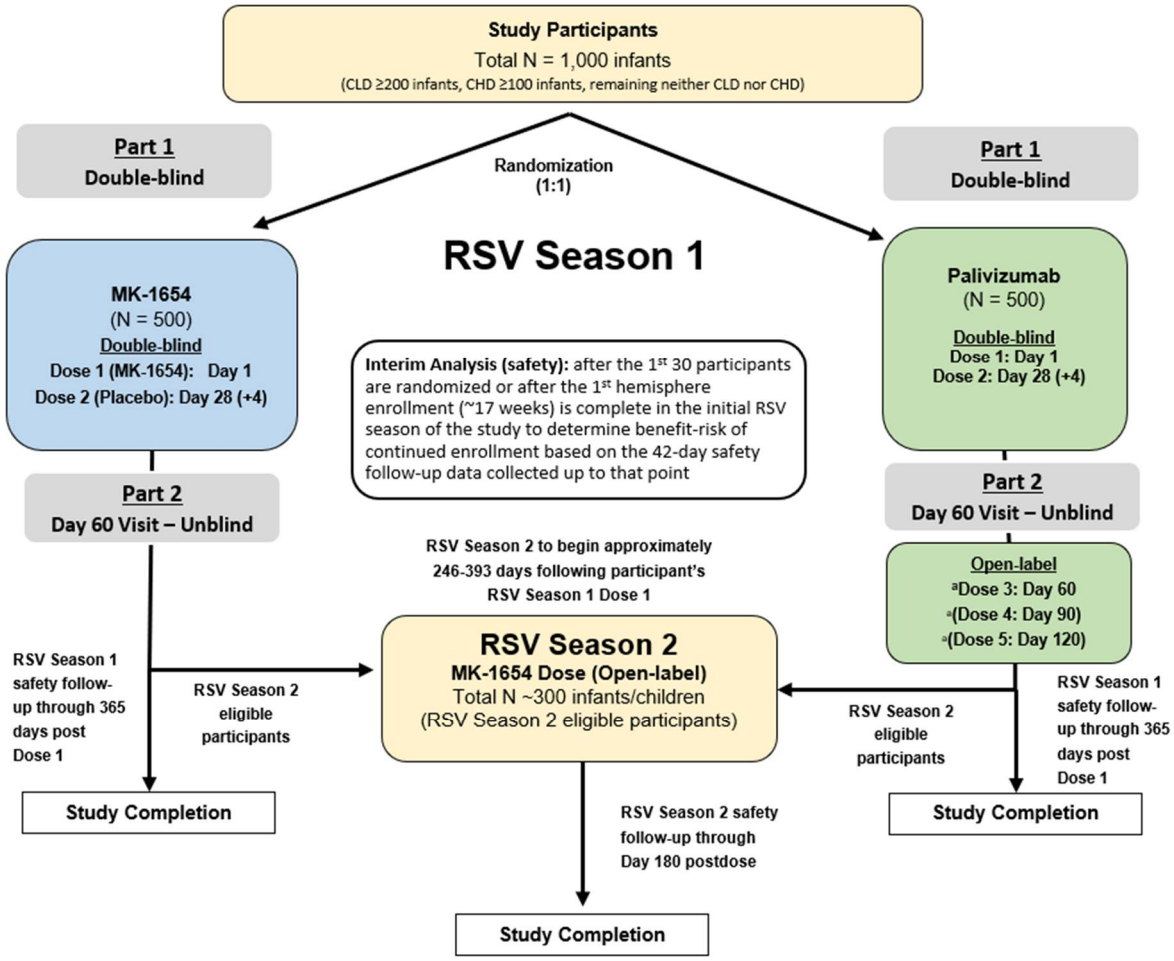
Study Accepts Healthy Participants: Yes

A list of abbreviations used in this document can be found in Section 10.8 (Appendix 8).

1.2 Schema

The planned study design is depicted in Figure 1.

Figure 1 MK-1654-007 Study Design



Abbreviations: CHD=congenital heart disease; CLD=chronic lung disease; N=number of randomized participants; RSV=Respiratory Syncytial Virus

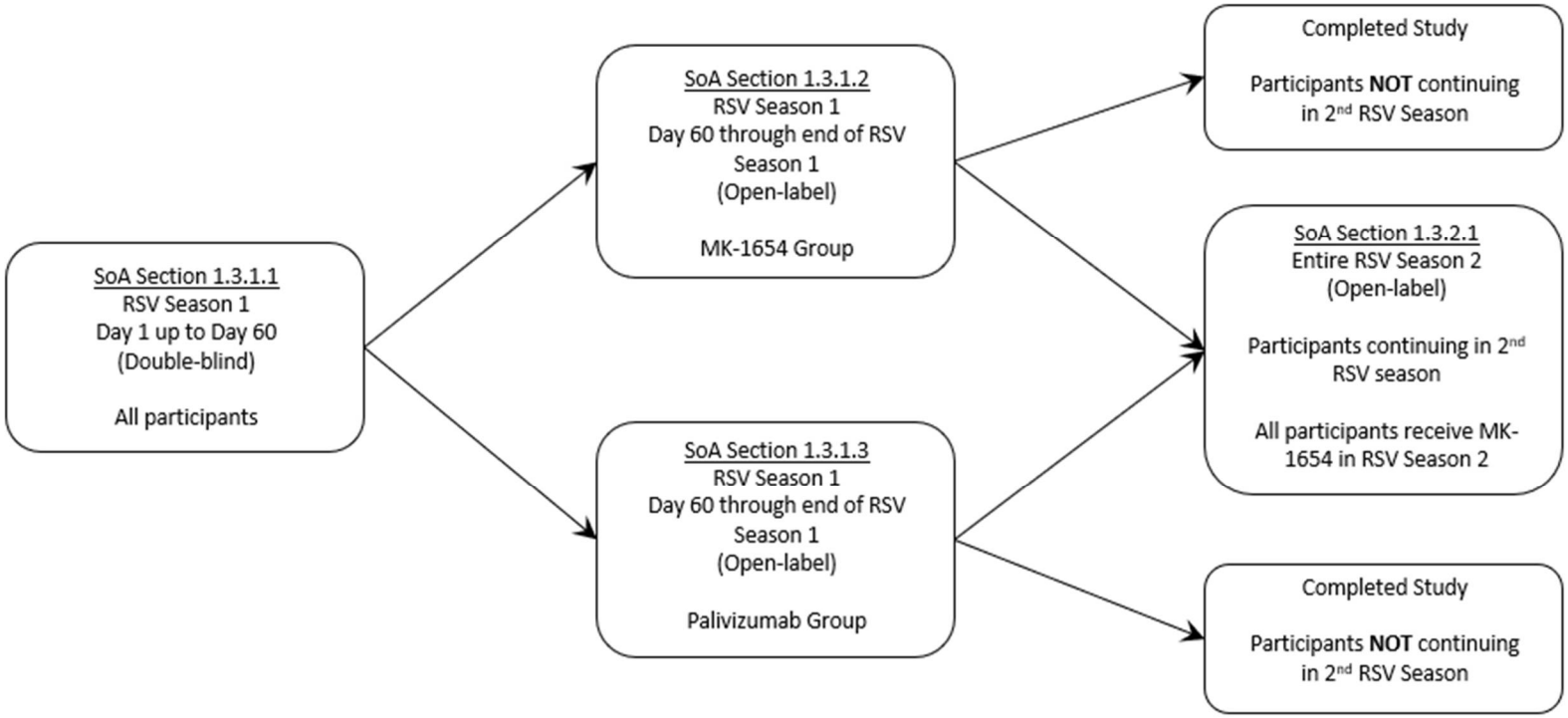
All doses administered intramuscularly.

[a] Each subsequent dose must be administered between 28-32 days after the previous dose. Receipt of palivizumab Doses 4 and 5 depend on enrollment date relative to RSV season. Note: If during the RSV season a participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the surgical procedure, additional study intervention may be administered post-surgery based on the Sponsor consultation.

1.3 Schedule of Activities

Participants will follow the SoAs in Section 1.3 as depicted in Figure 2.

Figure 2 MK-1654-007 Schedule of Assessments Flowchart



RSV=respiratory syncytial virus; SoA=schedule of activities

1.3.1 RSV Season 1 Schedule of Activities

1.3.1.1 Schedule of Activities RSV Season 1 Day 1 Up to Day 60 Visit (All Participants; Part 1 – Double-blind)

Study Period	Screening, Randomization, and Intervention			Follow-up RSV Season 1 (Day 1 Up to Day 60 Visit)							Notes
Visit Number/Title	1			TC	2	Weekly contact start	3	TC	4A	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 All Participants Part 1 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	28 (+4)	42 (+4)[c]	60[d] (see Section 1.3.1.2 and Section 1.3.1.3)	If indicated	[a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts. [c] At least 14 days after Dose 2. [d] Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2).
	Predose	Dose	Post-dose								
Administrative Procedures											
Informed Consent	X										Participants consented for 1 or 2 RSV seasons depending on eligibility (see Section 5.1 and Section 5.2).
Informed Consent for FBR	X										Participation in FBR is optional and consent must be obtained before collection of buccal swab DNA samples.
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	Concomitant medications will be collected from Day 1 to 14 days after Dose 2, afterwards only concomitant medications associated with an AE/SAE will be recorded.
Predose NP Sample Collection for RT-PCR Testing	X (if indicated)										Collect if respiratory infection symptoms are present within 7 days before the Day 1 visit. See Section 8.13.1.1 and Section 8.2.3.
Assignment of Randomization Number	X										

Study Period	Screening, Randomization, and Intervention			Follow-up RSV Season 1 (Day 1 Up to Day 60 Visit)							Notes
Visit Number/Title	1			TC	2	Weekly contact start	3	TC	4A	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 All Participants Part 1 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	28 (+4)	42 (+4)[c]	60[d] (see Section 1.3.1.2 and Section 1.3.1.3)	If indicated	[a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts. [c] At least 14 days after Dose 2. [d] Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2).
	Predose	Dose	Post-dose								
Drug Administration		X					X				Performed by unblinded study site personnel only. See Section 6.1, Section 6.2, and Section 8.1.8.1. MK-1654 group: MK-1654 administered at the Day 1 visit, and placebo administered at the Day 28 visit. Palivizumab group: Palivizumab administered at both the Day 1 and Day 28 visits.
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	X			
Safety Procedures											
Full Physical Examination including Weight and Length	X										
Brief Directed Physical Examination including Weight and Length					X		X			X[e]	[e] Perform brief directed examination at an unscheduled visit if necessary.
Vital Signs	X		X		X		X			X	See Section 8.3.2.
30-minute Postdose Safety Observation			X				X				Performed by blinded study site staff only. Vital signs should be repeated after the observation period. (See Appendix 7.2 for specific requirements for participants in the Czech Republic.)
AE/SAE Review	X			X	X	X	X	X		X	

Study Period	Screening, Randomization, and Intervention			Follow-up RSV Season 1 (Day 1 Up to Day 60 Visit)							Notes
Visit Number/Title	1			TC	2	Weekly contact start	3	TC	4A	UNSCH	See Section 8.13 for descriptions of study visits. UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 All Participants Part 1 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	28 (+4)	42 (+4)[c]	60[d] (see Section 1.3.1.2 and Section 1.3.1.3)	If indicated	[a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts. [c] At least 14 days after Dose 2. [d] Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2).
	Predose	Dose	Post-dose								
AESI Assessment		X (if indicated)								X	Required if indicated AESI require further assessment. See Section 8.4.8.
Venous Blood for ADA and Additional ADA Characterization				X (if indicated)						X	Collect only if participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI through Day 42. See Section 8.4.8.1 and Section 10.2 (Appendix 2).
Respiratory Virus Assessments											
Surveillance for Respiratory Infection Symptoms				X	X	←Weekly Contact→					Determine if participant had respiratory symptoms or was seen in a clinical setting. 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.
Pharmacokinetics/Immunogenicity/Pharmacodynamics											
Venous Blood for MK-1654 PK	X				X						
Venous Blood for ADA	X										
Venous Blood for RSV SNA	X				X						
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.

ADA=antidrug antibodies; AE=adverse event; AESI=adverse event of special interest; DNA=deoxyribonucleic acid; eDiary=electronic diary; FBR=future biomedical research; 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.

1.3.1.2 Schedule of Activities RSV Season 1 Day 60 Visit Through End of RSV Season 1 (MK-1654 Group; Part 2 – Open-label)

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)							Notes
Visit Number/Title	4A	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for description of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 MK-1654 Group Part 2 Scheduled Day and Window (Days):	60 (28-32 days after Dose 2)	150 (±5)	180 (±2[a])	240 (±5)	365 (+14)[b]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Continue weekly contact, each with a ±2-day window. [b] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Administrative Procedures								
Concomitant Medication Review	X	X	X	X	X	X[c]	X	Only concomitant medications associated with an AE/SAE will be recorded. [c] Concomitant medications will be collected for 42 days following an additional post-surgery dose of MK-1654.
MK-1654 Administration						X		See Section 6.1, Section 6.2, and Section 8.1.8.1.
Provide or Reactivate Device for eDiary Data Collection and Provide LAR Training						X		For participants using a study-provided device, provide eDiary if LAR previously returned the original study-provided device.
Review eDiary with LAR						X		Safety follow-up for 42 days after post-surgery dose. See Section 8.3.5.
Collect eDiary Device from LAR				X				
Review Inclusion/ Exclusion Criteria				X				For participants enrolled in 2 RSV seasons, review inclusion/exclusion criteria for RSV Season 2 to ensure participant meets RSV Season 2 eligibility requirements. See Section 5.1.1 and Section 5.2.1.

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)							Notes
Visit Number/Title	4A	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for description of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 MK-1654 Group Part 2 Scheduled Day and Window (Days):	60 (28-32 days after Dose 2)	150 (±5)	180 (±2[a])	240 (±5)	365 (+14)[b]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Continue weekly contact, each with a ±2-day window. [b] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Safety Procedures								
Brief Directed Physical Examination including Weight and Length	X	X		X		X	X[d]	[d] Perform brief directed examination at an unscheduled visit if necessary.
Vital Signs	X	X		X		X	X	See Section 8.3.2.
30-minute Postdose Safety Observation						X		Vital signs should be repeated after the observation period. (See Appendix 7.2 for specific requirements for participants in the Czech Republic.)
AE/SAE Review	X	X	X	X	X	X[e]	X	[e] Safety follow-up for 42 days after additional post-surgery dose of MK-1654.
AESI Assessment						X		Required if indicated AESI occurs within 42 days after additional post-surgery dose and requires further assessment. See Section 8.4.8.
Venous Blood for ADA and Additional ADA Characterization						X		Collect only if participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI within 42 days after additional post-surgery dose and requires further assessment. See Section 8.4.8.1 and Section 10.2 (Appendix 2).
Respiratory Virus Assessments								
Surveillance for Respiratory Infection Symptoms	←Weekly Contact→							Determine if participant had respiratory symptoms or was seen in a clinical setting. 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.

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)							Notes
Visit Number/Title	4A	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for description of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 MK-1654 Group Part 2 Scheduled Day and Window (Days):	60 (28-32 days after Dose 2)	150 (±5)	180 (±2[a])	240 (±5)	365 (+14)[b]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Continue weekly contact, each with a ±2-day window. [b] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
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.
Pharmacokinetics/Immunogenicity/Pharmacodynamics								
Venous Blood for MK-1654 PK		X		X		X[f]		[f] Additional blood draw(s) may be collected based on Sponsor consultation. See Section 8.
Venous Blood for ADA		X		X		X[f]		
Venous Blood for RSV SNA		X		X		X[f]		

ADA=antidrug antibodies; AE=adverse event; AESI=adverse event of special interest; CHD=congenital heart disease; ECMO=extracorporeal membrane oxygenation; eDiary=electronic diary; 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; SoA=Schedule of Assessments; TC=telephone call; UNSCH=unscheduled visit.

1.3.1.3 Schedule of Activities RSV Season 1 Day 60 Visit Through End of RSV Season 1 (Palivizumab Group; Part 2 – Open-label)

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)												Notes
Visit Number/Title	4A	TC	4B	TC	4C	TC	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 Palivizumab Group Part 2 Scheduled Day and Window (Days):	60[a]	74[a]	90[a,b]	104[a,b]	120[a,b]	134[a,b]	150 (±5)	180 (±2[c])	240 (±5)	365 (+14)[d]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Doses 3-5 must be administered between 28-32 days after the previous dose. Safety follow-up TCs must be conducted 14 days (±2 days) after each dose. [b] For those who do not require a dose at the Day 90 or 120 visits, the respective visit(s) and the associated 14-day safety follow-up TC will not be conducted. [c] Continue weekly contact, each with a ±2-day window. [d] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Administrative Procedures													
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	Only concomitant medications associated with an AE/SAE will be recorded.
Palivizumab Administration	X		X[e]		X[e]						X		See Section 6.1, Section 6.2, and Section 8.1.8.1. [e] Doses 4 and 5 will be administered as applicable (see Section 6.1 and Section 2.2.4).

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)												Notes
Visit Number/Title	4A	TC	4B	TC	4C	TC	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 Palivizumab Group Part 2 Scheduled Day and Window (Days):	60[a]	74[a]	90[a,b]	104[a,b]	120[a,b]	134[a,b]	150 (±5)	180 (±2[c])	240 (±5)	365 (+14)[d]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Doses 3-5 must be administered between 28-32 days after the previous dose. Safety follow-up TCs must be conducted 14 days (±2 days) after each dose. [b] For those who do not require a dose at the Day 90 or 120 visits, the respective visit(s) and the associated 14-day safety follow-up TC will not be conducted. [c] Continue weekly contact, each with a ±2-day window. [d] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Provide or Reactivate Device for eDiary Data Collection and Provide LAR Training											X		For participants using a study-provided device, provide eDiary if LAR previously returned the original study-provided device.
Review eDiary Data with LAR	X	X	X	X	X	X					X[f]		[f] Safety follow-up for 14 days after post-surgery dose. See Section 8.3.5.
Collect eDiary Device from LAR									X				
Review Inclusion/ Exclusion Criteria									X				For participants enrolled in 2 RSV seasons, review inclusion/exclusion criteria for RSV Season 2 before blood collection to ensure participant meets RSV Season 2 eligibility requirements. See Section 5.1.1 and Section 5.2.1.

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)												Notes
Visit Number/Title	4A	TC	4B	TC	4C	TC	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 Palivizumab Group Part 2 Scheduled Day and Window (Days):	60[a]	74[a]	90[a,b]	104[a,b]	120[a,b]	134[a,b]	150 (±5)	180 (±2[c])	240 (±5)	365 (+14)[d]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Doses 3-5 must be administered between 28-32 days after the previous dose. Safety follow-up TCs must be conducted 14 days (±2 days) after each dose. [b] For those who do not require a dose at the Day 90 or 120 visits, the respective visit(s) and the associated 14-day safety follow-up TC will not be conducted. [c] Continue weekly contact, each with a ±2-day window. [d] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Safety Procedures													
Brief Directed Physical Examination including Weight and Length	X		X		X		X		X		X	X[g]	[g] Perform brief directed examination at an unscheduled visit if necessary.
Vital Signs	X		X		X		X		X		X	X	See Section 8.3.2.
30-minute Postdose Safety Observation	X		X		X						X		Vital signs should be repeated after the observation period. (See Appendix 7.2 for specific requirements for participants in the Czech Republic.)
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X[h]	X	[h] Safety follow-up for 14 days after additional post-surgery dose of palivizumab.

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)												Notes
Visit Number/Title	4A	TC	4B	TC	4C	TC	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 Palivizumab Group Part 2 Scheduled Day and Window (Days):	60[a]	74[a]	90[a,b]	104[a,b]	120[a,b]	134[a,b]	150 (±5)	180 (±2[c])	240 (±5)	365 (+14)[d]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Doses 3-5 must be administered between 28-32 days after the previous dose. Safety follow-up TCs must be conducted 14 days (±2 days) after each dose. [b] For those who do not require a dose at the Day 90 or 120 visits, the respective visit(s) and the associated 14-day safety follow-up TC will not be conducted. [c] Continue weekly contact, each with a ±2-day window. [d] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Respiratory Virus Assessments													
Surveillance for Respiratory Infection Symptoms	←Weekly Contact→												Determine if participant had respiratory symptoms or was seen in a clinical setting. 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.

Study Period	Follow-up RSV Season 1 (Day 60 Visit through end of RSV Season 1)												Notes
Visit Number/Title	4A	TC	4B	TC	4C	TC	5	Weekly contact ends	6	TC	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 1 Palivizumab Group Part 2 Scheduled Day and Window (Days):	60[a]	74[a]	90[a,b]	104[a,b]	120[a,b]	134[a,b]	150 (±5)	180 (±2[c])	240 (±5)	365 (+14)[d]	If indicated	If indicated	See SoA in Section 1.3.1.1 for activities before the Day 60 visit. Participant's treatment assignment will be unblinded at the Day 60 visit (28-32 days after Dose 2). [a] Doses 3-5 must be administered between 28-32 days after the previous dose. Safety follow-up TCs must be conducted 14 days (±2 days) after each dose. [b] For those who do not require a dose at the Day 90 or 120 visits, the respective visit(s) and the associated 14-day safety follow-up TC will not be conducted. [c] Continue weekly contact, each with a ±2-day window. [d] Participants continuing into RSV Season 2 will begin RSV Season 2 up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1) (Section 4.2.1.1.1). See SoA in Section 1.3.2 for RSV Season 2. Participants not eligible for RSV Season 2 will be followed through the RSV Season 1 Day 365 TC.
Pharmacokinetics/Immunogenicity/Pharmacodynamics													
Venous Blood for MK-1654 PK									X[i]				[i] Participants continuing in RSV Season 2 will have blood sample collection for PK, ADA, and SNA at the Day 240 visit.
Venous Blood for ADA									X[i]				
Venous Blood for RSV SNA									X[i]				

ADA=antidrug antibodies; AE=adverse event; AESI=adverse event of special interest; CHD=congenital heart disease; ECMO=extracorporeal membrane oxygenation; eDiary=electronic diary; 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; SoA=Schedule of Assessments; TC=telephone call; UNSCH=unscheduled visit.

1.3.2 RSV Season 2 Schedule of Activities

1.3.2.1 Schedule of Activities RSV Season 2 (Subset of Participants Receiving MK-1654 Administration in RSV Season 2; Part 2 – Open-label)

Study Period	Intervention			Follow-up RSV Season 2 (through 180 days post RSV Season 2 dose)								Notes
Visit Number/Title	7			TC	8	Weekly contact start	9	10	TC Weekly contact ends	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 2 Part 2 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	42 (+7)	150 (±5)	180 (±2[b])	If indicated	If indicated	The Day 1 visit/Start of RSV Season 2 will occur up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1). [a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts.
	Predose	Dose	Post-dose									
Administrative Procedures												
Review Inclusion/ Exclusion Criteria	X											For participants enrolled in 2 RSV seasons, review inclusion/exclusion criteria to ensure participant meets RSV Season 2 eligibility requirements. See Section 5.1.1 and Section 5.2.1.
Medical History	X											Document changes to medical history collected in RSV Season 1.

Study Period	Intervention			Follow-up RSV Season 2 (through 180 days post RSV Season 2 dose)								Notes
Visit Number/Title	7			TC	8	Weekly contact start	9	10	TC Weekly contact ends	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 2 Part 2 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	42 (+7)	150 (±5)	180 (±2[b])	If indicated	If indicated	The Day 1 visit/Start of RSV Season 2 will occur up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1). [a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts.
	Predose	Dose	Post-dose									
Concomitant Medication Review	X		X	X	X	X	X	X	X	X[c]	X	Concomitant medications will be collected from Days 1 to 42 in RSV Season 2, afterwards only concomitant medications associated with an AE/SAE will be recorded. [c] Concomitant medications will be collected for 42 days following an additional post-surgery dose of MK-1654.
MK-1654 Administration		X								X[d]		[d] See Section 6.1, Section 6.2, and Section 8.1.8.1.
Provide or Activate Device for eDiary Data Collection and Provide LAR Training			X							X[e]		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). [e] Provide eDiary if LAR previously returned the original eDiary.
Review eDiary Data with LAR				X	X	X	X			X[f]		[f] Safety follow-up for 42 days after post-surgery dose. See Section 8.3.5.

Study Period	Intervention			Follow-up RSV Season 2 (through 180 days post RSV Season 2 dose)								Notes
Visit Number/Title	7			TC	8	Weekly contact start	9	10	TC Weekly contact ends	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 2 Part 2 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	42 (+7)	150 (±5)	180 (±2[b])	If indicated	If indicated	The Day 1 visit/Start of RSV Season 2 will occur up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1). [a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts.
	Predose	Dose	Post-dose									
Return eDiary Device from LAR										X[g]		[g] For participants using a study-provided device, return after the Day 180 weekly contact or 42 days of safety follow-up for the additional post-surgery dose of MK-1654, whichever is later.
Safety Procedures												
Brief Directed Physical Examination including Weight and Length	X				X		X	X		X	X[h]	[h] Perform brief directed examination at an unscheduled visit if necessary.
Vital Signs	X		X		X		X	X		X	X	See Section 8.3.2.
30-minute Postdose Safety Observation		X	X							X		Vital signs should be repeated after the observation period. (See Appendix 7.2 for specific requirements for participants in the Czech Republic.)
AE/SAE Review	X			X	X	X	X	X	X	X[i]	X	[i] Safety follow-up for 42 days after additional post-surgery dose of MK-1654.

Study Period	Intervention			Follow-up RSV Season 2 (through 180 days post RSV Season 2 dose)								Notes
Visit Number/Title	7			TC	8	Weekly contact start	9	10	TC Weekly contact ends	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 2 Part 2 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	42 (+7)	150 (±5)	180 (±2[b])	If indicated	If indicated	The Day 1 visit/Start of RSV Season 2 will occur up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1). [a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts.
	Predose	Dose	Post-dose									
AESI Assessment		X (if indicated)								X		Required if indicated AESI occurs within 42 days after the RSV Season 2 dose or an additional post-surgery dose and requires further assessment. See Section 8.4.8.
Venous Blood for ADA and Additional ADA Characterization				X (if indicated)						X		Collect only if participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI within 42 days after RSV Season 2 dose or an additional post-surgery dose and requires further assessment. See Section 8.4.8.1 and Section 10.2 (Appendix 2).
Respiratory Virus Assessment												
Surveillance for Respiratory Infection Symptoms				X	X	←Weekly Contact→						Determine if participant had respiratory symptoms or was seen in a clinical setting. 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.

Study Period	Intervention			Follow-up RSV Season 2 (through 180 days post RSV Season 2 dose)								Notes
Visit Number/Title	7			TC	8	Weekly contact start	9	10	TC Weekly contact ends	Post-surgery Follow-up	UNSCH	See Section 8.13 for descriptions of study visits. Post-surgery follow-up visit for participants who undergo 1) ECMO or 2) surgical intervention and require cardiopulmonary bypass during the procedure for CHD during the RSV season and are recommended during Sponsor consultation to receive additional study intervention (Section 8.1.8.1). UNSCH for respiratory infection and AESI assessment and early withdrawal, if indicated.
RSV Season 2 Part 2 Scheduled Day and Window (Days):	Day 1			3 (-1)[a]	7 (+2)	14 (±2[b])	42 (+7)	150 (±5)	180 (±2[b])	If indicated	If indicated	The Day 1 visit/Start of RSV Season 2 will occur up to 4 weeks before the start of their second RSV season (246 to 393 days after RSV Season 1 Dose 1). [a] If Day 3 is not a business day, the phone call should occur on Day 2. [b] ±2-day window applies to all weekly contacts.
	Predose	Dose	Post-dose									
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.
Pharmacokinetics/Immunogenicity/Pharmacodynamics												
Venous Blood Sample for PK					X			X		X[j]		[j] Additional blood draw(s) may be collected based on Sponsor consultation. See Section 8.
Venous Blood Sample for ADA					X			X		X[j]		
Venous Blood Sample for RSV SNA					X			X		X[j]		

ADA=antidrug antibodies; AE=adverse event; AESI=adverse event of special interest; CHD=congenital heart disease; ECMO=extracorporeal membrane oxygenation; eDiary=electronic diary; 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.

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 use 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 and the complications of RSV infection (such as MALRI). Palivizumab is available for use in pediatric patients at highest risk for complications of RSV infection, such as premature infants ≤35 weeks gestational age, and those with chronic heart and lung disease. However, the majority of RSV infections occur among otherwise healthy pre-term and full-term infants. An efficacious prophylactic agent has the potential to make a 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 as a single dose to be administered before the onset of the RSV season or, for those infants born during the RSV season, soon after birth.

This study is being conducted to evaluate the safety, tolerability, and efficacy of MK-1654 versus palivizumab and to evaluate the PK of MK-1654 in infants who are eligible and recommended to receive palivizumab (in accordance with national or local [state or provincial] guidelines or professional society recommendations) in their first RSV season (RSV Season 1; ie, infants ≤35 weeks gestational age or infants with CLD of prematurity or hemodynamically significant CHD, as defined in Inclusion Criterion #1b in Section 5.1). All participants will have a chronological age from birth up to 1 year and will be entering their first RSV season at the time that documented informed consent is provided (see

Section 4.2.1.1.1); 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). 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 (Section 5.1 and Section 5.2).

2.2 Background

Burden of RSV Infection in Infants

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

RSV is the most common cause of bronchiolitis, LRIs, and hospitalization in infants and is estimated to cause 28% of acute LRIs and 13% to 22% of deaths from acute LRIs in children under 5 years of age. A systematic review and modeling study of RSV estimated that in 2015, there were 33.1 million (UR: 21.6-50.3) episodes of RSV in children under 5 years of age worldwide, approximately 3.2 million (UR: 2.7-3.8) of which resulted in hospitalization. Almost half (45%) of these hospitalizations occurred in infants younger than 6 months [Shi, T., et al 2015]. Infants admitted with RSV present with a range of signs and symptoms including chest wall in-drawing, hypoxemia, wheezing, grunting, and apnea [Garcia, C. G., et al 2010] [Shi, T., et al 2015], many of whom develop complications such as pneumonia and sepsis. Those with uncomplicated cases are hospitalized for an average of 3 days. Hospital systems therefore devote a great deal of time and resources to ensuring appropriate care to infants and children infected with RSV [Shi, T., et al 2015]. 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, where underreporting and at-home deaths are more common; therefore, the number of deaths due to RSV worldwide may be even higher. 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 parents and caregivers [Bourgeois, F. T., et al 2009].

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]. However, the infant population in which palivizumab is recommended has narrowed 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 use of palivizumab. A highly potent mAb with extended half-life, like MK 1654, with a one-time administration given during the first RSV season would address an unmet need. Moreover, a fully human mAb administered only once (eg, MK-1654) should display a relatively lower incidence of hypersensitivity reactions compared with a humanized mAb that is given multiple times throughout the RSV season.

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 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.

A Phase 2b/3 randomized, placebo-controlled, double-blind study (PN004) is currently ongoing to assess the efficacy, safety, and PK of MK-1654 for the prevention of RSV-associated MALRI in healthy pre-term and full-term infants. The PN004 PK data will be compared with the PK data in this study population.

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

2.2.4 Information on Other Study-related Therapy

An active control (palivizumab) regimen will be used in this study, as listed in Table 2 (see Section 4.2.2). This is consistent with real-world practice as a prophylactic mAb for RSV infection in premature infants ≤35 weeks gestational age and those with CHD and CLD. Depending on enrollment date relative to the RSV season, participants randomized to the palivizumab group will receive 3 to 5 doses of palivizumab in RSV Season 1. The first dose will be given on RSV Season 1 Day 1, with subsequent doses every 28 (+4) days thereafter (inclusive of dosing day; minimum of 28 days between doses) through the end of RSV season, depending on the timing of enrollment relative to the RSV season consistent with standard of care (see Section 6.1).

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 500 infants will receive MK-1654/placebo and 500 infants will receive palivizumab in the participant's first RSV season for this study. Approximately 300 of these infants will receive MK-1654 before their second RSV season. With higher RSV neutralization potency as compared to palivizumab, MK-1654 may provide improved protection against RSV-associated MALRI and RSV-associated hospitalization, with a safety profile expected to be comparable to or better than palivizumab in the target population (infants ≤35 weeks gestational age or infants with CLD of prematurity or hemodynamically significant CHD with a chronological age from birth to 1 year and entering their first RSV season at the time that documented informed consent is provided). Although MK-1654 has not been previously studied for second RSV season dosing, it is expected to have a similar profile as when administered within the first year.

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 targets the RSV F protein.

A fully human mAb administered only once per season, 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 in a single season. 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 reduced 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 (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

This is an estimation study without hypotheses. The following objectives will be evaluated in the study population. The RSV Season 1 42-day safety follow-up period consists of safety data collected from Day 1 post Dose 1 through 14 days post Dose 2.

Primary Objectives	**Primary Endpoints**
• **RSV Season 1**: To evaluate the safety and tolerability of MK-1654 compared to palivizumab in RSV Season 1 as assessed by the proportion of participants experiencing AEs.	• Solicited injection-site AEs from Days 1 through 5 after each dose • 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 after each dose • Solicited systemic AEs from Days 1 through 5 after each dose • Anaphylaxis/hypersensitivity AESI from Days 1 through 42 post Dose 1 • Rash AESI from Days 1 through 42 post Dose 1 • Nonserious AEs from Days 1 through 42 post Dose 1 and 14 days after each subsequent dose • SAEs through the duration of participation in RSV Season 1
Secondary Objectives	**Secondary Endpoints**
• **RSV Season 1**: To estimate the efficacy of MK-1654 compared to palivizumab as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 150 post Dose 1 in RSV Season 1.	• 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

• **RSV Season 1**: To estimate the incidence of RSV-associated hospitalizations from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.	• RSV-associated hospitalization, defined as the following: ▪ Hospital admission for respiratory illness; AND ▪ RSV-positive RT-PCR NP sample
• **RSV Season 1**: To describe the serum PK concentration of MK-1654 at Days 7, 150, and 240 after the dose of MK-1654 in RSV Season 1.	• MK-1654 PK concentration
• **RSV Season 2**: To describe the safety of MK-1654 administered in RSV Season 2 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 from Days 1 through 180 postdose
• **RSV Season 2**: To describe the serum PK concentration of MK-1654 at Days 7 and 150 postdose in RSV Season 2.	• MK-1654 PK concentration
Tertiary / Exploratory Objectives	**Tertiary / Exploratory Endpoints**
• **RSV Season 1**: To estimate the efficacy of MK-1654 compared to palivizumab as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 post Dose 1 in RSV Season 1.	• RSV-associated MALRI (outpatient and inpatient), as defined above

• **RSV Season 1**: To estimate the incidence of RSV-associated hospitalizations from Days 1 through 180 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.	• RSV-associated hospitalization, as defined above
• **RSV Season 1**: To estimate the incidence of RSV-associated severe MALRI (outpatient and inpatient) from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.	• 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
• **RSV Season 2**: To estimate the incidence of RSV-associated MALRI (outpatient and inpatient) from Days 1 through 180 postdose MK-1654 in RSV Season 2.	• RSV-associated MALRI (outpatient and inpatient), as defined above
• **RSV Season 2**: To estimate the incidence of RSV-associated hospitalizations from Days 1 through 180 postdose MK-1654 in RSV Season 2.	• RSV-associated hospitalization, as defined above
• **RSV Season 1 and 2**: To estimate the incidence and magnitude of ADA to MK-1654 on – Day 1 (predose) and Days 150 and 240 post Dose 1 in RSV Season 1, and – Days 7 and 150 (postdose) in RSV Season 2.	• Incidence and magnitude (titer) of ADA to MK-1654

• **RSV Season 1 and 2**: To estimate the level of SNA to RSV A on – Day 1 (predose) and Days 7, 150, and 240 post Dose 1 in RSV Season 1, and – Days 7 and 150 (postdose) in RSV Season 2.	• Level (titer) of SNA to RSV A
• **RSV Season 1 and 2**: To determine RSV F gene sequence in NP samples collected in RSV Seasons 1 and 2 from infants infected with RSV who received MK-1654 or palivizumab.	• 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 partially blinded, randomized, active-controlled, multi-site study to evaluate the safety, tolerability, and efficacy of MK-1654 versus palivizumab and the PK of MK-1654 in infants who are eligible and recommended to receive palivizumab in their first RSV season. Part 1 of the study will be double-blind, and Part 2 will be open-label (see Section 1.3). 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 in either treatment group who continue to be at increased risk of RSV who are entering their second RSV season (see Section 5.1 and Section 5.2).

The Sponsor estimates that the study will require approximately 5 years from the time that documented informed consent is provided for the first participant until the last participant's last study-related contact or visit.

Overall, 1000 participants will be randomized in a 1:1 ratio to receive MK-1654 or palivizumab on RSV Season 1 Day 1 (double-blind). Randomization will be stratified according to the following factors:

1. Region:

- Northern Hemisphere
- Southern Hemisphere

2. Participant condition (see Section 5.1, Inclusion Criteria #1):

- CLD (≥200 infants)
- CHD (≥100 infants)
- Neither CLD nor CHD <29 weeks gestational age
- Neither CLD nor CHD ≥29 weeks gestational age

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. 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 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).

CLD and CHD participants will be eligible and consented for inclusion in 2 RSV seasons. Participants in the Early or Moderate Pre-term Group who meet the additional inclusion criteria for RSV Season 2 (see Section 5.1) will also be consented for participation in 2 RSV seasons.

All study participants will receive 2 blinded doses before unblinding in RSV Season 1:

- MK-1654 group: MK-1654 (Dose 1) and placebo (Dose 2)
- Palivizumab group: palivizumab (Dose 1 and Dose 2)

All participants, irrespective of treatment group, will have safety monitoring (AEs and SAEs), efficacy surveillance to monitor the incidence of RSV-associated MALRI and hospitalization, and blood sample collection as described in the SoA (see Section 1.3.1.1 SoA – RSV Season 1 Part 1).

Participant's treatment assignment will be unblinded at the Day 60 visit before any visit procedures. Participants in the MK-1654 group do not have any additional planned doses in RSV Season 1 and will continue with safety monitoring, efficacy surveillance, and blood sample collection as described in the SoA (see Section 1.3.1.2 SoA – RSV Season 1 Part 2 – MK-1654 Group). Participants in the palivizumab group will receive at least 3 and up to 5 single doses of palivizumab, once every 28 (+4) days (inclusive of dosing day; minimum of 28 days between doses), depending on the timing of enrollment relative to the RSV season. For calculating the visit windows for subsequent administrations, the day of the previous administration is considered Day 1. These participants will continue with safety monitoring and efficacy surveillance as described in the SoA (see Section 1.3.1.3 SoA – RSV Season 1 Part 2 – Palivizumab Group).

For infants enrolled and consented to participate in RSV Seasons 1 and 2, inclusion/exclusion criteria will be rechecked at the Day 240 visit for eligibility to continue in RSV Season 2 (see Section 5.1 and Section 5.2). Participants still eligible will begin the RSV Season 2 between 246 to 393 days after RSV Season 1 Dose 1, depending on the timing of enrollment relative to the RSV season (see Section 8.1.8.1). Participants in the palivizumab group who are continuing in RSV Season 2 will have blood sample collection at the Day 240 visit to serve as the baseline for RSV Season 2. All participants not continuing in RSV Season 2 will be monitored for safety for 365 days after receiving the first dose in RSV Season 1.

For participants continuing in RSV Season 2, a dose of MK-1654 will be administered (open-label) up to 4 weeks before the beginning of the participant's second RSV season (246 to 393 days after Dose 1 in RSV Season 1 during a routine RSV season). For participants who received MK-1654 in RSV Season 1, this will be a second dose. For participants who received palivizumab in RSV Season 1, this will be the first dose of MK-1654. Participants in RSV Season 2 will be followed for 180 days after the RSV Season 2 dose, including safety monitoring (AEs and SAEs), efficacy surveillance to monitor the incidence of RSV-associated MALRI and hospitalization, and blood sample collection as described in the SoA (see Section 1.3.2 SoA – RSV Season 2).

If during the RSV season a participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the procedure, Sponsor consultation will need to occur. The Sponsor consultation may determine that the participant receive an additional post-surgery dose of MK-1654 or palivizumab at the recommended dose based on their randomization allocation and the RSV season at the time of the procedure (see Section 8.1.8.1). The post-surgery follow-up activities are described in the SoAs (see Section 1.3) and in the guidance document provided by the Sponsor.

An IA is planned for this study and will be conducted by an external unblinded statistician and reviewed by an eDMC (see Section 10.1.4.3). The IA will occur after the first 30 participants are randomized (and after the Day 42 contact for safety follow-up) or after the first hemisphere enrollment (~17 weeks) is complete in the initial RSV season of the study, whichever occurs first to conduct an early assessment of safety. In addition to this IA, the eDMC will review available safety and RSV disease incidence data from this study approximately every 6 months (see Section 9.7).

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 evaluate the safety and tolerability of MK-1654 versus palivizumab and collect efficacy data to estimate the efficacy of MK-1654 relative to palivizumab in this population at increased risk for severe RSV, 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].

This study will also assess the PK of MK-1654 at various time points up to 240 days after the first dose to observationally compare the PK data in this population to the PK of MK-1654 determined in the Phase 2b/3 pivotal efficacy study (MK-1654-004 [PN004] in healthy pre-term and full-term infants). In addition, MK-1654 PK will be assessed for up to 150 days after the RSV Season 2 dose.

Since the PK of palivizumab has been well studied and described in the literature, blood samples will not be collected from infants who are enrolled for 1 RSV season in the palivizumab group after the participant's treatment assignment is unblinded at the Day 60 visit in RSV Season 1. These eligible participants in the palivizumab group who will receive MK-1654 in RSV Season 2 will have PK, ADA, and SNA blood samples collected according to the SoA (see Section 1.3.1.3 SoA – RSV Season 1 Part 2 – Palivizumab Group).

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Secondary and tertiary efficacy endpoints for this study are to estimate RSV-associated outpatient and inpatient MALRI (diagnosed as in Table 1) in RSV Seasons 1 and 2. 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]. A secondary efficacy endpoint is the estimation of efficacy against RSV-associated MALRI from Day 1 through Day 150 postdose (the length of a typical RSV season in a temperate climate) in RSV Season 1. Assessment of efficacy against RSV-associated hospitalization from Day 1 through Day 150 postdose in RSV Season 1 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, or 5 percentage points or more below baseline level in children with CLD or CHD with chronic underlying hypoxemia)[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)

CHD=congenital heart disease; CLD=chronic lung disease; 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 MALRI and hospitalization through 180 days postdose in RSV Seasons 1 and 2 and RSV-associated severe MALRI through 150 days postdose in RSV Season 1 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, or 5 percentage points or more below baseline level in children with CLD or CHD with chronic underlying hypoxemia) 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 aged 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 AESI have been defined for 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. 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 Section 10.3 (Appendix 3).

4.2.1.3 Pharmacokinetic Endpoints

4.2.1.3.1 MK-1654 Serum Concentration

A sparse PK collection of 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 Days 1 to 240 in RSV Season 1 and for 150 days postdose in RSV Season 2 (see Section 1.3) to determine the PK profile of the molecule, which will provide information regarding the MK-1654 PK profile in the target pediatric population.

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. Leftover serum may 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. 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.

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 palivizumab. 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 Comparator

Currently, palivizumab (Synagis™) is the only approved and marketed mAb for RSV prophylaxis. Palivizumab is modestly effective and has a general indication for pediatric patients with underlying conditions that place them at high risk for severe RSV disease; these conditions include pre-term birth at ≤35 weeks gestational age and cardiopulmonary conditions [Hussman, J. M., et al 2012] [Smart, K. A., et al 2010].

4.2.3 Rationale for the Use of Placebo in the MK-1654 Group

In order to allow for an unbiased assessment of safety and tolerability for 42 days after Dose 1 in RSV Season 1, participants randomized to receive a single dose of MK-1654 in their first RSV season will receive a placebo dose at the Day 28 visit. This second dose in the MK-1654 group in RSV Season 1 allows for blinding to be maintained through the 42-day safety collection period as palivizumab is administered as 3 to 5 monthly doses.

4.3 Justification for Dose

The doses of MK-1654 (105 mg in RSV Season 1 and 210 mg in RSV Season 2) in this study were 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 doses were selected based on the totality of information, including preclinical data, published clinical data for anti-RSV mAbs, and PK/pharmacodynamics 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 in their first RSV season. A 210 mg dose was selected for high-risk infants in their second RSV season on the basis of exposure matching. Briefly, a 210 mg dose administered to infants in their second RSV season is predicted to achieve exposures (ie, $AUC_{0\text{-}150d}$) that are similar to infants in their first RSV season who receive 105 mg.

Data from the ongoing Phase 1b/2a study (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). Similarly, infants in their second RSV season who receive 210 mg are predicted to have exposures (C_{max} and $AUC_{0-\infty}$) 6- and 4-fold lower, respectively, than the highest well-tolerated exposures observed in healthy adults.

The serum concentration of palivizumab decreases after ECMO or surgical interventions that require cardiopulmonary bypass. Based on this, participants who undergo ECMO or surgical repair involving cardiopulmonary bypass for their CHD during the RSV season will require Sponsor consultation to determine if these participants should receive an additional post-surgery dose of study intervention (MK-1654 or palivizumab at the recommended dose based on randomization allocation and the RSV season at the time of the procedure) after the procedure.

Refer to the IB for additional information.

4.4 Beginning and End-of-Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, 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.

Male/female infants ≤35 weeks gestational age or infants with CLD of prematurity or hemodynamically significant CHD, 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.

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. Recommended to receive palivizumab in accordance with national or local (eg, state or provincial) guidelines or professional society recommendations, **and** meets 1 or more of the following criteria:

    a) Early or Moderate Pre-term Group (excluding participants with CLD or hemodynamically significant CHD): ≤35 weeks, 0 days gestational age*.

    Note: Participants in the Early or Moderate Pre-term Group who meet the additional inclusion criteria for RSV Season 2, as described in Section 5.1.1, will be consented for participation in 2 RSV seasons.

    b) CLD/CHD Group:

    - CLD Participants: have CLD of prematurity (also known as bronchopulmonary dysplasia), as defined by:

        - American Academy of Pediatrics [American Academy of Pediatrics Committee on Infectious Diseases 2014]: ≤32 weeks, 0 days gestational age* and require medical intervention/management (ie, supplemental oxygen, bronchodilators, or chronic systemic corticosteroids) for at least 28 days after birth, or

        - Other national or local guidelines or professional society recommendations

    - CHD Participants: have hemodynamically significant CHD, as defined by:

        - American Academy of Pediatrics [American Academy of Pediatrics Committee on Infectious Diseases 2014]: Uncorrected or palliated cyanotic or

acyanotic disease associated with documented pulmonary hypertension (eg, systolic pulmonary arterial pressure ≥40 mmHg or ≥1/2 systolic blood pressure) or a requirement for daily medication to manage congestive heart failure, or as diagnosed by a pediatric cardiologist

- Other national or local guidelines or professional society recommendations

Note: CLD and CHD participants will be consented for inclusion in 2 RSV seasons, as described in Section 5.1.1.

*Gestational age at birth as calculated by the treating physician or qualified healthcare provider at the time of delivery or as documented in the medical record at the time of birth (eg, acceptable methods include assessment using prenatal [obstetric and/or sonographic evaluation using biometric markers] or postnatal [Ballard or New Ballard] methods).

2. Is available to complete the follow-up period:

   - Up to 575 days (180 days after RSV Season 2 dose) for participants eligible for RSV Season 2 dose of MK-1654, or

   - Approximately 365 days after the RSV Season 1 Dose 1 for all other participants.

Demographics

3. Is male or female and has a chronological age from birth up to 1 year and is entering their first RSV season at the time informed consent is provided. (See Appendix 7.2 for specific weight requirements for participants in the Czech Republic.)

Informed Consent

4. 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.

5.1.1 Additional Inclusion Criteria for Participation in RSV Season 2

Eligible participants will be consented at the beginning of the study for inclusion in RSV Season 2 for this study (and eligibility reconfirmed at the RSV Season 1 Day 240 and RSV Season 2 Day 1 visits [see the SoAs in Section 1.3]) if the participant meets 1 of the following inclusion criteria:

Type of Participant and Disease Characteristics

5. Participants enrolled in the CLD/CHD group as defined in Inclusion Criteria #1b. Participants with CHD are required to meet the following additional criteria:

- Have hemodynamically significant CHD at the beginning of RSV Season 2, or
- If the participant has had surgically repaired hemodynamically significant CHD that did not include ECMO or cardiopulmonary bypass:
  - Continues to require medications to manage CHD, or
  - Any additional medical intervention related to their CHD

6. Participants enrolled in the Early or Moderate Pre-term Group as defined in Inclusion Criteria #1a, with the following:
   - Neuromuscular disease or congenital pulmonary anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough
   - Down Syndrome (trisomy of chromosome 21)
   - Cystic fibrosis with nutritional compromise (eg, weight <10th percentile at time of enrollment)
   - Native Americans and Alaskan Indians or other indigenous populations at high risk for severe RSV disease

5.2 Exclusion Criteria

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

Medical Conditions

1. Requires mechanical ventilation at time of enrollment.
2. Has a life expectancy <6 months.
3. Has known hepatic or renal dysfunction, or chronic seizure disorder.
4. Is hospitalized at the time of randomization unless discharge is expected within 7 days after randomization.
5. Has severe immunodeficiency or is severely immunocompromised, including but not limited to:
   - AIDS (CD4 percentage <25%, or history of AIDS-Defining Condition),
   - leukemia, myeloproliferative disorder, or other malignancy and receiving or expected to receive chemotherapy during the study,

- status post solid-organ or bone marrow transplantation and on a systemic immunosuppressive regimen,

  OR

- severe combined immunodeficiency.

6. Has known hypersensitivity to any component of MK-1654 (refer to the IB for a list of components) or palivizumab (refer to the Synagis™ label for a list of components). (See Appendix 7.1 for specific requirements for participants in France.)

7. Has received other investigational agents at any time before study entry.

8. Is anticipated to have either of the following within 60 days after randomization: 1) surgical correction resulting in hemodynamically insignificant CHD or 2) cardiac surgical procedure that will require cardiopulmonary bypass.

9. Requires ECMO or continuous positive airway pressure at the time of enrollment or anticipated within 60 days after randomization.

10. Has an anticipated or planned cardiac transplantation to occur during the course of this study.

11. Has a bleeding disorder contraindicating intramuscular administration.

12. 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. (See Appendix 7.2 for specific requirements for participants in the Czech Republic.)

    Note: If the participant meets this exclusion criterion, the RSV Season 1 or RSV Season 2 Day 1 visits may be rescheduled for a time when this criterion is not met.

13. Has symptoms of LRI (defined in Section 8.2.1) within 7 days predose (Section 8.13.1).

    Note: If the participant meets this exclusion criterion, the RSV Season 1 or RSV Season 2 Day 1 visits may be rescheduled for a time when this criterion is not met.

Prior/Concomitant Therapy

14. 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

15. 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.

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

Diagnostic Assessments

Not applicable.

Other Exclusions

17. 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.

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

19. 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.

5.2.1 Exclusion Criteria for Participation in RSV Season 2

A participant may be eligible and consented at the beginning of the study for inclusion in RSV Season 2 for this study. Eligibility will be reconfirmed at the RSV Season 1 Day 240 and RSV Season 2 Day 1 visits (see the SoAs in Section 1.3), and the participant must be excluded from RSV Season 2 participation if they meet 1 of the following exclusion criteria:

20. Has a life expectancy <6 months.

21. Has known hepatic or renal dysfunction, or chronic seizure disorder.

22. Has severe immunodeficiency or is severely immunocompromised, including but not limited to:

    - AIDS (CD4 percentage <25%, or history of AIDS-Defining Condition),
    - leukemia, myeloproliferative disorder, or other malignancy and receiving or expected to receive chemotherapy during the study,
    - status post solid-organ or bone marrow transplantation and on a systemic immunosuppressive regimen,

      OR

    - severe combined immunodeficiency.

23. Had 1) ECMO or 2) surgical intervention during the RSV season for CHD and required cardiopulmonary bypass during the procedure in RSV Season 1.

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

25. Has bleeding disorder contraindicating intramuscular administration.

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

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

Note: If the participant meets the following criteria, the RSV Season 2 Day 1 visits may be rescheduled for a time when this criterion is not met:

- 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

- LRI symptoms (defined in Section 8.2.1) within 7 days predose

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

6 STUDY INTERVENTION

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

Clinical supplies 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	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
MK-1654	Experimental	MK-1654	Biological/ Vaccine	Solution	150 mg/mL	105 mg	IM	Single dose in RSV Season 1[a] (Day 1 visit)	Test Product	IMP	Sponsor
MK-1654	Experimental	Placebo	Other	Solution	0 mg/mL	0 mg	IM	Single dose in RSV Season 1 (Day 28 visit)	Placebo	IMP	Sponsor or site
MK-1654	Experimental	MK-1654	Biological/ Vaccine	Solution	150 mg/mL	210 mg	IM	Single dose in RSV Season 2[a] (Day 1 visit)	Test Product	IMP	Sponsor
Palivizumab	Active Comparator	Palivizumab	Biological/ Vaccine	Solution	100 mg/mL	15 mg/kg body weight	IM	3 to 5 monthly doses in RSV Season 1[a] (starting at Day 1 visit)	Comparator	IMP	Sponsor or site
Palivizumab	Active Comparator	MK-1654	Biological/ Vaccine	Solution	150 mg/mL	210 mg	IM	Single dose in RSV Season 2[a] (Day 1 visit)	Test Product	IMP	Sponsor

AxMP=auxiliary medicinal product; IM=intramuscular; RSV=respiratory syncytial virus

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

Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences in the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

[a] If during the RSV season a participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the surgical procedure, additional study intervention may be administered post-surgery based on the Sponsor consultation.

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

Specific calculations or evaluations required to be performed in order to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is provided in Section 4.3. Palivizumab should be prepared and administered in accordance with local palivizumab product information.

MK-1654, placebo (0.9% sodium chloride, USP sterile saline), and palivizumab will be prepared by a pharmacist or medically qualified study personnel (see Section 6.3.3 for blinding requirements).

Note: To avoid unblinding, a blinded dose (RSV Season 1: Dose 1 and 2) may not be administered as 2 injections.

Vials 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 1:1 ratio to MK-1654 or palivizumab.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Region

- Northern Hemisphere
- Southern Hemisphere

2. Participant condition:

- CLD (≥200 infants)
- CHD (≥100 infants)
- Neither CLD nor CHD <29 weeks gestational age
- Neither CLD nor CHD ≥29 weeks gestational age

6.3.3 Blinding

In Part 1 of this study (up to the Day 60 visit), a double-blinding technique will be used. MK-1654, palivizumab, and placebo will be prepared and administered in a blinded fashion by an unblinded pharmacist or medically qualified study personnel not otherwise involved in the conduct of the study. Unblinded study personnel should not have contact with participants for any study-related procedures/assessments postdose (prior to unblinding), including all safety follow-up procedures. The participant's legally acceptable representative,

the investigator(s), and Sponsor personnel or delegate(s) will be unaware of the study intervention assignments.

Part 2 of this study (time of unblinding through duration of participation in the study) is conducted as open-label therefore, the Sponsor, investigator, and participant/participant's legally acceptable representative will know the intervention administered.

6.4 Study Intervention Compliance

Participant study intervention compliance is defined in this study as a participant who receives the protocol-specified doses of MK-1654, placebo, and/or palivizumab for their assigned treatment group for the respective RSV season (see Section 1.3).

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 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 study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant's legally acceptable representative.

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 a visit (when study intervention is given), they should be administered in the contralateral (opposite) thigh/deltoid muscle (per standard of care) from that used for the 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). Other monoclonal or polyclonal antibody should not be administered within 30 days BEFORE randomization through 60 days AFTER RSV Season 1 Day 1.

Note: See Appendix 7.2 for specific requirements regarding concomitant vaccinations for participants at sites in the Czech Republic.

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 (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. Any AEs will be reported according to the guidelines in Section 8.4 and Section 10.3 (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.

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.13.6.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.13.6.

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

- The participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant'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 prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- 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 [EMEA/CPMP 2008]. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Each participant may have a maximum of 4 planned blood draws during RSV Season 1 and participants enrolled to participate in 2 RSV seasons may have an additional 2 planned blood draws during RSV Season 2 (see Section 1.3 and Table 10). Based on Sponsor consultation, additional blood draw(s) may be collected for participants who undergo the following during the RSV season: 1) ECMO or 2) surgical intervention for CHD and require cardiopulmonary bypass during the surgical procedure.

The maximum amount of blood obtained from each participant is dependent upon the participant's weight at the visit. Blood collection should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% during a single blood collection visit. With total volume of blood estimated at 80 to 90 ml/kg body weight; the total blood collected at a single visit (1%) is approximately 0.8 ml/kg, and approximately

2.4 ml/kg (3%) during a 4-week period. If the participant weighs <1 kg, then the participant should not have blood drawn at that visit [EMEA/CPMP 2008].

The planned maximum blood draw volume collected from each infant ranges from 3.4 to 13.0 mL, depending on enrollment assignment and participation duration. Based on the planned blood draws, the approximate total maximum blood volume drawn per participant in RSV Season 1 is 8.2 mL, and for those participants continuing into RSV Season 2, the approximate total maximum blood volume drawn is 13.0 mL (Table 10). 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 and Section 10.2 [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. 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. At RSV Season 1 Day 240 and RSV Season 2 Day 1, inclusion and exclusion criteria will be re-reviewed to assess continued eligibility for participation in RSV Season 2.

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 the RSV Season 1 Day 1 visit. 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. For participants continuing to RSV Season 2, at the Day 1 visit of RSV Season 2, only changes to medical history collected in RSV Season 1 will be documented.

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 the RSV Season 1 Day 1 visit up to 14 days post Dose 2 in RSV Season 1, up to 42 days postdose in RSV Season 2 in the eDiary, and up to 42 days after an additional post-surgery dose of MK-1654 in either RSV season. Outside these safety follow-up periods, only concomitant medications associated with and AE/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 participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.13.1. Pre-study 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 Treatment/Randomization Number

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

A single participant cannot be assigned more than 1 treatment/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 palivizumab) will be administered at Visit 1 (Day 1) (see Section 6.1), after the participant is deemed eligible for the study. Blinded study intervention (placebo for the MK-1654 group and palivizumab for the palivizumab group) will be administered at the Day 28 visit. The palivizumab group will receive subsequent doses of palivizumab every 28 (+4) days thereafter (inclusive of dosing day; minimum of 28 days between doses) through the end of RSV season, for a total of 3 to 5 doses depending on the timing of enrollment relative to the RSV season, consistent with standard of care. For calculating the visit windows for subsequent administrations, the day of the previous administration is considered Day 1. Participants continuing with RSV Season 2 will receive a dose of MK-1654 up to 4 weeks before the start of their second RSV season (246 to 393 days after Dose 1 in RSV Season 1).

If during the RSV season a participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the procedure, Sponsor consultation will need to occur to discuss the post-surgery follow-up. The Sponsor consultation should occur as soon as possible after the procedure is scheduled or the need for the procedure is identified. The decision will be made during the Sponsor consultation whether or not the participant will receive an additional post-surgery dose of MK-1654 or palivizumab at the recommended dose based on their randomization allocation and the RSV season at the time of the procedure. The timing of the post-surgery dose will be discussed during the Sponsor consultation but should occur once the participant is medically stable, prior to discharge from the hospital, or ideally within 5 days after discharge. Participants who have these specified procedures in RSV Season 1 will not be eligible to participate in RSV Season 2 (Exclusion Criteria #23) and will be followed through the RSV Season 1 Day 365 phone call.

MK-1654, placebo, or palivizumab will be administered via IM injection into the side of the participant's thigh (vastus lateralis) or deltoid muscle as per standard of care. To avoid unblinding, a blinded dose (RSV Season 1: Dose 1 and 2) may not be administered as 2 injections. Study staff administering study intervention will be blinded/unblinded 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). 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. (See Appendix 7.2 for specific postdose observation requirements for participants in the Czech Republic.)

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in Section 1.3.

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 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 Virus) Assessments

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

8.2.1 Surveillance for Respiratory Infection Symptoms

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

Weekly surveillance will be conducted via an electronic questionnaire or phone call. Based on the responses on the electronic questionnaire, the site may contact the participant's legally

acceptable representative for further information. Contact must be performed by appropriately trained site staff. The Sponsor will provide each site with a guidance document outlining the weekly surveillance assessment. In addition, site staff will review the eDiary data with the legally acceptable representative (see Section 8.3.5). If the initial contact is unsuccessful, the site staff should make a total of 3 additional attempts for each scheduled contact. All attempts to contact the participant's legally acceptable representative will be recorded in the contact log (or equivalent).

In addition to weekly active surveillance, the legally acceptable representative will be instructed at the RSV Season 1 Day 1 visit (and reminded during the weekly surveillance) 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:
     - 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; 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 infection 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 or worsening LRI signs/symptoms arise during an existing respiratory infection 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 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 sample collection for RT-PCR testing at the central laboratory.

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, respiratory rate, 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, or 5 percentage points or more below baseline level in children with CLD or CHD with chronic underlying hypoxemia); 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 Virus 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.

All swabs collected for NP sampling by a qualified designee will be sent to the central laboratory for analysis. The analysis will determine the common viral cause(s) of LRI as well as the strain of RSV (ie, RSV A or B) if RSV is detected. Additional details are available in the laboratory manual.

An NP sample should be collected for RT-PCR testing for respiratory virus 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 virus 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 virus 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, respiratory rate, and SpO2 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 assessment (see Section 8.2.2.2) and any AESI assessments (see Section 8.4.8).

- Body temperature and respiratory rate 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 postdose at the 30-minute postdose safety observation period at the RSV Season 1 Day 1 visit and at the subsequent required scheduled and unscheduled visits, as indicated in the SoA (Section 1.3).

Rectal is the preferred method of obtaining participant's temperature, where allowed by local practice. 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 for 5 days after each dose. Temperature readings should be taken at approximately the same time each day with the thermometer provided by the study.

If an elevated temperature is detected using the axillary method (≥100.0°F [≥37.8°C]), the temperature should be confirmed by rectal measurement, where allowed by local practice. Only the confirmatory rectal measurement should be recorded. If the rectal measurement cannot be performed, the original axillary measurement should be recorded.

Fever is defined as any rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C). All fevers must be reported Day 1 through 14 days post Dose 2 and for 14 days after each subsequent dose in RSV Season 1 and for 42 days postdose in RSV Season 2 unless the fever is a symptom of another reported AE. In addition, all fevers must be reported for 42 days postdose for participants who receive an additional post-surgery dose of MK-1654 in either RSV Season 1 or 2. 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 after administration of study intervention, the participant must undergo an additional 15-minute postconcomitant vaccination observation period at the study site for any AEs.

Note: See Appendix 7.2 for specific concomitant vaccinations and postdose observation requirements for participants in the Czech Republic.

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 all applicable eDiary entries. 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 safety follow-up periods in RSV Season 1 (Day 1 through 14 days post Dose 2 and 14 days after each subsequent dose) and RSV Season 2 (42 days postdose), and with the participant's legally acceptable representative at the time points indicated in the SoA (see Section 1.3).

If a participant is administered an additional post-surgery dose (see Section 8.1.8.1), they will be followed for safety for 42 days after a dose of MK-1654 or 14 days after a dose of palivizumab. The eDiary device will be provided to the participant's legally acceptable

representative, if previously returned. For participants using a study-provided eDiary, the device will be collected as specified in the SoA (see Section 1.3).

Noncompliance with the eDiary will require retraining by the site as soon as possible to ensure accurate and complete data capture.

Legally acceptable representatives will use the eDiary to record the following information in RSV Season 1:

1. Solicited daily body temperature to identify fever* for 5 days after each dose (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)** are collected for 5 days after each dose;

   ****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) for 5 days after each dose;

4. Anaphylaxis/hypersensitivity AESI on (see Section 8.4.8.1):

   - Day 1 through 14 days post Dose 2, and
   - For 42 days after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1)

5. Rash AESI on (see Section 8.4.8.2):

   - Day 1 through 14 days post Dose 2, and
   - For 42 days after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1)

6. Any other AEs:

   - Day 1 through 14 days post Dose 2,
   - For 14 days after each dose of palivizumab, and
   - For 42 days after an additional post-surgery dose of MK-1654 or for 14 days after an additional post-surgery dose of palivizumab (see Section 8.1.8.1)

7. Concomitant medications and nonstudy vaccinations:

   - Day 1 through 14 days post Dose 2, and

- For 42 days after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1)

Legally acceptable representatives will use the eDiary to record the following information in RSV Season 2:

1. Solicited daily body temperature to identify fever* occurring within 5 days postdose;

   ***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)** are collected within 5 days 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) for 5 days after each dose;

4. Anaphylaxis/hypersensitivity AESI occurring within 42 days after the RSV Season 2 dose and after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1);

5. Rash AESI occurring within 42 days after the RSV Season 2 dose and after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1);

6. Any other AEs occurring within 42 days after the RSV Season 2 dose and after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1); and

7. Concomitant medications and nonstudy vaccinations occurring within 42 days after the RSV Season 2 dose and after an additional post-surgery dose of MK-1654 (see Section 8.1.8.1).

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 10.3.4).

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 in RSV Seasons 1 and 2 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 of that RSV season, 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 the phone call.

If Day 3 is not a business day, the phone call should occur on Day 2. If the first attempt on Day 3 in either RSV season 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 in either RSV season, site staff should continue to try to contact 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 SoAs.

- 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 last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

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

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

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

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

All AEs, SAEs, and other reportable safety events must be reported by the investigator:

- From the time of intervention randomization through 14 days following RSV Season 1 Dose 2,
- For 14 days following each subsequent dose of palivizumab in RSV Season 1 (planned and additional post-surgery doses),
- For 42 days following the RSV Season 2 dose,
- For 42 days after an additional post-surgery dose of MK-1654 in either RSV season, and
- Any SAE through participant’s study completion.

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 if the event is considered related to study intervention.

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

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

Table 3 Reporting 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 if: drug/vaccine related. (Follow ongoing to outcome)	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

AESI=adverse event of special interest; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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 from Day 1 through 14 days post Dose 2 in RSV Season 1 and within 42 days postdose in RSV Season 2 will be reported to the Sponsor. In addition, participants who receive an additional post-surgery dose of MK-1654 in either RSV Season 1 or 2 will be followed for 42 days postdose. Only AESI that occur outside these safety follow-up periods that meet the SAE criteria (see Section 10.3.2) 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 10.3.4 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 (or equivalent) 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.
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 the RSV Season 1 Day 1 visit, 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 or during weekly surveillance contact (through 14 days post Dose 2 in RSV Season 1, within 42 days postdose in RSV Season 2, or within 42 days after an additional post-surgery dose of MK-1654 in either RSV season), 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 and Section 10.2 [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.
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 the RSV Season 1 Day 1 visit, the investigator will provide anticipatory guidance to the legally acceptable representative for suspected rash events.

If any rash event is reported in the eDiary or during weekly surveillance contact (Day 1 through 14 days post Dose 2 in RSV Season 1, within 42 days postdose in RSV Season 2, or within 42 days after an additional post-surgery dose of MK-1654 in either RSV season), 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 virus 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 FBR, the following specimens will be obtained as part of FBR:

- 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 (RSV Season 1 Day 1 Visit Predose)

At the RSV Season 1 Day 1 visit, 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. Participants who have the following are not eligible for enrollment, but may be rescreened:

- 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 (see Section 5.2 Exclusion Criteria #12) (See Appendix 7.2 for specific requirements for participants in the Czech Republic.)
- LRI symptoms (defined in Section 8.2.1) within 7 days predose (see Section 5.2 Exclusion Criteria #13)

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 ARI listed in Section 8.2.1 have been present within 7 days before the RSV Season 1 Day 1 visit, an NP sample should be collected. Collecting an NP sample at this visit

does not exclude an infant from participating in the study. See Section 8.13.1 if symptoms of LRI are present within 7 days predose.

8.13.2 Randomization/Dose Administration/Observation

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.

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 dose via 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 after each dose for any immediate AEs (see Section 8.3.4). (See Appendix 7.2 for specific postdose observation requirements for participants in the Czech Republic.) This observation must be performed by the blinded investigator and/or study staff for Doses 1 and 2 in RSV Season 1.

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 RSV Season 1 Day 1 after predose screening procedures as per protocol. However, if randomization and study medication administration cannot be conducted on Day 1, they may be conducted within 5 days of the predose screening procedures (RSV Season 1 Day 1).

Prior to randomization in the IRT system and administration of study medication, 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 scheduled study visit, the participant should be brought in for an unscheduled visit (at the study site, at home, or at an alternate study site location; see Section 8.13.5). The unscheduled visit should follow the applicable Day 150 visit procedures based on the participant's treatment assignment and the current RSV Season (1 or 2).

If the participant withdraws consent while attending a scheduled visit, any additional assessments and procedures needed for the participant's respective 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 Alternate Study Site

Every attempt should be made to assess the participant at the study site for all scheduled study visits and for any unscheduled or post-surgery follow-up visits (see Section 1.3). 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 for the Day 1 and Day 28 visits in RSV Season 1 to maintain blinding. Study site visits are preferred for all scheduled in-person postdose follow-up visits 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 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.

8.13.6 Discontinued Participants Continuing to be Monitored in the Study

In this study, a participant may discontinue from study intervention but continue to participate in subsequent protocol visits as outlined in Section 1.3, as long as the participant's legally acceptable representative does not withdraw consent. Protocol-specified activities should occur at these visits.

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 3, Multicenter, Randomized, Partially Blinded, Palivizumab-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease
Treatment Assignment	A total of 1000 participants will be randomized in a 1:1 ratio to the MK-1654 or palivizumab groups on Day 1 (double-blind) in RSV Season 1. All participants who continue into RSV Season 2 will receive 1 dose of MK-1654.
Analysis Populations	Efficacy: Full Analysis Set (FAS) and Per-Protocol Efficacy (PPE) Safety: All Participants as Treated (APaT) Pharmacokinetic: Per-Protocol (PP)
Primary Endpoint(s)	**Safety** • Number of participants with solicited injection-site AEs from Days 1 through 5 after each dose in RSV Season 1. • Number of participants with fever as measured by solicited daily body temperatures from Days 1 through 5 after each dose in RSV Season 1. • Number of participants with solicited systemic AEs from Days 1 through 5 after each dose in RSV Season 1. • Number of participants with anaphylaxis/hypersensitivity AESI from Days 1 through 28 after Dose 1 and Days 1 through 14 after Dose 2 in RSV Season 1. • Number of participants with rash AESI from Days 1 through 28 after Dose 1 and Days 1 through 14 after Dose 2 in RSV Season 1. • Number of participants with nonserious AEs from Days 1 through 28 after Dose 1 and 14 days after each subsequent dose in RSV Season 1. • Number of participants with SAEs through the duration of study participation in RSV Season 1.

Key Secondary Endpoints	**Efficacy** • Number of participants with RSV-associated MALRI occurring from Days 1 through 150 post Dose 1 in RSV Season 1. • Number of participants with RSV-associated hospitalization occurring from Days 1 through 150 post Dose 1 in RSV Season 1. **Safety** • Number of participants with solicited injection-site AEs from Days 1 through 5 postdose in RSV Season 2. • Number of participants with fever as measured by solicited daily body temperatures from Days 1 through 5 postdose in RSV Season 2. • Number of participants with solicited systemic AEs from Days 1 through 5 postdose in RSV Season 2. • Number of participants with anaphylaxis/hypersensitivity AESI from Days 1 through 42 postdose in RSV Season 2. • Number of participants with rash AESI from Days 1 through 42 postdose in RSV Season 2. • Number of participants with nonserious AEs from Days 1 through 42 postdose in RSV Season 2. • Number of participants with SAEs from Days 1 through 180 postdose in RSV Season 2. **Pharmacokinetic** • MK-1654 PK concentration in RSV Seasons 1 and 2.
Statistical Methods for Key Efficacy / Pharmacokinetic Analyses	**Efficacy** The efficacy of MK-1654 compared to palivizumab with respect to the RSV-associated MALRI endpoint in RSV Season 1 will be estimated and the 95% CI of efficacy will be obtained based on the modified Poisson regression with robust variance method proposed by Zou [Zou, G. 2004]. The incidence of RSV-associated hospitalization in the MK-1654 and palivizumab groups in RSV Season 1 will be estimated and the exact 95% CIs will be provided using the Chi-square distribution for Poisson variable method. **Pharmacokinetic** Population PK modeling will be used to estimate PK parameters for each participant (eg, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$), which will be summarized in a separate population PK modeling report. Additionally, individual concentration values for each PK sample collected will be summarized by timepoint.
Statistical Methods for Key Safety Analyses	There are no a priori clinical events identified in this study as Tier 1 events. Tier 2 events identified in this study include solicited injection-site AEs, fever as measured by solicited daily body temperatures, solicited systemic AEs, drug-related AEs, any SAEs, discontinuations due to AEs, anaphylaxis/hypersensitivity AESI, rash AESI, nonserious AEs, and AEs by SOC observed in ≥1% of participants in at least 1 group. Estimates and 95% CIs for between-treatment differences in the percentage of participants with events will be calculated using the unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	An IA will occur after the first 30 participants are randomized or after the first hemisphere enrollment (~17 weeks) is complete in the initial RSV season of the study, whichever occurs first. Safety follow-up data for these participants through the RSV Season 1 Day 42 phone call will be included in this IA. Summaries of the safety, available PK data, and available incidence of RSV-associated MALRI and RSV-associated hospitalization will be reviewed by the eDMC and a recommendation on whether the study should continue will be made by the eDMC. Details are provided in Section 9.7.
Multiplicity	No multiplicity adjustment is planned as there is no hypothesis testing in this study.
Sample Size and Power	A total of 1000 participants will be randomized in a 1:1 ratio to receive either MK-1654 or palivizumab in RSV Season 1. Section 9.9.2 provides information about the precision of this study to estimate the incidence of AEs.

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 until the Sponsor study team, investigators, and participants are unblinded to the participant's treatment assignment at the RSV Season 1 Day 60 visit. Prior to unblinding each participant's treatment assignment, the participant's available safety data will be reviewed and locked.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented using IRT.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. There is no formal hypothesis testing in this study.

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

The first secondary efficacy endpoint is the number of participants with RSV-associated MALRI (outpatient and inpatient) occurring from Days 1 through 150 post Dose 1 in the MK-1654 and palivizumab groups in RSV Season 1, as described in Section 4.2.1.1. RSV-associated outpatient and inpatient MALRI is 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.

The other secondary efficacy endpoint is the number of participants with RSV-associated hospitalization occurring from Days 1 through 150 post Dose 1 in the MK-1654 and palivizumab groups in RSV Season 1, defined as hospital admission for respiratory illness; AND RSV-positive RT-PCR NP sample.

The tertiary efficacy endpoints for this study are:

- Number of participants with RSV-associated MALRI occurring from Days 1 through 180 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.
- Number of participants with RSV-associated hospitalization occurring from Days 1 through 180 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.
- Number of participants with RSV-associated severe MALRI occurring from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.
- Number of participants with RSV-associated MALRI occurring from Days 1 through 180 postdose MK-1654 in RSV Season 2.
- Number of participants with RSV-associated hospitalization occurring from Days 1 through 180 postdose MK-1654 in RSV Season 2.
- Number of participants hospitalized with RSV-associated LRI from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.
- Number of participants hospitalized with RSV-associated LRI from Days 1 through 180 postdose MK-1654 in RSV Season 2.
- Number of participants with RSV-associated outpatient and inpatient MALRI excluding cases where other pathogens are found from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.
- Number of participants with physician-assessed wheezing from Days 1 through 150 post Dose 1 in RSV Season 1 in the MK-1654 and palivizumab groups.
- Number of participants with physician-assessed wheezing from Days 1 through 180 postdose MK-1654 in RSV Season 2.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, physical examinations, and vital signs.

The primary safety endpoints for RSV Season 1 are:

- Number of participants with solicited injection-site AEs (redness/erythema, swelling, and pain/tenderness) from Days 1 through 5 after each dose.

- Number of participants with fever (defined as maximum rectal temperature ≥102.2°F [≥39.0°C] or axillary temperature ≥101.7°F [≥38.7°C]) from Days 1 through 5 after each dose.

- Number of participants with solicited systemic AEs (irritability, drowsiness, and appetite lost) from Days 1 through 5 after each dose.

- Number of participants with anaphylaxis/hypersensitivity AESI from Days 1 through 28 after Dose 1 and Days 1 through 14 after Dose 2.

- Number of participants with rash AESI from Days 1 through 28 after Dose 1 and Days 1 through 14 after Dose 2.

- Number of participants with any nonserious AEs from Days 1 through 28 after Dose 1 and 14 days after each subsequent dose.

- Number of participants with SAEs through the duration of participation in RSV Season 1.

The secondary safety endpoints for RSV Season 2 are:

- Number of participants with solicited injection-site AEs (redness/erythema, swelling, and pain/tenderness) from Days 1 through 5 postdose.

- Number of participants with fever (defined as maximum 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 with 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 with any nonserious AEs from Days 1 through 42 postdose.

- Number of participants with SAEs from Days 1 through 180 postdose.

9.4.3 Pharmacokinetic, Pharmacodynamic, and Immunogenicity Endpoints

The secondary pharmacokinetic endpoints are:

- PK concentration of MK-1654 at Days 7, 150, and 240 after the dose of MK-1654 in RSV Season 1.

- PK concentration of MK-1654 at Days 7 and 150 after the dose of MK-1654 in RSV Season 2.

The tertiary immunogenicity endpoints are:

- Incidence and magnitude of ADA to MK-1654 on Day 1 (predose), Days 150 and 240 post Dose 1 in RSV Season 1, and Days 7 and 150 postdose in RSV Season 2.

The tertiary pharmacodynamic endpoints are:

- The titer of SNA to RSV A on Day 1 (predose) and Days 7, 150, and 240 post Dose 1 in RSV Season 1, and Days 7 and 150 postdose in RSV Season 2.

An additional tertiary endpoint is:

- RSV F gene sequence determined by deep sequencing in NP samples from infants infected with RSV in RSV Seasons 1 and 2.

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 estimation of efficacy and for the estimation of incidence of RSV-associated disease. The FAS population consists of all randomized participants who receive at least 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 between 0 and 12 days after symptom onset and between 7 days before and 12 days after 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 estimation of efficacy and incidence of RSV-associated disease. To be eligible for inclusion in the PPE population, study participants must satisfy the following criteria:

- Receive a complete regimen of the correct clinical material corresponding to the treatment group the participants were randomized into (ie, 1 dose of MK-1654 for participants randomized to the MK-1654 group and 3 to 5 doses of palivizumab within the protocol-specified windows for participants randomized to the palivizumab group based on the date of enrollment and the predefined RSV season end date at each site),

- Have at least 1 follow-up visit/contact for assessment of RSV disease,

- Do not undergo 1) ECMO or 2) surgical intervention for CHD requiring cardiopulmonary bypass during the efficacy follow-up period (Day 150 or Day 180), 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 database lock 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 between 0 and 12 days after symptom onset and between 7 days before and 12 days after symptom worsening.

For both analysis populations, if a participant with symptoms of respiratory infection prior to dosing has an NP sample collected predose on RSV Season 1 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 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized/allocated participants who received at least 1 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. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

9.5.3 Pharmacokinetic Analysis Population

The PP population will serve as the primary population for the analysis of PK data in this study. The PP population consists of all randomized participants who receive a dose of MK-1654 and who do not have deviations from the protocol that may substantially affect the results of the PK endpoints.

The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the final database lock.

9.5.4 Immunogenicity Analysis Population

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

9.6 Statistical Methods

Statistical analyses for efficacy, safety, and PK analyses are described in Section 9.6.1, Section 9.6.2, and Section 9.6.3, respectively. No hypothesis testing for efficacy will be performed in this study. Nominal p-values may be computed for 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 estimate the efficacy of MK-1654 compared to palivizumab against RSV-associated MALRI through Day 150 post Dose 1 in RSV Season 1, 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 palivizumab 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.

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) and participant condition (CLD, CHD, neither CLD nor CHD ≥29 weeks gestational age, and neither CLD nor CHD <29 weeks gestational age) as covariates. If the number of participants in any stratum is too small and/or convergence cannot be achieved, the covariate may be excluded from the model. To allow for differences in follow-up times among the participants, the log of the follow-up time as the offset term will be added in the modified Poisson regression.

The incidence of RSV-associated hospitalization occurring from Days 1 through 150 post Dose 1 in the MK-1654 and palivizumab groups in RSV Season 1 will be estimated and the exact 95% CIs will be provided using the Chi-square distribution for Poisson variable method [Ulm, K. 1990].

An additional analysis to estimate the efficacy of MK-1654 compared to palivizumab against RSV-associated MALRI from Day 1 through the end of the first RSV season will be performed. In this analysis, only infants who develop RSV-associated MALRI from Day 1 through the end of their RSV season will be defined as cases. In other words, the efficacy follow-up duration to be included in the analysis will be until either the date of the end of the RSV season or the Day 150 date, whichever occurs first, thereby only including the relevant period of risk of RSV disease for each infant. A similar analysis will be performed for the endpoint of RSV-associated hospitalization and the incidence of this endpoint along with the CI will be estimated for each treatment group. The key efficacy analyses for secondary endpoints are summarized in Table 6.

For the efficacy analyses, cases of both RSV A and RSV B associated MALRI (or hospitalization) will be counted as endpoints. The efficacy of MK-1654 relative to palivizumab in RSV Season 1 against RSV A associated MALRI and RSV B associated MALRI will also be estimated separately. Similarly, the incidence of RSV A associated hospitalization and RSV B associated hospitalization in each treatment group will be estimated separately.

The incidence of RSV-associated MALRI and RSV-associated hospitalization through Day 180 postdose MK-1654 in RSV Season 2 and the corresponding 95% CIs will be computed:

- Separately by treatment group to which participants were randomized to in RSV Season 1, and
- Both treatment groups combined.

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
Secondary Endpoints				
Incidence of RSV-associated outpatient and inpatient MALRI from Day 1 through Day 150 post Dose 1 in RSV Season 1	P/S	Modified Poisson regression (estimate, 95% CI)	FAS/PPE	Missing data will not be imputed
Incidence of RSV-associated hospitalization from Day 1 through Day 150 post Dose 1 in RSV Season 1	P/S	Exact 95% CIs using the Chi-square distribution for Poisson variable (estimate, 95% CI)	FAS/PPE	Missing data will not be imputed
Incidence of RSV-associated outpatient and inpatient MALRI from Day 1 through the end of RSV Season 1	S	Modified Poisson regression (estimate, 95% CI)	PPE	Missing data will not be imputed
Incidence of RSV-associated hospitalization from Day 1 through the end of RSV Season 1	S	Exact 95% CIs using the Chi-square distribution for Poisson variable (estimate, 95% CI)	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; RSV=respiratory syncytial virus; S=supportive approach.

[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 participants' first and second

RSV seasons. Comparisons between the 2 groups will be made in RSV Season 1 only. The primary comparison of safety endpoints in RSV Season 1 will be after the first 2 doses in each group, ie, after the MK-1654 and placebo doses versus after the first 2 palivizumab doses. A supplemental comparison of safety endpoints in RSV Season 1 will be after the MK-1654 and placebo doses versus after all doses in the palivizumab group.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as SOC terms) and events that meet PDLCs in laboratory and vital signs parameters are either prespecified 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 AEs of particular interest 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

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (via the unstratified Miettinen and Nurminen method [1985]).

Membership in Tier 2 requires that at least 1% of the participants in any treatment group have the event. 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.

In addition to individual events that occur in 1% or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, an SAE, an AE which is both drug-related and serious, discontinuation due to an AE, solicited injection-site AE, solicited systemic AE, solicited AE of fever measured by body temperatures, anaphylaxis/hypersensitivity AESI, rash AESI, and nonserious AE will be considered Tier 2 endpoints.

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 Palivizumab	Descriptive Statistics
Tier 2	Any AE[a]	X	X
	Any SAE	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 Post Dose 1 in RSV Season 1[b] and 42 Days Postdose in RSV Season 2	X	X
	Rash AESI Days 1-42 Post Dose 1 in RSV Season 1[b] and 42 Days Postdose in RSV Season 2	X	X
	Nonserious AEs Days 1-42 Post Dose 1 in RSV Season 1[b] and 42 Days Postdose in RSV Season 2	X	X
	AEs by SOC (incidence ≥1% of participants in one 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 of special interest; CI=confidence interval; RSV=respiratory syncytial virus; SAE=serious adverse event; SOC=System Organ Class; X=results will be provided.

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

[b] Days 1-42 post Dose 1 in RSV Season 1 consists of safety data collected from Day 1 post Dose 1 through 14 days post Dose 2.

9.6.3 Statistical Methods for Pharmacokinetic Analysis

Statistical methods for the PK analysis are provided below. Additional details of this analysis will be specified in a separate modeling analysis plan.

PK Analysis After Dose Administration in RSV Season 1:

Sparse PK collection is planned for the pediatric participants receiving MK-1654 in this study. Thus, population PK modeling will be used to estimate PK parameters for each participant (eg, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$), which will be summarized in a separate population

PK modeling report. Additionally, individual concentration values for each PK sample collected will be summarized. ADA will be evaluated together with PK data to understand the effect of ADA on PK.

PK Analysis After Dose Administration in RSV Season 2:

The MK-1654 concentration after the dose given prior to the start of RSV Season 2 will be summarized by time point using descriptive statistics.

9.6.4 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.

9.7 Interim Analyses

An IA will occur after the first 30 participants are randomized or after the first hemisphere enrollment (~17 weeks) is complete in the initial RSV season of the study, whichever occurs first to conduct an early assessment of safety. Safety follow-up data for these participants through the RSV Season 1 Day 42 phone call will be included in this IA. Summaries of the safety, available PK data, and available incidence of RSV-associated MALRI and RSV-associated hospitalization will be reviewed by the eDMC and a recommendation on whether the study should continue will be made by the eDMC. If the study stops at the IA, no further participants will be enrolled. However, participants who have already been enrolled in the study will continue to be monitored for safety for 365 days postdose in RSV Season 1. In addition to this IA, the eDMC will review available safety and RSV disease incidence data from this study approximately every 6 months as outlined in the eDMC charter.

If the study does not stop at the IA, the study will continue until all 1000 participants have been enrolled and have completed all follow-up assessments per the protocol (365 days post Dose 1 in RSV Season 1, and 180 days postdose in RSV Season 2 [for participants receiving a RSV Season 2 dose]). At that time, a database lock will be executed. All analyses to evaluate the primary, secondary, and tertiary objectives of the study will be conducted and a CSR will be written.

If enrollment in this study is slower than expected, an IA may be performed when at least 600 participants have completed follow-up through 180 days post Dose 1 in RSV Season 1. Only data from participants who have completed the RSV Season 1 Day 60 visit and have been unblinded will be included in this IA. A database lock will be executed, and the data will be summarized and presented in a report.

The IAs will be conducted by an external unblinded statistician. Ongoing PK bioanalysis and PK modeling will be conducted by an external bioanalysis group and a separate, unblinded modeling group, respectively. Treatment-level results and/or participant-level data from the IAs will be provided by the unblinded statistician to the eDMC. The extent to which individuals are unblinded with respect to results of the IA will be documented by the unblinded statistician. The results of IA will not be shared with the investigators before the completion of the study.

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.

9.8 Multiplicity

No adjustment will be made for multiplicity as there is no formal hypothesis testing.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

A secondary objective of the study is to estimate the efficacy of MK-1654 compared to palivizumab as assessed by the incidence of RSV-associated MALRI (outpatient and inpatient) occurring from Days 1 through 150 post Dose 1 in RSV Season 1. The choice of sample size takes into account various factors including difficulties of enrolling this particular population, as well as estimates of efficacy and the associated levels of precision for different sample sizes. Based on the published literature and assumptions listed below, the expected range of efficacy of MK-1654 versus palivizumab is 25% to 40%, and a total sample size of 1000 participants in this study provides reasonable precision around these efficacy estimates.

Table 8 shows the precision for estimating the incidence rate of RSV-associated MALRI in the MK-1654 and palivizumab groups and the precision for estimating the efficacy of MK-1654 relative to palivizumab for RSV-associated MALRI with a sample size of 500 participants per treatment group under the following assumptions:

- RSV-associated MALRI incidence is 15% in this population.
- The attrition rate is 10% in the PPE population.
- In order to estimate the incidence rates of RSV-associated MALRI in the MK-1654 and palivizumab groups, MK-1654 efficacy against RSV-associated MALRI is assumed to be 70% while palivizumab efficacy against RSV-associated MALRI is varied from 45% to 70% in 5% increments based on estimates in the published literature.
- Another scenario is presented where MK-1654 efficacy against RSV-associated MALRI is assumed to be 65% and 60% when the palivizumab efficacy against RSV-associated

MALRI is assumed to be 70% to assess the impact of this assumption on the precision of the efficacy estimates.

Table 8 Precision for Estimating the Efficacy of MK-1654 Relative to Palivizumab Against RSV-associated MALRI

Observed Incidence for MK	Observed Incidence for Pali	Estimate of Efficacy of MK vs. Pali (%)	95% CI for Efficacy of MK vs. Pali (%)[a]	95% CI for MK Incidence[b]	95% CI for Pali Incidence[b]
0.06	0.045	-33.3	(-147.7, 22.0)	(0.040, 0.087)	(0.028, 0.069)
0.0525	0.045	-16.7	(-127.0, 30.7)	(0.034, 0.078)	(0.028, 0.069)
0.045	0.045	0	(-97.1, 42.3)	(0.028, 0.069)	(0.028, 0.069)
0.045	0.0525	14.3	(-62.6, 50.3)	(0.028, 0.069)	(0.034, 0.078)
0.045	0.06	25.0	(-35.9, 56.5)	(0.028, 0.069)	(0.040, 0.087)
0.045	0.0675	33.3	(-17.2, 61.4)	(0.028, 0.069)	(0.046, 0.096)
0.045	0.075	40.0	(-4.6, 64.5)	(0.028, 0.069)	(0.052, 0.105)
0.045	0.0825	45.5	(5.9, 67.3)	(0.028, 0.069)	(0.058, 0.114)

CI=confidence interval; MALRI=medically attended lower respiratory infection; MK=MK-1654; Pali=palivizumab; RSV=respiratory syncytial virus.

[a] Based on 1000 simulations from a modified Poisson regression model with a 10% attrition rate.

[b] Exact CI for Poisson variable using the Chi-square distribution.

9.9.2 Sample Size and Power for Safety Analyses

A total of 1000 participants will be randomized in a 1:1 ratio to receive either MK-1654 and placebo or palivizumab in RSV Season 1. The probability of observing at least 1 SAE in this study depends on the number of participants dosed and the underlying percentage of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 500 participants in the MK-1654 group if the underlying incidence of a SAE is 0.33% (1 of every 303 participants receiving MK-1654). There is a 50% chance of observing at least 1 SAE among 500 participants in the MK-1654 group if the underlying incidence of a SAE is 0.14% (1 of every 714 participants receiving MK-1654). If no SAEs are observed among the 500 participants in the MK-1654 group, this study will provide 97.5% confidence that the underlying percentage of participants with a SAE is <0.74% (1 in every 136 participants in the MK-1654 group).

9.10 Subgroup Analyses

Subgroup analyses based on the following subgroups will be performed for selected safety and efficacy endpoints: (1) Southern Hemisphere and Northern Hemisphere regions and (2) participant condition (CLD, CHD, neither CLD nor CHD <29 weeks gestational age, and neither CLD nor CHD ≥29 weeks gestational age).

9.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each dose 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, placebo, or palivizumab per dosing schedule.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will

support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

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 ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests described in Table 9 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 planned for RSV Seasons 1 and 2 for participants in the study are provided in Table 10. The maximum amount of blood drawn from each participant is dependent upon weight at each study visit. Blood collection should not exceed 3% of the total blood volume during a period of 4 weeks, and should not exceed 1% during a single blood collection visit [EMEA/CPMP 2008]. With total volume of blood estimated at 80 to 90 ml/kg body weight, the total blood collected at a single visit (1%) is approximately 0.8 ml/kg, and approximately 2.4 ml/kg (3%) during a 4-week period. If the participant weighs <1 kg, then the participant should not have blood drawn at that visit. 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.
- 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, Section 8.4.8.1, and Table 9).
- Additional tests may be performed at any time during the study based on Sponsor consultation or as determined necessary by the investigator or required by local regulations (ie, additional blood draw[s] may be collected for participants who undergo the following during the RSV season: 1) ECMO or 2) surgical intervention for CHD and require cardiopulmonary bypass during the procedure).
- 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 9 Laboratory Assessments in the MK-1654-007 Study

Laboratory Assessments	**Parameters**
Protocol-required Laboratory Assessments	
Virology	• RT-PCR assay for RSV and other community respiratory virus infections • 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/isotyping if indicated
Pharmacodynamics	• Assay for SNA against RSV
Safety (if indicated)	• Assay for ADA to MK-1654, and additional ADA characterization/isotyping 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. [a] A sufficient amount of serum will be stored for further characterization of immunogenicity, if needed.	

Table 10 Blood Draw Schedule and Approximate Blood Sample Volumes Drawn Per Study Visit for Participants Who Weigh ≥3 kg

Study Period	RSV Season 1[a]				Total Blood Volume[a,b,c] for RSV Season 1	RSV Season 2[a]		Total Blood Volume[a,b,c] for RSV Season 2	Total Blood Volume[a,b,c] for RSV Seasons 1 and 2
	Screening, Randomization, and Intervention	Follow-up (through end of RSV Season 1)				Follow-up (through 180 days post RSV Season 2 dose)			
Visit Number/Title	**1**	**2**	**5**	**6**		**8**	**10**		
Scheduled Day and Window (Days):	**Day 1** Predose	**7** (+2)	**150** (±5)	**240** (±5)		***RSV Season 2*** **7** (+2)	***RSV Season 2*** **150** (±5)		
MK-1654 Group – 1 RSV Season									
Blood Volume[b,c]	2.4 mL	1.0 mL	2.4 mL	2.4 mL	8.2 mL	-	-	-	8.2 mL
MK-1654 Group – 2 RSV Seasons									
Blood Volume[b,c]	2.4 mL	1.0 mL	2.4 mL	2.4 mL	8.2 mL	2.4 mL	2.4 mL	4.8 mL	13.0 mL
Palivizumab Group – 1 RSV Season									
Blood Volume[b,c]	2.4 mL	1.0 mL	-	-	3.4 mL	-	-	-	3.4 mL
Palivizumab Group – 2 RSV Seasons									
Blood Volume[b,c]	2.4 mL	1.0 mL	-	2.4 mL	5.8 mL	2.4 mL	2.4 mL	4.8 mL	10.6 mL

RSV=respiratory syncytial virus

[a] Based on Sponsor consultation, additional blood draw(s) may be collected for participants who undergo the following during the RSV season: 1) ECMO or 2) surgical intervention for CHD and require cardiopulmonary bypass during the procedure.

[b] The blood sample volume at each visit and total blood sample volume for RSV Seasons 1 and/or 2 are the maximum collection volumes for each visit/season. Actual blood collection volume is dependent on the infant's weight at the visit (1% of total blood volume).

[c] In the event a participant experiences a Grade 3 or 4 anaphylaxis/hypersensitivity AESI postdose (see Section 1.3 and Section 8.4.8.1), an additional blood sample (1.2 mL) is required.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

- Exacerbation of a chronic or intermittent 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.

- Surgical procedure(s) 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, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

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

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

e. Is a congenital anomaly/birth defect

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

f. Other important medical events

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

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

10.3.4 Additional Events Reported

Additional events that require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of 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. 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 11 through Table 15. 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 10.3.2. 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 Day 1 through Day 5 postdose will be evaluated by maximum size.

Table 11 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 12 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.
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 13 Elevated Temperature (Rectal) Severity Grading Scale

	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Elevated Temperature (°C) [a] (°F) [a]	≥38.0 to <39.0 ≥100.4 to <102.2	≥39.0 to <40.0 ≥102.2 to <104.0	≥40.0 ≥104.0 for ≤24 hours	≥40.0 ≥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 14 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; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated
Hypersensitivity	Allergic reaction; systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous 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

AESI Term	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 15 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

AESI Term	Severity Grade			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 (eg, erythema, purpura, epidermal detachment and mucous membrane detachment)
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 Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

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

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

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

  - No, there is not a reasonable possibility of Sponsor's product relationship:

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

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

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

SAE reporting to the Sponsor via paper CRF

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

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

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[3, 4]

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[3, 4]

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or 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[3, 4]

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

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

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

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses 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[3, 4]

Participants or legally acceptable representatives may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants or legally acceptable representatives may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. withdrawal and/or destruction. 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 before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3, 4]

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

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

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

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

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

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

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

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

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

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

12. Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 France

Exclusion Criteria

A potential participant from an investigator site located in France 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 following change:

Exclusion Criteria #6: Has known hypersensitivity to any component of MK-1654 (refer to the IB for a list of components) or palivizumab (refer to the Synagis™ label for a list of components **and contraindications**).

10.7.2 The Czech Republic

Inclusion/Exclusion Criteria

A potential participant from an investigator site located in the Czech Republic 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 following changes:

Inclusion Criteria #3: Is male or female **weighing ≥1 kg,** has a chronological age from birth up to 1 year, and entering their first RSV season at the time informed consent is provided.

Exclusion Criteria #12: Has had a recent illness with rectal temperature ≥100.5°F (≥38.1°C) or axillary temperature ≥100.0°F (≥37.8°C) within **7 days** predose. If the participant meets this exclusion criterion, the RSV Season 1 or RSV Season 2 Day 1 visits may be rescheduled for a time when this criterion is not met.

Concomitant Therapy

Any concomitant vaccinations should not be administered within 7 days BEFORE or AFTER any administration of MK-1654 (ie, RSV Season 1 Dose 1, RSV Season 2 dose, or in the event that the participant undergoes 1) ECMO or 2) surgical intervention for CHD and requires cardiopulmonary bypass during the surgical procedure which leads to an additional dose of MK-1654 post-surgery based on the Sponsor consultation).

Postdose Safety Observation Period

The 30-minute postdose safety observation assessments will be conducted at 30 minutes postdose, but participants will continue to be monitored by study personnel for at least 1 hour postdose for any immediate AEs (Section 8.3.4).

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADA	Antidrug antibodies
AE	Adverse event
AESI	Adverse event(s) of special interest
AIDS	Acquired immunodeficiency syndrome
APaT	All Participants as Treated
ARI	Acute respiratory infection
$AUC_{0-\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-150d}	Area under the concentration-time curve from time 0 extrapolated to Day 150
BSA	Body surface area
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHD	Congenital heart disease
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
CRF	Case Report Form
CSR	Clinical Study Report
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Control
ECG	Electrocardiogram
ECI	Event of clinical interest
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form

Abbreviation	Expanded Term
EDC	Electronic data collection
eDiary	Electronic diary
eDMC	External Data Monitoring Committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ER	Emergency room
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
F protein	Fusion glycoprotein
FAS	Full Analysis Set
FBR	Future biomedical research
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
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
ILI	Influenza-like illness
IM	Intramuscular(ly)
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous(ly)
LAR	Legally acceptable representative
LRI	Lower respiratory infection

Abbreviation	Expanded Term
mAb	Monoclonal antibody
MALRI	Medically attended lower respiratory infection
mRNA	Messenger ribonucleic acid
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)
PP	Per-protocol
PPE	Per-protocol efficacy
RESCEU	Respiratory Syncytial Virus Consortium in Europe
RNA	Ribonucleic acid
RR	Respiratory rate
RSV	Respiratory syncytial virus
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
$t_{1/2}$	Half-life
T_{max}	Time to maximum plasma concentration
TC	Telephone call
UNSCH	Unscheduled visit
UR	Uncertainty Range
US/USA	United States

Abbreviation	Expanded Term
USP	United States Pharmacopeia
WHO	World Health Organization

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