Official Protocol Title:	A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus
NCT number:	NCT04086472
Document Date:	13-OCT-2020

Title Page

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Protocol Title: A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus

Protocol Number: 005-05

Compound Number: MK-1654

Sponsor Name:

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

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT	2018-003347-28

Approval Date: 13 October 2020

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

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

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-1654-005-05	13-Oct-2020	The protocol amendment 03 is being amended to include leftover 'Nasal Wash for RSV Virology' samples for future biomedical research (FBR).
MK-1654-005-03	26-Sep-2019	The PROTOCOL AMENDMENT SUMMARY OF CHANGES section on Page 4 of PN005 Amendment 02 is being revised to resolve the inadvertent inclusion of template text due to an administrative error internal to the Sponsor, which stated "Current literature supports use of this class of drugs in a higher age range for this patient population." The text should have read: The original protocol is being amended to incorporate specific text advising participants to avoid contact with groups of people vulnerable to RSV infection for two weeks after they are discharged from the quarantine unit and to add a phone call for safety follow-up approximately 180 days after dosing MK-1654 or placebo.
MK-1654-005-02	23-Sep-2019	The original protocol is being amended to incorporate specific text advising participants to avoid contact with groups of people vulnerable to RSV infection for two weeks after they are discharged from the quarantine unit and to add a phone call for safety follow-up approximately 180 days after dosing MK-1654 or placebo.
MK-1654-005-01	19-Jul-2019	The original protocol is being amended to incorporate a study design update that increases the total number of participants from 70 (14 participants per intervention arm) to 80 (16 per arm) and to eliminate time points for some procedures.
MK-1654-005-00	27-Feb-2019	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [05]

Overall Rationale for the Amendments:

The protocol amendment 03 is being amended to include leftover 'Nasal Wash for RSV Virology' samples for future biomedical research (FBR). The protocol amendment 04 (dated 06-Mar-2020) was created proactively to increase total number of participants to receive MK-1654 or placebo if needed due to unexpected discontinuation rate but the protocol amendment was never implemented in this study. The protocol amendment 04 was labelled "obsolete" in Sponsor's official document repository.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA) 8.9 Future Biomedical Research Sample Collection	Added footnote bullet "u" to "Nasal Wash for RSV Virology" row. Added bullet "Leftover main study nasal wash sample from nasal wash for RSV virology samples stored for future research".	After further review of appropriate scientific analyses for this study, the Sponsor determined that leftover 'Nasal Wash for RSV Virology' samples may provide additional opportunity to inform the scientific understanding of viral replication in participants who received placebo or MK-1654 by performing sequencing of RSV recovered from these samples.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus

Short Title: Phase 2a RSV Human Challenge Study of MK-1654 in Healthy Participants

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

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

This study is to be conducted in adult male and female healthy participants.

Primary Objectives	Primary Endpoints
- To determine if a single, IV dose of MK-1654 when administered at 1 of 4 dose levels results in a reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to IV placebo. - Hypothesis: At least 1 of the 4 dose levels of a single, IV MK-1654 administered dose prior to intranasal inoculation with respiratory syncytial virus (RSV-A Memphis 37b) reduces the Area Under the Viral Load-time Curve (VL-AUC) from Day 2 through Day 11 (inclusive) after viral inoculation compared to IV placebo.	- Area Under the Viral Load-time Curve (VL-AUC) determined by RT-qPCR from Day 2 through Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40)
Secondary Objectives	Secondary Endpoints
- To estimate the effect of each of the 4 dose levels of IV MK-1654 on the incidence of symptomatic RSV infection after intranasal inoculation (with RSV A Memphis 37b) compared to IV placebo.	- Symptomatic RSV infection between Day 2 and Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40) Symptomatic RSV infection is defined as presence of at least two quantifiable RT-qPCR at two or more consecutive days, plus symptoms of either any grade from two different symptoms from the subject symptom card (SSC) or at least one Grade 2 symptom from one or more respiratory categories.

- To evaluate the safety and tolerability of increasing doses of IV MK-1654 compared to IV placebo.	- Adverse Events (AEs) and serious AEs (SAEs)
- To estimate the MK-1654 serum concentration after administration of increasing doses of IV MK-1654.	- MK-1654 serum concentration on Days 1, 8, 15, 29, 40 and 57
- To estimate RSV serum neutralizing antibody titers after administration of IV MK-1654 compared to IV placebo and after intranasal inoculation (with RSV Memphis 37b).	- RSV A serum neutralizing antibody titers on Days 1, 29, 40, and 57

Overall Design:

Study Phase	Phase 2		
Primary Purpose	Prevention		
Indication	Prevention of medically attended lower respiratory infections (MALRI) caused by RSV A and B strains in infants born ≥29 weeks of gestation and ≤8 months of age at the time of dosing		
Population	Serosuitable healthy male and female volunteers 18-55 years (inclusive) of age		
Study Type	Interventional		
Intervention Model	Parallel This is a single-site study.		
Type of Control	Placebo-controlled		
Study Blinding	Double-blind		
Masking	Participant or Subject	Investigator	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 34 weeks from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.		

Number of Participants:

Approximately 80 participants will be allocated/randomized such that approximately 65 evaluable participants complete the study as described in Section 9.9.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Regimen/ Treatment Period/</th><th>Use</th></tr>
<tr><td rowspan="2">MK-1654/ Placebo[a]</td><td>MK-1654</td><td>100 mg, 200 mg, 300 mg and 900 mg</td><td rowspan="2">Once</td><td rowspan="2">IV</td><td rowspan="2">Single IV infusion on Day 1</td><td rowspan="2">Experimental</td></tr>
<tr><td>Placebo</td><td>0 mg</td></tr>
<tr><td colspan="7">Abbreviations: IV= Intravenous
[a] Participants will be randomized to receive MK-1654 100, 200, 300 or 900 mg or placebo in a 1:1:1:1:1 ratio and will be inoculated with RSV A Memphis 37b on Day 29.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>80 participants (16 participants per each MK-1654 dose and 16 placebo)</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 26 weeks from the randomization through the final contact. Participants will be screened for suitability for the study under a separate study site generic screening process. Following signing the study specific Informed Consent Form (ICF) eligibility will be confirmed and then each participant will be randomized to receive the assigned intervention on Day 1. Participants will have outpatient visits post treatment and prior to inoculation. Up to 2 days prior to RSV A Memphis 37b inoculation the participants will be admitted to quarantine where they will stay until inoculation on Day 29 through until 11 days post inoculation. After the end of the quarantine period each participant will be followed through Day 180.</td></tr>
</table>

Study Governance Committees:

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

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

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

Table 1 MK-1654/Placebo Dose and Inoculation Scheme

MK-1654/ Placebo[a]	Number of Participants	Treatment Day	Inoculation Day	Poststudy Visit[b]
100 mg	16	Day 1	29 (± 2 days)	57 (± 4 days)
200 mg	16	Day 1	29 (± 2 days)	57 (± 4 days)
300 mg	16	Day 1	29 (± 2 days)	57 (± 4 days)
900 mg	16	Day 1	29 (± 2 days)	57 (± 4 days)
Placebo	16	Day 1	29 (± 2 days)	57 (± 4 days)

a. Participants will be randomized to receive one of 4 dose levels of MK-1654 or placebo at a ratio of 1:1:1:1:1. The suggested doses may be adjusted downward based on new available safety, tolerability, and/or pharmacokinetic data observed in this study or in other studies for the program.

b. Two safety follow-up phone calls will be performed approximately 33 and 123 days after the poststudy visit on Day 90 and Day 180 respectively.

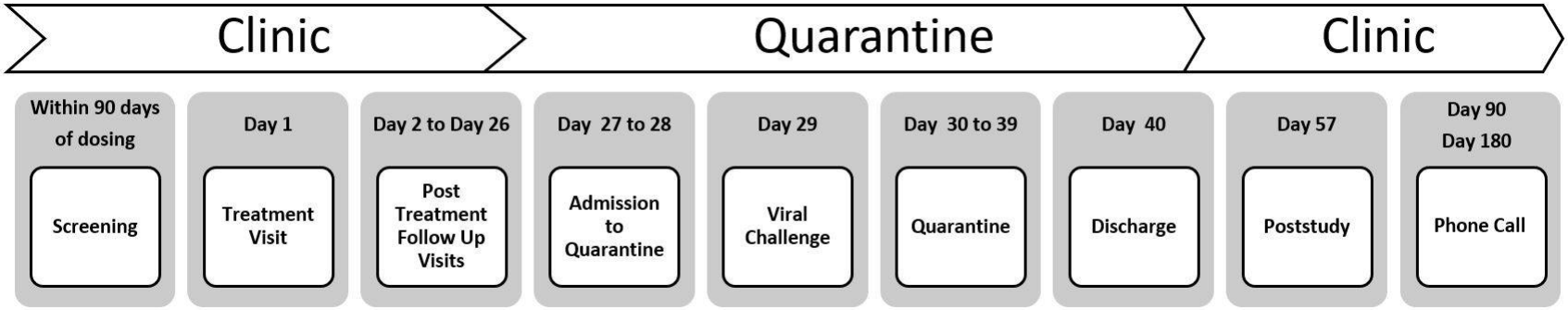

Figure 1 Study Design Diagram

1.3 Schedule of Activities (SoA)

28 Day Post Infusion Inoculation	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5													Early withdrawal visit – pre-inoculation	Early withdrawal visit – post inoculation	Visit 6	D90 Phone Follow-up (± 5 days)	D180 Phone Follow-up (± 7 days)
Study Phase	Screening[a]	Outpatient			Inpatient															Poststudy Visit		
Study Day [b]	Day -90 to -1	IMP Dosing Day 1	D 8	D 15	D 27	D 28	Inoculation DAY 29 (± 2 days)	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40			D57 [b] (± 4 days)		
Administrative and General Procedures																							
Informed Consent	X[c]																						
Informed Consent for Future Biomedical Research	X[d]																						
Demographics	X[d]																						
Eligibility Criteria	X[d]																						
Participant Identification Card	X[d]																						
Medical & Medication History	X	X																					
HIV, Hepatitis A/B/C	X				X[c]																		
Assignment of screening number	X																						
Treatment Randomization[e]		X																					
MK-1654/Pbo Infusion[f,g]		X																					
RSV A Memphis 37b inoculation							X																
Alcohol Breath Testing	X	X[h]			X[c]																		
Urine drugs of abuse[i]	X	X[h]			X[c]																		
Cotinine test	X																						

28 Day Post Infusion Inoculation	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5														Early withdrawal visit – pre-inoculation	Early withdrawal visit – post inoculation	Visit 6	D90 Phone Follow-up (± 5 days)	D180 Phone Follow-up (± 7 days)
Study Phase	Screening[a]	Outpatient			Inpatient																Poststudy Visit		
Study Day [b]	Day -90 to -1	IMP Dosing Day 1	D 8	D 15	D 27	D 28	Inoculation DAY 29 (± 2 days)	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40			D57 [b] (± 4 days)		
Efficacy Assessment																							
Respiratory pathogen screens (NPS)					X[c]																		
hVIVO Symptom Diary Card						X	tds	tds	tds	tds	tds	tds	tds	tds	tds	tds	tds	X					
Nasal Wash for RSV Virology[j, u]					X[c]				BID	BID	BID	BID	BID	BID	BID	BID	BID	X		X			
(paper) Tissue distribution[k]						X	X	X	X	X	X	X	X	X	X	X	X						
(paper) Tissue collection[k]							X	X	X	X	X	X	X	X	X	X	X	X		X			
Pharmacokinetics and Pharmacodynamic Assessment																							
Blood for RSV Serologies[l, u]	X	X[h]					X											X			X		
Blood (PBMC) [u]					X													X			X		
Nasal Weck-Cel sample for MK-1654 PK and RSV Antibodies[m, u]		X[h]			X[c]																X		
Blood for Genetic Analysis[n, u]		X[h]																					
Blood for mRNA Analysis[o, u]		X[h]				X								X							X		
Blood for Serum MK-1654[u]		X[h, v]	X	X			X											X			X		
Archive serum sample for ADA[u]		X[h]																			X		

28 Day Post Infusion Inoculation	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5														Early withdrawal visit – pre-inoculation	Early withdrawal visit – post inoculation	Visit 6	D90 Phone Follow-up (± 5 days)	D180 Phone Follow-up (± 7 days)
Study Phase	Screening[a]	Outpatient			Inpatient																Poststudy Visit		
Study Day [b]	Day -90 to -1	IMP Dosing Day 1	D 8	D 15	D 27	D 28	Inoculation DAY 29 (± 2 days)	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40			D57 [b] (± 4 days)		
Safety Assessment																							
Weight and BMI[p]	X	X[h]																	X	X	X		
Vital Signs (heart rate, blood pressure, respiratory rate, O2 saturation and temperature)[q]	X	X[h]	X	X	X[c]		X[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medication monitoring/review	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician Assessment (CPE)	X	X[h]	X		X[c]													X	X	X			
Physician Assessment (DPE)				X			X[r]	X	X	X	X	X	X	X	X	X	X				X		
ECG[s]	X	X[h]	X		X[c]						X				X			X		X	X		
Spirometry	X	X[h]			X[c]										X			X		X	X		
Urinalysis	X	X[h]			X[c]										X			X		X	X		
Safety Laboratory Test	X	X[h]	X		X[c]						X				X			X	X	X	X		
Pregnancy test (urine)[t]	X	X[h]			X[c]													X	X	X	X		

a. All screening procedures will be performed under the hVIVO generic screening process. Historical pre-screening data collected through the hVIVO generic screening process within 90 days (90 days for viral serology and 56 days for other assessments including safety laboratory test) of randomization may be used to determine eligibility without the need to repeat the assessments following study specific consent.
b. Outpatient and follow-up visits will allow for a flexible time window during which the participant may attend. Post dosing visits: ± 1 day; RSV inoculation visit: ± 2 days. Day 1 predose procedures may be performed within 3 hours of, but prior to, IMP dosing. All inpatient visits should all occur in line with inoculation day, there is no flexibility window for inpatient study days post inoculation during Visit 5. Participants who are dosed with MK-1654/Placebo but not inoculated with RSV A Memphis 37b will not have an inpatient visit and will be followed for safety monitoring on Day 57 visit. If the Day 57 poststudy follow up visit occurs on or near national holidays, the time variance can be extended to + 6 days/-4 days (Day 63/Day 53) if necessary.
c. The procedure may be conducted either day.

28 Day Post Infusion Inoculation	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5													Early withdrawal visit – pre-inoculation	Early withdrawal visit – post inoculation	Visit 6	D90 Phone Follow-up (± 5 days)	D180 Phone Follow-up (± 7 days)
Study Phase	Screening[a]	Outpatient			Inpatient															Poststudy Visit		
Study Day [b]	Day -90 to -1	IMP Dosing Day 1	D 8	D 15	D 27	D 28	Inoculation DAY 29 (± 2 days)	D30	D31	D32	D33	D34	D35	D36	D37	D38	D39	D40			D57 [b] (± 4 days)		

d. Procedure may be conducted on either day demarcated with the corresponding footnote but must occur on the same day as Informed Consent, post-Informed Consent.
e. The randomization (allocation) number is assigned prior to study drug administration.
f. Participants will be monitored during the administration of MK-1654 or placebo and for 2 hours after the completion of administration for signs and symptoms of a systemic injection/infusion reactions.
g. MK-1654/Placebo will be infused over approximately of ~2 hours on Day 1. Infusion time may increase based upon tolerability. Refer to Section 6 and the trial pharmacy manual for additional information on the preparation and administration of study drug.
h. Assessment to be carried out predose. Baseline safety assessment procedures of Day 1 may be performed within 3 hours of dosing, the baseline lab assessments do not need to be reviewed prior to MK-1654/placebo administration.
i. UDS will be conducted per hVIVO standard operating procedures.
j. Nasal Wash for RSV Virology samples will be taken for RSV quantification (RT-qPCR and plaque assay) and for assessment of participant RSV infectivity status [Qualitative integrated cycler polymerase chain reaction (qic-PCR)] prior to discharge (Day 39).
k. Tissue distribution and collection will be carried out daily at 08:00 ± 1 hour.
l. Blood for RSV serum neutralizing antibody titers will be collected once before MK-1654/placebo infusion (within 3 hours of dosing), and once immediately after the end of MK-1654/placebo infusion (i.e., no more than 15 min after the end of the infusion, see footnote v.), for a total of two collections for antibody titer on Day 1.
m. Nasal Weck-Cel samples will be taken before MK-1654/placebo infusion on Day 1,on Day 27 or 28 (prior to nasal wash samples and at least 24 hours prior to RSV A Memphis 37b inoculation on Day 29). Leftover nasal Weck-Cel eluent from the MK-1654 PK sample may be used for RSV antibody assays.
n. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research once the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
o. PAXGene tube collection for mRNA sequence analysis. 2.5 mL (1 tube) to be collected, up to 5 mL (2 tubes) if necessary and within the maximum allowable blood collection volume per participant.
p. Height used to calculate BMI will be taken from screening data.
q. All vital sign assessments will be single measurements. HR and BP will be performed within 3 hours of dosing MK-1654. Tympanic temperature measurements will be taken in clinic.
r. Assessment to be carried out pre-inoculation.
s. Pre-dose ECGs should be obtained on Day 1 within 3 hours of dose. All ECG measurements will be single measurements.
t. If urine pregnancy is positive, then blood sample should be tested for serum pregnancy. Serum pregnancy test will be performed on admission (Day 27/28).
u. All leftover samples from participants dosed with MK-1654/placebo will be stored for future biomedical research.
v. Day 1 blood for serum MK-1654 PK should be taken at pre-dose and 1, 2, and 4 hrs post-initiation of infusion. The 2 hr PK sample on Day 1 will be obtained immediately after the end of infusion (i.e. no more than 15 min after the end of the infusion).

2 INTRODUCTION

2.1 RSV Clinical Manifestations and Epidemiology

Respiratory syncytial virus (RSV) causes upper and lower respiratory tract illness worldwide. The virus is transmitted primarily via droplets from the sneeze, cough, or breathing of an infected person, or via contamination of environmental surfaces with infectious secretions [Hall, C. B. 1981]. RSV epidemics occur yearly during late fall, winter, and early spring (lasting about 5 months) in temperate climates, and throughout the year with a less predominant cyclical pattern in the tropics [Haynes, A. K., et al 2013] [Stensballe, L. G., et al 2003] [Bloom-Feshbach, K., et al 2013]. There is a single RSV serotype with two major antigenic subgroups, A and B strains [Borchers, A. T., et al 2013]. Both strains often co-circulate during epidemics, though one may predominate [Mufson, M. A., et al 1988] [Akerlind, B. 1986] [Gilca, R., et al 2006] [Borchers, A. T., et al 2013]. By the end of the first year of life, approximately 70% of children will have been infected with RSV; 30-75% will have been infected twice by the second year of life [Glezen, W. P., et al 1986] [Hall, C. B., et al 2009] [Ohuma, E. O., et al 2012]. Reinfection with RSV occurs throughout life and is generally associated with mild upper respiratory tract infection in healthy older children and immunocompetent adults [Hall, C. B. 2001] [Borchers, A. T., et al 2013]. The clinical manifestations of RSV reinfection in older adults are variable, with symptoms ranging from a mild cold to severe respiratory distress [Falsey, A. R. 2000], [Walsh, E. E. 2012].

2.1.1 Epidemiology of RSV Infection in Infants

RSV is the most common cause of acute lower respiratory infection (ALRI) in infants and children [Hall, C. B., et al 2009] [Nair, H., et al 2010] [Bont, L., et al 2016]. Globally, it was estimated in 2005 that RSV caused 33.8 million episodes of ALRI (~22% of all ALRI) and 3.4 million episodes of severe ALRI requiring hospitalization among children <5 years old worldwide [Nair, H., et al 2010]. Mortality from RSV infection is significant, with an estimated 66,000-199,000 childhood deaths in 2005 worldwide [Nair, H., et al 2010]. The overwhelming majority of these deaths occur in children below the age of 2 years and in developing countries [Nair, H., et al 2010] [Bont, L., et al 2016]. The most recent estimates of global RSV disease burden showed that, in 2015, there were no substantial changes in the number of new episodes of RSV-ALRI and related hospital admissions compared to 2005, but a lower number of in-hospital deaths [Shi, T., et al 2015]. Moreover, for children younger than 6 months, Shi et al reported about 1.4 million hospital admissions and 27,300 in-hospital deaths due to RSV-ALRI in 2015 worldwide [Shi, T., et al 2015].

RSV also accounts for a substantial proportion of outpatient visits in both pre-term and full-term infants and children younger than 5 years, leads to the development of some chronic respiratory illnesses, and results in workdays missed by caregivers [Paramore, L. C., et al 2004] [Bourgeois, F. T., et al 2009] [Diez-Domingo, J., et al 2014] [Garcia, C. G., et al 2010]. An estimated 2.2% (1.7 million visits) of all US primary care visits of children <5 years old in 2000 were due to RSV infection. Pre-term infants with RSV averaged 12.4 physician office visits during first year of life for any cause versus 5 visits for infants with no respiratory pathology [Diez-Domingo, J., et al 2014]. Moreover, children previously infected

with RSV also have a higher risk of developing some chronic respiratory conditions including recurrent wheezing and asthma [Polack F. P. 2015] [Paes, B., et al 2016]. Pre-term infants are more likely to develop recurrent wheezing than full-term infants, with estimated prevalence of recurrent wheezing of 18% in the first year of life among preterm infants [Polack F. P. 2015] [Paes, B., et al 2016], and 10% among full term infants [Polack F. P. 2015] [Paes, B., et al 2016]. Moreover, observational studies indicate that RSV infection during infancy may lead to increased risk of subsequent recurrent wheezing [Polack F. P. 2015] [Paes, B., et al 2016]. Lastly, RSV infection in infants leads to significantly more workdays missed by caregivers than influenza (716,404 days vs 246,956 days over two seasons, respectively). Almost two thirds of caregivers missed at least one day of work due to a child's RSV infection [Bourgeois, F. T., et al 2009]. Given the lack of routine RSV testing in both the inpatient and outpatient settings in general, the total burden of RSV infection is likely to be underestimated.

Pre-term infants, and those with underlying medical conditions, are pre-disposed to severe RSV infection. A prophylactic monoclonal antibody (mAb), palivizumab (Synagis™, MedImmune), is approved for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk for RSV disease [U.S. Prescribing Information 2017]. However, the majority of infants with RSV infection have no predisposing risk factors and are otherwise healthy. Therefore, there is a need for prophylaxis to prevent RSV infection in the overwhelming majority of healthy pre-term and full-term infants. MK-1654 is a neutralizing mAb against RSV, with attributes to facilitate its application as an RSV prophylactic for all infants.

2.1.2 RSV Pathogenesis and Mechanisms of Immune Protection

The incubation period after RSV exposure ranges from 2 to 8 days after the virus enters the body through the upper respiratory tract. In susceptible individuals (e.g infants, older adults), the virus may spread to the lower respiratory tract where it can cause symptoms of bronchitis, bronchiolitis, pneumonia and respiratory distress (collectively called LRI). Primary infection and subsequent reinfections result in immune responses to RSV. These immune responses include 1) the generation of serum neutralizing activity (SNA), through antibodies predominantly targeted to the RSV fusion (F) protein, 2) RSV specific mucosal IgA and IgG and 3) CD4 T-helper and CD8 cytotoxic T cell responses to RSV peptide antigens. Despite these immune responses, reinfection occurs throughout life. Each of these mechanisms may contribute to the more mild disease observed in healthy children and younger adults. Quantitative insight into the contribution of each mechanism is limited and no established correlates of protection exist. SNA to the RSV F protein, when present at high enough titer, can reduce the incidence of severe RSV. Specifically, both polyclonal sera rich in RSV neutralizing antibodies (i.e RespiGam), as well as anti-RSV F protein monoclonal antibodies (i.e. palivizumab and motavizumab (a more potent version of palivizumab)), reduce the incidence of RSV LRI and hospitalizations in infants [Griffiths, C., et al 2017].

Despite these observations the relationship between SNA and protection from RSV infection, particularly with respect to upper respiratory tract infection, is poorly defined. This understanding is important to the development of any protective mechanism that relies upon neutralizing activity against the RSV F protein, including passive immunization with

monoclonal antibodies like MK-1654, and active vaccination approaches, such as RSV F protein subunit vaccines.

In an ongoing Phase 1a study in healthy male participants (MK-1654 PN001), MK-1654 has been safe and generally well tolerated at doses up to 300mg IM and 3000mg IV, results in dose dependent PK with a serum half-life of ~75-87days and a corresponding increase in SNA, reflective of biologically active MK-1654 in the sera. Importantly, doses of MK-1654 can be chosen to yield predictable SNA titers in healthy participants.

2.1.3 Summary of RSV Inoculation Model

RSV A Virus Inoculation strain Memphis-37b strain has been utilized in over 1000 healthy participants in at least 19 clinical studies. RSV inoculation of healthy participants was shown to infect approximately 65 - 85% of placebo participants and produced mild to moderate upper respiratory tract illness.

Additionally, another strain of live RSV (Memphis 37c) has been used as an inoculation agent and was shown to be safe in over 77 healthy young adults across three studies. RSV infection was not associated with any serious adverse side effects.

The study virus, like many viruses, can cause more substantial health issues such as myocarditis (inflammation or damage to the heart muscle). However, the chance of this resulting in serious or permanent changes is rare, as most cases are minor and resolve without any lasting changes. In previous virus inoculation studies, uncommonly blood tests have shown a change suggestive of myocarditis, although in these few participants the blood tests returned to normal without treatment and were not associated with specific symptoms or ECG changes.

2.2 Study Rationale

Similar to other ongoing MK-1654 Phase 1a studies in healthy adult participants (PN001 and PN003), this study is also a randomized, placebo-controlled, double-blind study. This study will also implement an intranasal inoculation with RSV A Memphis 37b to investigate study endpoints.

This study is being conducted to assess the efficacy of a single IV MK-1654 dose administered over increasing dose levels to study population in an RSV experimental intranasal inoculation model. The primary objective is to determine whether administration of a single, IV dose of MK-1654 reduces nasal viral load after intranasal inoculation with RSV A Memphis 37b compared to IV placebo. Viral load will be determined by the Area Under the Viral Load-time Curve (VL-AUC). The secondary objective is to estimate the incidence of symptomatic RSV infection after intranasal inoculation (with RSV A Memphis 37b) for each of the doses of IV MK-1654 compared to IV placebo. These data will provide proof that MK-1654 can reduce nasal viral load and symptomatic RSV infection in adults after experimental RSV inoculation. They will also facilitate a quantitative understanding of the relationships between MK-1654 PK, SNA titers and experimental RSV infection in healthy adults that can be extended to other populations (e.g., infants), clinical manifestations

[e.g. lower respiratory tract infection (LRTI)] and preventative approaches (e.g. F protein-based vaccines) through modeling.

2.3 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-1654 (IB Edition 2).

2.3.1 Pharmaceutical and Therapeutic Background

MK-1654 is a fully human mAb targeting the RSV F protein, which the virus utilizes to enter host cells and fuse infected cells with adjacent cells, spreading the virus by syncytia formation. The F protein is considered a key antigen for protective immunity, based on natural immunity studies, and active and passive immunization approaches (ie, palivizumab) [American Academy of Pediatrics Committee on Infectious Diseases. 2014] [Graham, B. S., et al 2015]. As outlined in the IB, 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. Compared to palivizumab, MK-1654 exhibits greater potency both in vitro and in the preclinical cotton rat model. Mutations in the Fc region of MK-1654 result in an extended half-life such that a single dose of MK-1654 will sustain therapeutic levels for 5 months in the majority of infants entering their first RSV season (see IB for details).

2.3.2 Preclinical and Clinical Studies

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

2.3.2.1 Ongoing Clinical Studies

Protocol 001

The first clinical trial (PN001) is evaluating the safety and PK of rising single IM and IV doses of MK-1654. As the study is ongoing, it remains blinded. PN001 is a 2 Part, randomized, placebo-controlled, double-blind trial of MK-1654 in healthy male participants and female participants of non-child bearing potential 19 to 59 years of age. The trial consists of 7 panels conducted in two parts: Part 1 included 5 dose escalation panels (Panels A-E) and Part 2 included 2 expansion panels (Panels F and G). In all panels, participants were randomized 3:1 to receive a single dose of MK-1654 or placebo. No participant received more than one dose of MK-1654. The doses administered in Part 1 included 100 mg IM (Panel A), 300 mg IM (Panel B), 300 mg IV (Panel C), 1,000 mg IV (Panel D), and 3,000 mg IV (Panel E) of MK-1654. Part 2 expansion cohorts received 300 mg IM (Panel F) and 1,000 mg IV (Panel G) of MK-1654. Drug dosed IM was administered as either a single bolus injection (100 mg) in the vastus lateralis or in divided bolus injections (300 mg) in either the vastus lateralis or deltoid. Drug dosed IV was administered as a single infusion over 2.5 hours.

Preliminary Blinded Safety Summary

As of 21-Dec-2018 the trial is ongoing and blinded, although mean group level change from baseline reports for laboratory assessments, electrocardiograms or vital sign measurements are available and were reviewed. To date 152 participants have been enrolled in the trial. Panels A-F have completed the 1-year safety follow-up period while Panel G is ongoing and includes safety data to ~300 days post MK-1654 administration. Administration of MK-1654 has been generally well tolerated in healthy male participants and female participants of non-child bearing potential in all doses up to 300 mg IM and up to 3,000 mg IV.

No deaths have been reported and no participants have discontinued from the trial due to an AE. One participant experienced a serious adverse event (SAE) of tibia fracture associated with an accident that was not considered drug related by the investigator. No dose limiting tolerability issues or dose dependent pattern of drug-related AEs have been observed. Study pause rules have not been met at any point in the trial. No clinically significant laboratory AEs have been reported in the trial.

Seventy-one (71) participants reported clinical AEs during the treatment and observation period in the 152 participants receiving MK-1654 or placebo. Most AEs reported were generally transient and considered mild to moderate in intensity by the investigator. Apart from the SAE described above no severe intensity AEs have been reported. The most commonly reported treatment emergent AEs include headache, nasal congestion, oropharyngeal pain, rhinorrhea, and vessel puncture site hemorrhage. There were no treatment-related changes in mean laboratory assessments, ECGs, or vital sign measurements in participants that received MK-1654 compared to placebo. MK-1654 administered IM was generally well tolerated in terms of local reactogenicity, with only 3 participants reporting mild injection site pain and 1 participant reporting injection site hemorrhage among the 80 participants dosed with up to 300 mg of MK-1654 or placebo between Panels A, B and F.

Two clinical events of interest were reported (2 cases of rash within 90 days of trial drug administration) and are summarized below.

One participant was administered either 300 mg MK-1654 or placebo IM injection (blinded) and reported sneezing, mild in intensity, approximately 3 hours post injection. The following day the participant reported the AEs of generalized pruritus and papules, which evolved to generalized urticaria. All AEs were mild in intensity. No trigger for the urticaria other than drug administration was identified in the participant's history or upon physical examination. However, the participant stated that there were multiple erythematous papules on [redacted] right hand prior to dosing that were not reported to the staff. The participant denied similar skin reactions in the past. All AEs resolved within approximately 14 days from onset and before a dermatology consult could be obtained. All AEs associated with the dermatological event were considered related to treatment.

Another participant was administered either 300 mg MK-1654 or placebo IV infusion (blinded). Twenty-nine (29) days after trial drug administration the participant reported a generalized maculopapular rash mild in intensity. The rash lasted approximately two weeks

before resolving. The rash was not associated with pruritus. The investigator considered this AE related to treatment.

Lastly, two of 114 participants treated with MK-1654 were positive for treatment emergent ADA thus far in the study.

Preliminary PK Summary

Mean concentration-time profiles for MK-1654 are provided in [Figure 2]. The median T_{max} for MK-1654 was ~6-10 days for IM doses and 4 hours for IV doses. The apparent terminal elimination phases appeared to be parallel for all IM and IV panels, suggesting similar elimination half-lives for all doses and routes of administration. A preliminary non-compartmental analysis (NCA) of the adult serum PK data was performed and results are provided in [Table 2] The estimated bioavailability was approximately 72-76% following a 300 mg IM injection. The geometric mean (GM) apparent terminal half-life of MK-1654 ranged from ~75-87 days. Both $AUC_{0-\infty}$ and C_{max} increased approximately dose proportionally following IV administration.

MK-1654 has no endogenous target in humans and thus in the absence of RSV infection has no pharmacodynamics effects. However, biologic activity of MK-1654 in the serum after administration is reflected by increases in RSV A serum neutralizing antibody (SNA) titers [reported as the dilution titer resulting in a 50% viral neutralization (NT50)]. As expected, serum neutralizing antibody titers increased in a dose-dependent manner among those administered MK-1654 IM and IV (data not shown) and demonstrated a strong relationship with MK-1654 concentration [Figure 3].

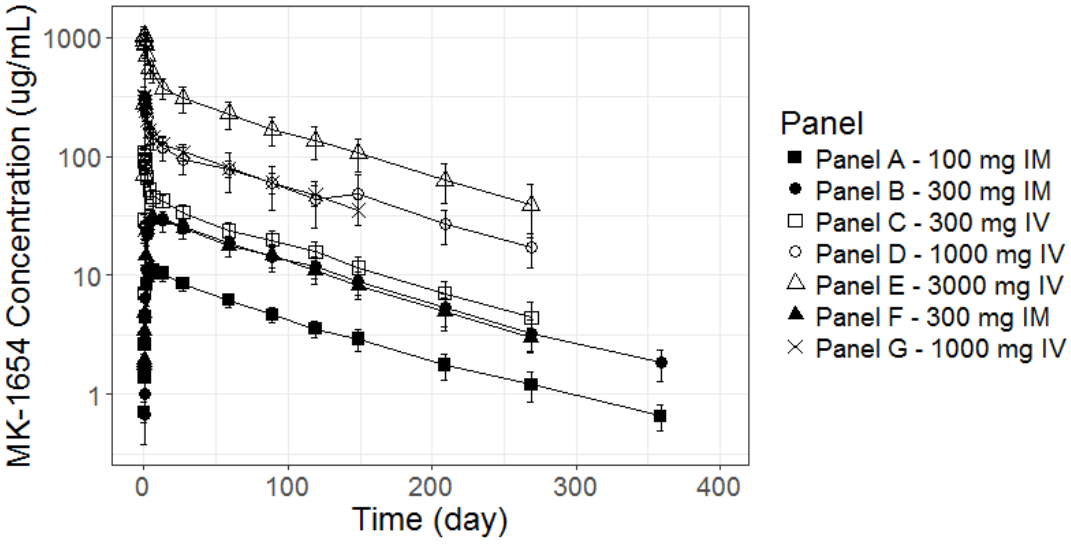

Figure 2 Mean ± Standard Deviation Serum Concentration-Time Profiles in Healthy Adults Following a Single Dose of MK-1654

Table 2 Summary of PK Parameters in Healthy Adults following a Single Dose of MK-1654

Treatment	Panel	Dose (mg)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	C_{150} (µg/mL)	T_{max} † (day)	$t_{½}$ (day)
MK-1654 IM	A	100	11.1 (18.1)	1220 (17.3)	2.85 (23.1)	6.0 (2 - 13)	86.6 (13.3)
	B	300	31.2 (11.6)	3,690 (19.3)	8.57 (21.9)	9.5 (4 - 27)	86.2 (14.2)
	F	300	30.8 (26.2)	3,390 (22.3)	7.87 (23.8)	6.0 (2 - 13)	77.1 (18.1)
MK-1654 IV	C	300	107 (12.3)	5,050 (17.7)	11.3 (22.3)	0.17 (0.1 - 0.17)	81.7 (15.0)
	D	1000	326 (18.7)	15,200 (49.7)	35.1 (195)	0.17 (0.1 - 0.33)	74.9 (48.0)
	E	3000	1,050 (15.8)	45,100 (33)	97.1 (59.9)	0.17 (0.1 - 0.17)	78.1 (24.5)
	G	1000	320 (11.3)	15,400 (17.7)	34.1 (24.3)	0.17 (0.1 - 0.33)	76.0 (15.7)

Value are reported in geometric mean (% geometric CV) unless otherwise noted.
† Median (Min-Max)

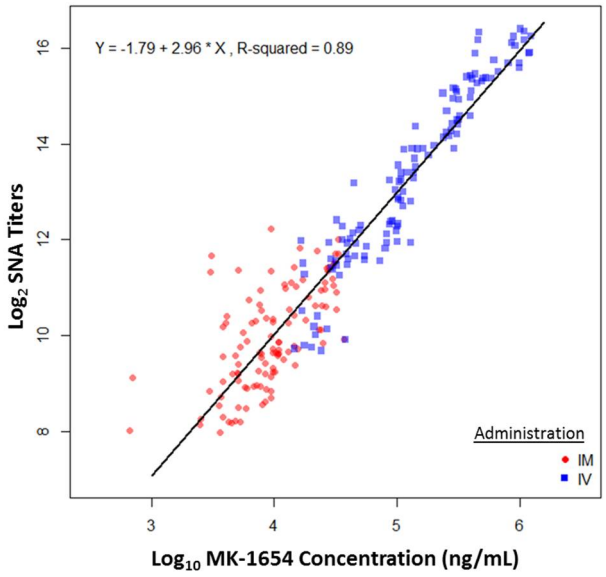

Figure 3 Linear Relationship between Log2 SNA Titers vs. Log10 MK-1654 Concentration (ng/mL) following IM and IV Administration

Protocol 003

MK-1654 Protocol 003 is an ongoing randomized, placebo-controlled, double-blind trial of MK-1654 in healthy male Japanese participants 20 to 55 years of age with one-year of safety follow-up. As of 31-Dec -2018, planned total 44 participants have received MK-1654 or placebo at doses up to 300mg IM and 1000 mg IV. No participants have completed the study to date. As of 31-Dec-2018, no deaths, treatment related serious adverse events (SAEs), discontinuations due to adverse events (AEs), dose limiting tolerability issues, clinically significant laboratory AEs, or dose dependent pattern of drug-related AEs have been reported.

2.4 Benefit/Risk Assessment

Healthy participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

This study is to be conducted in adult male and female healthy participants.

Objectives	Endpoints
Primary	
• To determine if a single, IV dose of MK-1654 when administered at 1 of 4 dose levels results in a reduction in viral load after intranasal inoculation (with RSV A Memphis 37b) compared to IV placebo. • Hypothesis: At least 1 of the 4 dose levels of a single, IV MK-1654 administered dose prior to intranasal inoculation with respiratory syncytial virus (RSV-A Memphis 37b) reduces the Area Under the Viral Load-time Curve (VL-AUC) from Day 2 through Day 11 (inclusive) after viral inoculation compared to IV placebo.	• Area Under the Viral Load-time Curve (VL-AUC) determined by RT-qPCR from Day 2 through Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40)

Objectives	Endpoints
Secondary	
• To estimate the effect of each of the 4 dose levels of IV MK-1654 on the incidence of symptomatic RSV infection after intranasal inoculation (with RSV A Memphis 37b) compared to IV placebo.	• Symptomatic RSV infection between Day 2 and Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40) Symptomatic RSV infection is defined as presence of at least two quantifiable RT-qPCR at two or more consecutive days, plus symptoms of either any grade from two different symptoms from the subject symptom card (SSC) or at least one Grade 2 symptom from one or more respiratory categories.
• To evaluate the safety and tolerability of increasing doses of IV MK-1654 compared to IV placebo.	• Adverse Events (AEs) and serious AEs (SAEs)
• To estimate the MK-1654 serum concentration after administration of increasing doses of IV MK-1654.	• MK-1654 serum concentration on Days 1, 8, 15, 29, 40 and 57
• To estimate RSV serum neutralizing antibody titers after administration of IV MK-1654 compared to IV placebo and after intranasal inoculation (with RSV Memphis 37b).	• RSV A serum neutralizing antibody titers on Days 1, 29, 40, and 57
Tertiary/Exploratory	
• To estimate the effect of administration of IV MK-1654 on mucus production after intranasal inoculation (with RSV A Memphis 37b) compared to IV placebo.	• Mucus weight between Day 2 and Day 11 after viral inoculation (time windows to be defined)
• To estimate the effect of administration of IV MK-1654 on RSV nasal viral load, total symptom scores and daily symptom scores after intranasal inoculation (with RSV A Memphis 37b) over different time windows between Days 2 and 11 compared to IV placebo.	• Area Under the Viral Load-time Curve (VL-AUC) by RT-qPCR, total symptom scores and daily symptom scores from Day 2 through Day 11 (time windows to be defined) after viral inoculation

Objectives	Endpoints
• To estimate the effect of IV MK-1654 on RSV nasal viral loads determined by quantitative culture after intranasal inoculation (with RSV A Memphis 37b) over different time windows between Days 2 and 11 after viral inoculation compared to IV placebo	• Area Under the Viral Load-time Curve (VL-AUC) determined by quantitative culture between Day 2 and Day 11 after viral inoculation (windows to be defined)
• To characterize the immune response to intranasal inoculation (with RSV Memphis 37b) after administration of IV MK-1654 compared to IV placebo	• D25 competing antibody titers to RSV F protein on Days 29 and 57 • ELISPOT to measure T cell responses to RSV F derived peptides on Days 27, 40, and 57
• To estimate MK-1654 concentrations in nasal mucosal fluid samples obtained before and after administration of IV MK-1654 or IV placebo, and before and after intranasal inoculation (with RSV A Memphis 37b).	• MK-1654 concentration in nasal mucosal fluid on Days 1, 28 and 57
• To estimate anti-RSV F antibody (IgA and IgG) concentrations and RSV neutralizing activity in nasal mucosal fluid samples collected by Weck-Cel obtained before administration of IV MK-1654 or IV placebo, and 28 days after intranasal inoculation with RSV A Memphis 37b.	• Anti-RSV F antibody (IgA and IgG) concentrations and RSV neutralizing activity in nasal mucosal fluid on Study Days 1 and 57
• To characterize the immune response in healthy adults to intranasal inoculation with RSV A Memphis 37b after administration of MK-1654 with whole blood mRNA and excess serum, PBMCs and nasal fluid samples.	• Immune response biomarkers to be determined

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, single-site, double-blind study of MK-1654 in healthy male and female participants 18 to 55 years (inclusive) of age, screened to be in the bottom quartile of participants for immunogenicity to the RSV A Memphis 37b (inoculation strain) as determined by microneutralization assay. This study will be conducted in conformance with Good Clinical Practices (GCP).

Participants will be pre-screened under a separate protocol for SNA (PRNT assay) activity against the inoculation strain. As per protocol of the vendor, those participants in the lower quartile will be screened for eligibility for this study. Up to 80 participants who meet eligibility criteria will be randomized to receive placebo or 100, 200, 300 or 900 mg of MK-1654 in a 1:1:1:1:1 treatment ratio according to the Sponsor's computer-generated allocation schedule. Participants will receive a single IV dose of MK-1654 or placebo (0.9% sodium chloride, B.P.) on Day 1 of the study. On Day 29 of the study up to 70 participants will be inoculated with RSV A Memphis 37b in order to have the required number of evaluable participants for the analysis (see Section 9.9). Participants will remain domiciled for 11 days post inoculation. Participants will be queried daily while domiciled for symptoms of RSV infection using a standardized questionnaire starting on Day 28. Nasal wash samples will be collected and tested for RSV viral load by RT-qPCR 1 or 2 days before inoculation and then twice daily from Day 31 through Day 39. A single nasal wash sample for RSV viral load by RT-qPCR will be collected on Day 40. Key samples to measure MK-1654 PK and SNA will be collected throughout the study as outlined in the SoA. No participant will receive more than one dose of MK-1654. All participants inoculated with RSV A Memphis 37b will be followed for safety monitoring for approximately 28 days after RSV A Memphis 37b inoculation. Nasal wash samples will be tested for the presence of virus prior to discharge. Participants will only be discharged when virus levels are below that which are considered a potential risk of RSV transmission to others. In case any symptoms are present, but no virus is detected, discharge is at the Investigator's discretion.

Participants who are dosed with MK-1654 or placebo, but not inoculated with RSV A Memphis 37b, will be followed for safety monitoring for approximately 56 days post IMP dosing at the poststudy visit. In addition, two safety follow-up phone calls will be performed approximately 33 and 123 days after the poststudy visit on Days 90 and 180, respectively (within the visit windows allowed per protocol).

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

4.2.1 Rationale for Study Design

MK-1654 is a fully human, neutralizing mAb to RSV with mutations to extend its half-life, being developed as a passive IM immunization to protect infants against RSV disease. The purpose of this RSV challenge study is to provide proof of efficacy for MK-1654 in humans. The protocol follows a double blind, placebo-controlled design. Participants will be inoculated with RSV A Memphis 37b, approximately 28 days, after administration of a single, IV dose of MK-1654 at one of 4 different dose levels or placebo. A reduction in nasal viral load has been chosen as the primary efficacy measure as a sensitive and predictable indicator of viral replication. The incidence of symptomatic RSV infection is the secondary efficacy measure. Participants will be domiciled for at least 11 days and followed for 28 days after inoculation with RSV A Memphis 37b, which is a sufficient amount of time for participants to clear the RSV A Memphis 37b virus and detect any potential complications of the inoculation, respectively. To understand the relationship between MK-1654 and protection from RSV A Memphis 37b inoculation, serum will be collected throughout to measure MK-1654 PK and SNA titers. Serum and PBMCs will also be collected to understand in exploratory analyses how MK-1654 affects humoral and cellular immune responses to RSV A Memphis 37b inoculation, respectively. Taken together, the design will provide a robust efficacy evaluation of MK-1654 in healthy adults.

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

The study will evaluate the efficacy of the prophylactic treatment with IV MK1654 compared to placebo in healthy adult participants inoculated with RSV-A Memphis 37b. This will be assessed by comparing the level of nasal viral load and the rate of symptomatic RSV infection in each MK-1654 dose group with the placebo group.

4.2.2.2 Safety Endpoints

In support of the safety objective to evaluate the safety and tolerability profile of MK-1654, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs and inspection of other trial parameters including vital signs, physical examination, electrocardiogram (ECG), infusion reaction assessments, and standard laboratory safety tests at time points specified in the SoA (Section 2). Adverse events are graded and recorded according to Appendix 3. Additional safety monitoring may be performed at the discretion of the investigator.

The safety follow-up period will be 180 days post-dose. Participants will be monitored post-dose with a scheduled onsite safety observation period. Study staff will monitor participants through 2 hours post-dose for symptoms of infusion and hypersensitivity reactions to MK-1654 with VS and physical examinations as needed. See below in this subsection for a brief discussion on infusion and hypersensitivity reactions. Participants will then return to the study site for efficacy, safety, PK and PD assessments as set out in Section1.3 SoA.

Instructions for supportive care are outlined in Section 6.5.1. RSV infection symptoms and AEs will also be documented on a validated diary card.

Although not observed thus far in the MK-1654 clinical program, as with all biologic medications, MK-1654 carries a risk of acute systemic reactions upon exposure. These reactions can be categorized as common acute infusion reactions and acute hypersensitivity reactions. In adults, common acute systemic infusion reactions are usually mild, and may manifest with rigors, back pain, abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes in heart rate or blood pressure. Acute hypersensitivity reactions typically occur after repeated exposures, but can occur with the first dose. In addition to signs similar to common acute infusion reactions, participants may develop urticaria, wheezing, coughing, facial swelling, angioedema, and more significant changes in vital signs. An anaphylactic reaction is a severe type of acute infusion reaction characterized by cutaneous and mucosal symptoms such as generalized hives, pruritus or flushing, swollen lips-tongue-uvula and angioedema, accompanied by respiratory compromise (bronchospasm, stridor, or hoarseness) and/or changes in blood pressure (hypotension), per the 2006 Sampson criteria for anaphylaxis (Grade 4 reaction) [Sampson, H. A., et al 2006].

The risk of any of these acute systemic injection reactions to the MK-1654 antibody is considered very low as it contains only human elements. MK-1654 has no endogenous target in humans. Across 2 ongoing clinical studies in adults (P001 and P003) in adults, no acute safety reactions to MK-1654, including acute systemic injection reactions, have been identified in participants, as described in Section 2.3.3.

4.2.2.3 Pharmacokinetic Endpoints

Serum PK of MK-1654

The serum PK of MK-1654 will be measured on pre-dose, and on Days 1 (1, 2, 4 hr), 8, 15, 29, 40 and 57 post-dose to define the PK profile of MK-1654 (e.g. Cmax) when administered IV. PK will be measured using a validated bioanalytical assay.

Nasal PK of MK-1654

The PK of MK-1654 in nasal samples will be measured on Days 1, 27 or 28, and 57 to characterize the PK concentrations of MK-1654 in nasal Weck-Cel samples. PK will be measured using a qualified bioanalytical assay.

4.2.2.4 Pharmacodynamic Endpoints

This study will evaluate the effect of single doses of MK-1654 on SNA titers against RSV A. Exploratory analyses may be performed to define the immune response to intranasal RSV Memphis 37b inoculation after administration of MK-1654 or placebo through measurement of serum D25 competing antibodies to RSV F protein and enzyme linked immunospot assay (ELISPOT) against RSV F peptides.

To better characterize the pharmacodynamic effects of MK-1654 on the response to RSV Memphis 37b inoculation, other exploratory assays may be performed with excess serum or nasal samples from PK, antibody titer assays or excess peripheral blood mononuclear cells (PBMCs), and with whole blood mRNA, as applicable, at the discretion of the Sponsor.

Anti-Drug Antibodies (ADA) were rarely observed in MK-1654 P001. In this study, blood for ADA samples will be collected and archived. The presence and titer of ADAs will be measured if needed to help interpret efficacy, PK, SNA or other data.

4.2.2.5 Planned Exploratory Biomarker Research

4.2.2.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.2.6 Future Biomedical Research

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

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

4.2.3 Rationale for the Use of Comparator/Placebo

This study is being conducted to assess the efficacy of increasing doses of IV MK-1654 administered to study population in an RSV experimental challenge model. To this end, a placebo comparator is required to document the influence of MK-1654 on RSV viral load, symptomatic infection rate and symptoms scores after inoculation with the challenge strain.

4.3 Justification for Dose

4.3.1 Rationale for Dose Selection

The doses of 100 mg, 200 mg, 300 mg, and 900 mg were chosen to be likely to cover the potential range of minimally-protective SNA titers to highly-protective SNA titers. This range was determined by consideration of both published clinical data (SNA and incidence rate of RSV disease from clinical efficacy and viral challenge studies in pediatric, younger adult, and elderly participants) and data from the MK-1654 cotton rat RSV challenge model. These data allowed estimation of the lowest SNA titers likely to be protective and of the SNA titers likely to provide near-complete protection in the healthy adult population of this viral challenge study. The relationships between doses of MK-1654 and serum concentration of MK-1654 is well understood in the study population (Figure 2), as is the relationship between serum concentration of MK-1654 to SNA titer (Figure 3). These two relationships (dose to concentration and concentration to SNA titer) relate dose to expected SNA titer, and were then combined with the published SNA titer and protection data to predict doses with the desired protection levels.

As this is a Phase 2 study in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.3.2 Rationale for Dose Interval and Study Design

MK-1654 is intended to be given as a single dose to infants prior to the onset of the RSV season. The half-life of MK-1654 in adults has been documented to be ~75-87days. Given the long half-life, and to reflect the intended use of MK-1654 in efficacy studies and in clinical practice, a single administration of MK-1654 or placebo will be used in this study.

We have chosen 28 days after administration of MK-1654 or placebo for viral inoculation based upon an analysis of the PK data from P001. Approximately 28 days is needed to allow for complete biodistribution of the antibody and achieve steady state concentrations in serum.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws

from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall study end will then not be identified until the Sponsor has made the decision to end the study following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Healthy male participants and female participants between the ages of 18 through 55 years (inclusive) 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

To be eligible for inclusion in this study, the participant must:

1. In good health with no history of major medical conditions that will interfere with participant safety, as defined by medical history, physical examination (including vital signs), ECG, and routine laboratory tests and determined by the Investigator at a screening evaluation.

2. Participants will have a documented medical history either prior to entering the study and/or following medical history review with the study physician at screening.

Demographics

3. Participant is male or female.

4. Participant is from 18 years to 55 years of age inclusive, at the time of signing the study specific informed consent.

5. A total body weight ≥ 50 kg and Body Mass Index (BMI) ≥ 18 kg/m^2 and ≤ 30kg/m^2.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

6. Male participants must agree to the contraceptive requirements below at dosing and continuing until 90 days after dosing/28 days after viral inoculation – whichever is later.

    - Use a condom with a spermicide to prevent pregnancy in a female partner or to prevent exposure of any partner (male and female) to the IMP.

    - Male sterilisation with the appropriate post vasectomy documentation of the absence of sperm in the ejaculate (*please note that the use of condom with spermicide will still be required to prevent partner exposure).* This applies only to males participating in the study.

    - In addition, for female partners of child bearing potential, that partner must use another form of contraception such as one of the highly effective methods mentioned below for female participants.

    - True abstinence - sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

In addition to the contraceptive requirements above, male participants must agree not to donate sperm until 90 days after the date of dosing.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. Female participants of childbearing potential must have a negative pregnancy test at screening and prior to dosing.

    Female participants of **childbearing potential** must use **one form** of highly effective contraception. Hormonal methods must be in place from at least 2 weeks prior to dosing. The contraception use must continue until 30 days after dosing/28 days after the date of viral inoculation - whichever is later. Highly effective contraception is as described below:

    - Established (a minimum of 2 weeks prior to dosing) use of hormonal methods of contraception described below.

1. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

    1) oral

    2) intravaginal

    3) transdermal

2. progestogen-only hormonal contraception associated with inhibition of ovulation:

    1) oral

    2) injectable

    3) implantable

    Note: when hormonal methods of contraception are used, male partners are required to use a condom with a spermicide.

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- Bilateral tubal ligation
- Male sterilisation (with the appropriate written documentation from the participant to confirm the vasectomy) where the vasectomised male is the sole partner for that woman.
- True abstinence - sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

8. Female participants who are no longer of child bearing potential.

- Women no longer of child bearing potential (post-menopausal females are defined as having a history of amenorrhea for at least 12 months with no alternative medical cause, otherwise they should have documented status as being surgically sterile or post hysterectomy (e.g. tubal ligation, hysterectomy, bilateral salpingectomy and bilateral oophorectomy) and/or by FSH level >40 IU/mL, confirmed by laboratory).

Informed Consent

9. The participant provides written informed consent/assent for the study, including for future biomedical research.

Additional Categories

10. Serosuitable* to the challenge virus within 90 days of IMP dosing.

    * The serology result obtained suggests that the participant is sensitive to RSV infection, i.e. they are likely to be infected following inoculation with the challenge virus.

5.2 Exclusion Criteria

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

Medical Conditions

1. Females who: Are breastfeeding or have been pregnant within 6 months prior to the study enrollment.

2. Any history or evidence of any clinically significant or currently active cardiovascular, respiratory, dermatological, gastrointestinal, endocrinological, haematological, hepatic, immunological (including immunesuppression), metabolic, urological, renal, neurological, or psychiatric disease (including participants with a history of depression and/or anxiety with associated severe psychiatric comorbidities, for example psychosis; participants with a history of depression of any severity within the last 2 years prior to IMP dosing should only be included if the PHQ-9 score is less than or equal to 4). The following conditions apply:

    - Participants with clinically mild atopic eczema/atopic dermatitis and clinically mild psoriasis may be included at the Investigator's discretion (e.g., if small amounts of regular topical steroids are used, no eczema in cubital fossa; moderate to large amounts of daily dermal corticosteroids is an exclusion).

    - Rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of IMP dosing. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the PI’s discretion.

    - Participants with a physician diagnosed underactive thyroid who have been controlled on treatment for at least 6 months with evidence of a normal thyroid function test (TFT) can be included at the discretion of the PI.

- Any concurrent serious illness including history of malignancy that may interfere with the aims of the study or a participant completing the study. Basal cell carcinoma within 5 years of initial diagnosis or with evidence of recurrence is also an exclusion.

- Participants reporting physician diagnosed migraine can be included as long as there are not associated neurological symptoms such as hemiplegia or visual loss. Cluster headache/migraine or prophylactic treatment for migraine is an exclusion.

- Participants with physician diagnosed mild Irritable Bowel Syndrome (IBS) not requiring regular treatment can be included at the discretion of the PI.

3. Any significant abnormality altering the anatomy of the nose in a substantial way or nasopharynx that may interfere with the aims of the study and in particular any of the nasal assessments or viral inoculation, (historical nasal polyps can be included, but large nasal polyps causing current and significant symptoms and/or requiring regular treatments in the last month will be excluded).

4. Any clinically significant history of epistaxis (large nosebleeds) within the last 3 months prior to IMP dosing and/or history of being hospitalized due to epistaxis on any previous occasion.

5. History or currently active symptoms suggestive of upper or lower respiratory tract infection within 6 weeks prior to IMP dosing.

6. And/or other major disease that, in the opinion of the Investigator, may interfere with a participant completing the study and necessary investigations.

7. History of anaphylaxis-and/or a history of severe allergic reaction or significant intolerance to any food or drug, as assessed by the PI.

8. Confirmed positive test for drugs of abuse prior to randomization.

9. History or presence of alcohol addiction, or excessive use of alcohol (weekly intake in excess of 28 units alcohol; 1 unit being a half glass of beer, a small glass of wine or a measure of spirits), or excessive consumption of xanthine containing substances (e.g. daily intake in excess of 5 cups of caffeinated drinks e.g. coffee, tea, cola).

10. Is positive for human immunodeficiency virus (HIV), active hepatitis A (HAV), B (HBV), or C (HCV) test.

Prior/Concomitant Therapy

11. Evidence of receipt of vaccine within the 4 weeks prior to IMP dosing.

12. Intention to receive any vaccine(s) before the last day of Follow-up. (NB. No travel restrictions will apply after the poststudy visit).

13. Receipt of blood or blood products, or loss (including blood donations) of 470 mL or more of blood during the 3 months prior IMP dosing or planned during the 3 months after the final visit.

14. Use within 7 days prior to IMP dosing of any medication or product (prescription or over-the-counter), for symptoms of hay fever, dermatitis, nasal congestion or respiratory tract infections including the use of regular nasal or dermal corticosteroids or antibiotics, apart from those described and allowed in exclusion criteria 2.

15. Receipt of systemic (intravenous and/or oral) glucocorticoids or systemic antiviral drugs within 6 months prior to IMP dosing.

16. Received chronic (defined as more than 14 continuous days) or current administration of a systemic immunosuppressant or other immune modifying drug, including any dose of oral corticosteroids, within 6 months prior to dose administration. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

17. Use or anticipated use during the conduct of the study of concomitant medications (prescription and/or non-prescription), including vitamins or herbal and dietary supplements within the specified windows (within 7 days prior to IMP dosing), unless in the opinion of the Principal Investigator, the medication will not interfere with the study procedures, outcomes, or compromise participant safety.

18. Has a history (participant recall) of receiving any human immunoglobulin preparation such as IVIG or RhoGAM.

Prior/Concurrent Clinical Study Experience

19. Receipt of any investigational drug within 3 months prior to IMP dosing.

20. Receipt of three or more investigational drugs within the previous 12 months prior to IMP dosing.

21. Prior participation in another Human Viral Challenge study with a respiratory virus of the same virus family in the preceding 3 months taken from the date of viral challenge in the previous study to the date of expected viral inoculation in this study.

22. Prior participation in any RSV related (vaccine, monoclonal antibody or small molecule) interventional trial.

Diagnostic Assessments

23. A forced expiratory volume in 1 second (FEV1) < 80%.

24. Presence of fever, defined as participant presenting with a temperature reading of ≥ 37.9 ^{o}C on day of IMP dosing.

Other Exclusions

25. Participants who have smoked ≥ 10 pack years at any time [10 pack years is equivalent to one pack of 20 cigarettes a day for 10 years]).

26. Venous access deemed inadequate for the phlebotomy and demands of the study.

27. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

28. Any contraindication for IV infusion.

29. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

There are no meal or dietary restrictions in this study.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

The consumption of caffeine or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) should be limited from 72 hours prior to IMP dosing and 72 hours prior to quarantine admission.

5.3.2.2 Alcohol and Tobacco Restrictions

Participants will not be allowed to consume alcohol or use tobacco/nicotine products from 72 hours prior to IMP dosing and 72 hours prior to quarantine admission, and while in the clinic unit. However, participants that use tobacco/nicotine products during the restriction period may be continued in the study with the approval of the sponsor, if in the opinion of the Investigator cessation of smoking during the quarantine will not lead to withdrawal symptoms, which would impact an accurate recording of RSV infection-related symptoms as recorded on the Symptom Diary Card.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from 72 hours prior to each clinic visit including the poststudy visit and throughout quarantine phase.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the electronic case report forms (eCRF) entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
MK-1654	Experimental	Active	Biological /Vaccine	Vial	100 mg/mL	100, 200, 300 and 900 mg	IV Infusion	Single administration	Experimental	IMP	Sponsor
Placebo	Placebo comparator	Placebo	Other	IV solution for infusion	Not applicable	Not applicable	IV Infusion	Single administration	Placebo	IMP	Site (hVIVO)
RSV A Memphis 37b virus	Not Applicable	Virus Inoculation	Virus	Not Applicable	Approximately 4 Log10 PFU/mL*	Approximately 4 Log10 PFU*	Intranasal	Single administration	Virus challenge	NIMP, Challenge Virus	Site (hVIVO)

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

The challenge virus will be prepared to have an inoculum concentration of between 3.5 Log10 PFU/mL and 5 Log10 PFU/mL, the details of which will be outlined in the Analytical Plan.

All supplies indicated in Table 3 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 and the pharmacy manual 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 provided to the site by the Sponsor as a separate document. The rationale for selection of doses to be used in this study is provided in Section 4.3.

MK-1654 and placebo (0.9% sodium chloride, USP sterile saline) will be prepared by an unblinded pharmacist or qualified study site personnel (see Section 6.3.3). MK-1654 and placebo will be administered in a single 100 mL intravenous infusion in 0.9% sodium chloride using a volumetric pump over ~2 hours on Day 1. The bag for IV infusion should be prepared as outlined in the trial pharmacy manual.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

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

6.3.2 Stratification

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

6.3.3 Blinding

A double-blinding technique will be used. MK-1654 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

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

Listed below are specific restrictions for concomitant therapy or vaccination:

- Immunoglobulins and/or any blood products within the 3 months preceding the administration of the study drug or at any time during the study.
- Chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune-modifying drug within 6 months prior to dose administration and through poststudy visit (Day 57).
- Medication or product (prescription or over-the-counter) for symptoms of nasal congestion or respiratory tract infection during the inpatient quarantine visit.

6.5.1 Rescue Medications and Supportive Care

As outlined in the IB and Section 4.2.1.1, the risk of acute infusion reactions to MK-1654 is considered very low as it has not been observed in prior clinical studies. Therefore, no prophylactic pre-medications to reduce the risk of infusion reactions will be given prior to MK-1654 or placebo administration. However, acute infusion reactions and anaphylaxis are still possible. Thus, all participants will be observed for 2 hours post-dose for acute reactions to MK-1654 and evaluated for infusion reactions. Severe infusion reactions, including hypersensitivity reactions, must be promptly treated with medical management, appropriate monitoring, and life-saving measures. Appropriate resuscitation equipment and a physician/designee and/or study staff will be readily available during the period of drug administration through the 2-hour post-dose onsite safety observation period. Less severe infusion reactions may respond to medical management. Acetaminophen and antihistamines may be administered per investigator discretion after the initiation of treatment on Day 1 without prior consultation with the Sponsor.

Participants who experience infusion reactions, including hypersensitivity reactions, in conjunction with the study intervention should receive appropriate supportive care measures as deemed necessary by the treating physician including, but not limited to, corticosteroids, fluids and hospitalization. Participants should be carefully observed until complete resolution of all signs and symptoms, if a reaction occurs. Any adverse experiences will be reported according to the guidelines in Section 8.4 and Section 10.3 (Appendix 3).

6.6 Dose Modification

The suggested doses may be adjusted downward at the discretion of the sponsor based upon newly available safety, tolerability and/or PK data from this study or other studies of the program.

6.6.1 Stopping Rules

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

If any of the below stopping rules are met, the study will be paused and no further dosing will occur until the Sponsor has reviewed the totality of data available. Study may be continued upon joint agreement with the Sponsor and investigator.

1) An individual participant reports a Serious Adverse Event considered related to the study drug by the investigator.

2) Any unexpected virus-related SAE or unexpected virus-related AEs of clinical concerns have been reported following Human Viral Inoculation (expectedness will be assessed by referring to the inoculation virus dossier).

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable for this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter (PCL).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9 and 8.12.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study.

Post IMP dosing a participant must be discontinued prior to inoculation but continue to be monitored in the study for any of the following reasons:

- Rhinitis (including hay fever) which is clinically active or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days of admission to quarantine.
- Positive human immunodeficiency virus (HIV), active hepatitis A (HAV), B (HBV), or C (HCV) test within 60 days of inoculation.
- Any clinically significant epistaxis (large nosebleeds) from signing the study-specific consent to admission to quarantine.
- Any nasal or sinus surgery from signing the study-specific to admission to quarantine.
- Presence of fever following admission to the quarantine unit and prior to inoculation.
- History or currently active symptoms suggestive of upper or lower respiratory tract infection within 6 weeks prior quarantine admission
- Use of herbal supplements within 7 days prior to inoculation unless in the opinion of the Principal Investigator, the supplements will not interfere with the study procedures or compromise participant safety.
- Use of over the counter medications (e.g. paracetamol or ibuprofen) where the dose taken over the preceding 7 days prior to the planned date of Viral Inoculation has exceeded the maximum permissible 24-hour dose (e.g. $\geq$ 4 g paracetamol over the preceding week), unless in the opinion of the Principal Investigator, the medication will not interfere with the study procedures or compromise participant safety.

- Receipt of immunoglobulins and/or any blood products within the 3 months preceding the administration of the study drug or at any time during the study.

- Chronically used medications, vitamins or dietary supplements, including any medication known to be moderate / potent inducer or inhibitor of CYP450 enzymes, within 21 days prior to the planned date of inoculation, unless in the opinion of the Principal Investigator, the medication will not interfere with the study procedures or compromise participant safety.

- In the opinion of the investigator, the subject is no longer able to comply with the protocol and requirements of the inpatient stay.

7.2 Participant Withdrawal From the Study

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

A participant must be withdrawn from the study if:

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9.1. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 320.5mL (Appendix 8).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

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

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

Consent form or ICF throughout the protocol refers to the study specific consent form (ICF).

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

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or designee who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 2 weeks (or longer if appropriate) before the IMP dosing.

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur 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 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

In a situation where rerandomization of the participants is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff.

Study medication will be administered by unblinded study staff, as described in the pharmacy manual.

8.1.8.1 Timing of Dose Administration

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

MK-1654 and placebo will be administered in a single 100 mL continuous intravenous infusion in 0.9% sodium chloride using a volumetric pump over ~2 hours on -Day 1, as set out in the SoA and specified in the Pharmacy Manual. The bag for IV infusion should be prepared as outlined in the trial pharmacy manual.

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

Table 4 MK-1654 IV Infusion Rate

MK-1654 Dose	100 mg	200 mg	300 mg	900 mg
Total MK-1654 Dose	100 mg	200 mg	300 mg	900 mg
[MK-1654] in IV bag	1 mg/ml	2 mg/ml	3 mg/ml	9 mg/ml
Target rate of infusion	50 ml/hr (50 mg/hr)	50 ml/hr (100 mg/hr)	50 ml/hr (150 mg/hr)	50 ml/hr (450 mg/hr)
Infusion time	~2 hrs	~2 hrs	~2 hrs	~2 hrs
Note: These are suggested target infusion rates; at the discretion of the investigator rates may be slower than listed, and hence infusion times longer. Total infusion time will not exceed 6 hours in duration without prior consultation with the Sponsor. Infusion rates may not exceed those listed in the table.				

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 1.3 protocol-specified procedure is performed]) to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of

discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's 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 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 qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

8.1.11 Domiciling

Participants will report to the clinical research unit (CRU) on Day 27, 2 days prior to the scheduled day of RSV A Memphis 37b virus inoculation and remain in the unit until 11 days post inoculation on Day 40. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

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

Critical Equipment for this study includes:

- ECG machine (site equipment): Calibration should be performed according to the manufacturer's specifications.
- Spirometry: Calibration should be performed according to the manufacturer's specifications.
- Equipment for Vital Sign Measurements: Calibration should be performed according to the manufacturer's specifications.
- Infusion pump (site equipment): Calibration should be performed according to the manufacturer's specifications.

8.2 Intranasal Administration of the Challenge Virus

The Challenge Virus is RSV-A Memphis 37b.

8.2.1 Production

The RSV-A Memphis 37b challenge virus was produced via a nasal aspirate collected from a pediatric patient infected with RSV. The isolate underwent minimal passage in cell culture under cGMP conditions at Meridian Life Science®, Inc. USA to produce the master GMP challenge virus stock and was stored in 25% sucrose to preserve the infectivity of the virus. The challenge virus stock underwent quality and release criteria testing as part of the GMP manufacture (identity, appearance, sterility, infectivity, and contaminants), all according to pre-determined specifications, and has subsequently also passed an extensive panel of adventitious agent testing. To meet the needs of different clinical applications and using GMP diluent where required, different inoculation preparations have subsequently been made from the master challenge virus stock, all of which have undergone appropriate release testing prior to clinical use.

8.2.2 Supply and Accountability

The Challenge Virus is stored in a secure -80 °C freezer (normal temperature range -60 °C to -90 °C). hVIVO is obliged to establish a system for control of Challenge Virus in accordance with hVIVO SOPs and as detailed in the Analytic Plan (AP) or a separate Note to File (NTF).

The Investigator will maintain accurate records of receipt and condition of all Challenge Virus inoculum stock used for inoculation in accordance with hVIVO SOPs, including details and dates of the quantities dispensed and used in the study. Any departures from the protocol-dispensing regimen will be fully documented.

Accountability records must be maintained as per the hVIVO SOPs. All Challenge Virus storage and accountability records will be available for verification by auditors.

8.2.3 Preparation and Administration

Virus inoculum will be prepared according to the hVIVO AP and administered in accordance with hVIVO's SOPs. Each participant will be allocated a unique vial containing the Challenge Virus and will receive the inoculum intranasally.

The time from the Challenge Virus inoculum thawing to inoculation should be no longer than 2 hours. All administrations will be made by a member of the clinical team and witnessed by a second member of the team. The exact time of inoculation will be recorded in the administration log and the participant's source notes. Accurate records will be kept of when and how much study inoculum is prepared and used. The oversight process will be signed off prior to administration of the Viral Inoculation. Any non-compliance or problems with the inoculation will be recorded in the participant's source notes and reported to the PI.

Following inoculation, participants will be closely observed specifically for potential allergic reactions within 30 minutes, and for the following 24 hours. Participants will continue to be monitored throughout the clinical phase of the study.

8.2.4 Disposal

Disposal of used and unused Virus inoculum vials will be in accordance with hVIVO's SOPs.

8.3 Efficacy Assessments

Compliance with the efficacy and safety assessments (along with study treatment use) is essential, and any non-compliance noted by the investigator or designee should result in consultation with the participant on corrective measures needed to ensure compliance.

8.3.1 RSV Symptoms Diary Card

Each participant will be provided a Symptom Diary Card (SDC) to record any RSV infection related symptoms starting from the day prior to the viral inoculation to 11 days post the

inoculation. The use of diary card will be reviewed with the participants at the study site, as indicated in the SoA.

The SDC will be completed once on Study Day 28 and Study Day 40. From Study Day 29 to Study Day 39 the SDC will be completed at three times daily at approximately the same time each day (± 1 hour).

8.3.2 Nasal Wash for RSV Virology

During the quarantine period, experienced site staff will collect nasal wash samples from each participant prior and following inoculation with RSV, as specified in the SoA (Section 2). Instructions for collection, storage, and handling/shipment of nasal wash specimen and testing for RSV by polymerase chain reaction (PCR) and plaque assay are provided in the AP.

Nasal wash samples will be collected 1 or 2 days before inoculation and then twice daily from Day 31 through Day 39. From Study Day 31 to Study Day 39, nasal wash sample collections will occur 12 hours apart ± 1 hour. A single nasal wash sample will be collected on Day 27 or 28 and on Day 40.

8.3.3 Nasopharyngeal Swab

Nasopharyngeal swabs will be performed to collect samples of nasopharyngeal cells and epithelial lining fluid for:

- Respiratory pathogen screen

Tolerance of the procedure may be determined at the screening visit.

8.4 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

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

8.4.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. As a minimum the following systems will be included on the physical exam; General appearance, Skin, Eyes, Ears, Nose, Throat, Heart, Lungs, Abdomen, Peripheral pulses, Lymph nodes, Neurological/ nervous system, Musculoskeletal, Head, neck, and thyroid.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. As a

minimum the following systems will be included on the directed physical exam; Ear, Nose, Throat, Chest (via stethoscope).

Assessment and grading of any upper respiratory tract (URT) (nasal discharge, otitis, pharyngitis, sinus tenderness) and lower respiratory tract (LRT) symptoms (abnormal breath sounds externally [e.g. stridor] and on chest auscultation [wheezing or rhonchi, crepitations] will be performed. Physician-reported assessments of viral challenge related illness will be graded in accordance with their intensity and documented in the source data.

Following viral inoculation, URT and LRT symptoms (as described above) will be expected and presumed to represent virus infection consequent to viral inoculation and will not be additionally captured as AEs unless they meet the definition of an AE, and are deemed to be clinically significant (in the opinion of the Investigator) to be classed as AEs.

Following viral inoculation all unexpected (in the opinion of the Investigator) directed physical examination findings will be captured as AEs, along with all other occurrences that meet the criteria for an AE.

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

8.4.2 Vital Signs

- Tympanic temperature pulse rate, respiratory rate, O^2 saturation, and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Vital signs will be measured in a supine position after 5 minutes rest. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions

- A different arm may be used each time and arm used for vital signs measurement will be recorded the case report form (CRF).

- All vital signs will be measured and recorded as single measurements.

- Temperature and respiratory rate will be measured and recorded as single measurements. The same method must be used for all measurements for each individual participant and should be the same for all participants. From Study Day 29 to Study Day 40, vital signs and temperature readings should be taken at the same time each day ± 1 hour

8.4.2.1 Resting Vital Signs

The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements. Measurements will be assessed with a

completely automated device. Manual techniques will be used only if an automated device is not available.

All vital sign assessments will be single measurements. HR and BP will be performed within 3 hours of dosing MK-1654 on Day 1 predose.

8.4.3 Electrocardiograms

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

Participants should be supine for at least 5 minutes prior to each electrocardiogram (ECG) measurement.

The correction formula to be used for QTc is Fredericia.

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

Pre-dose ECGs should be obtained on Day 1 prior to IMP dosing at the discretion of the investigator. All ECG measurements will be single measurements.

8.4.4 Safety Phone Call Follow-up

Two safety follow-up phone calls will be performed approximately 33 and 123 days after the poststudy visit (within the visit windows allowed per protocol). The safety follow-up phone call must be performed by appropriately trained study site staff. If the initial call is unsuccessful, the study site staff should make a total of 3 attempts. All attempts to contact the participants will be recorded in the source documents. The calls will facilitate the collection of relevant safety information. The participant will be interviewed to obtained information relating to AEs and SAEs. All safety information described by the participant must be documented in the source documents.

8.4.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

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

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study, 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.

8.5 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

The investigator 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 remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.5.3.

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

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

AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of intervention allocation/randomization through the end of study visit, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

8.5.2 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.

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

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

8.5.4 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 wth 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.5.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

Not applicable.

8.5.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.6.

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

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

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

3. Signs or symptoms of a hypersensitivity or other infusion reaction within 48 hours of trial drug administration, including but not limited to fever > 39.6 °C, hypotension, hypoxia, mental status changes, hives, urticaria, wheezing, angioedema, bronchospasm, anaphylaxis, or syncope.

8.6 Treatment of Overdose

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

8.7 Pharmacokinetics

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

8.7.1 Blood Collection for Serum MK-1654

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

8.7.2 Nasal Mucosal Sample (Weck-Cel) for MK-1654 PK

Samples will be tested for MK-1654 concentrations. The nasal mucosal sample will be collected prior to nasal wash sample if the 2 samples will be collected on the same study day. Sample collection, storage and shipment instructions for the nasal mucosal samples will be provided in the trial operations/laboratory manual.

8.8 Pharmacodynamics

8.8.1 Neutralizing Antibody Titers against RSV A and Other RSV Serologies

Virus neutralization gives the most precise answer to the question of whether or not an individual has antibodies that can neutralize the infectivity of RSV. Sample collection, storage, and shipment instructions for serum samples are provided in the operations/laboratory manual.

An ELISA will be used to detect serum D25 competing antibodies to RSV F protein. Sample collection, storage, and shipment instructions for serum samples are provided in the operations/laboratory manual.

8.8.2 Nasal Mucosal Sample (Weck-Cel) for RSV Antibodies

Leftover nasal Weck-Cel eluent from the MK-1654 PK sample may be used for RSV antibody assays. Samples will be tested for anti-RSV F antibody (IgA or IgG) concentrations and RSV neutralizing activity in nasal mucosal fluid. As stated in Section 8.7.2, sample collection, storage and shipment instructions for the nasal mucosal samples will be provided in the trial operations/laboratory manual.

8.8.3 Enzyme Linked Immunospot Assay (ELISPOT)

Respiratory syncytial virus antigen-specific T-cell function will be measured by ELISPOT assay. Sample collection, storage, and shipment instructions for PBMC samples are provided in the operations/laboratory manual.

8.8.4 Blood for RNA

RNA isolated from whole blood will be profiled as needed to understand the immune response to MK-1654 and viral inoculation. Sample collection, storage, and shipment instructions for RNA samples are provided in the operations/laboratory manual.

8.8.5 Blood for ADA

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

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover main study serum from MK-1654 assay stored for future research
- Leftover main study serum from RSV Serologies stored for future research
- Leftover main study PBMC stored for future research
- Leftover main study RNA from mRNA analysis stored for future research
- Leftover main study serum from ADA stored for future research
- Leftover main study nasal mucosal fluid from Nasal Weck-Cel samples stored for future research
- Leftover main study nasal wash sample from nasal wash for RSV virology samples stored for future research.

8.10 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.11 Biomarkers

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

- Blood (DNA) for Genetic Analysis

8.12 Visit Requirements

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

8.12.1 Screening Visit

Participants will be screened under the hVIVO generic screening process. Participants who fulfill inclusion and exclusion criteria for this study through the hVIVO generic screening protocol, including being serosuitable within 90 days and having normal or not clinically significant abnormal laboratory safety data within 56 days, will be invited for a randomization visit.

At the randomization visit, inclusion/exclusion criteria will be confirmed prior to randomization. A protocol specific consent form will be signed prior to randomization on Day 1. Participants may be rescreened after consultation with the Sponsor. If participants are rescreened outside the screening window (within 90 days for serosuitability and 56 days for laboratory safety data) a new consent form will need to be signed and screening procedures that are outside of the screening window should be repeated. Rescreen procedures cannot be conducted the day prior to randomization if there is Day 1 procedures planned per protocol.

8.12.2 Treatment Period

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

On Day 1, after all pre-dose procedures have been completed, participants will be assigned a unique randomization number associated with a specific treatment as defined by a computer-generated allocation schedule.

Participants will be administered study drug as indicated in section 6. Participants on Day 1 who have an acute illness or fever prior to the administration of study drug may be rescheduled as long as their Day 1 visit falls within the screening window (within 90 days for serosuitability and 56 days for laboratory safety data of the first screening).

8.12.3 Intranasal RSV Inoculation Period

The post inoculation period is from Day 29 through Day 40. All randomized participants up to 70 participants will be administered RSV intranasally on Day 29. A detailed description of the preparation and administration of RSV is provided in the Procedures Manual and/or the AP. The trial site will be responsible for recording the lot number, manufacturer, and expiry date of applicable supplies related to RSV administration.

To reduce the risk of passing the Challenge Virus to others, participants will be asked to avoid contact with vulnerable people for 2 weeks after they leave quarantine. For the purposes of this protocol, a vulnerable individual is as follows:

1. Elderly persons aged 65 years or older;
2. Children aged under 2 years;
3. Anyone who lives in a nursing home;
4. Anyone with a low resistance to infection or who takes drugs that lower their resistance;
5. Anyone who is having or is about to have drug treatment for cancer (chemotherapy);
6. Anyone who has chronic obstructive pulmonary disease (COPD), emphysema or other severe lung disease;
7. Anyone who has heart disease such as heart failure, has had a heart attack or heart surgery;
8. Anyone with cerebral palsy, epilepsy, who has seizures or who has had a stroke;
9. Anyone who has had a bone marrow or solid organ transplant;
10. Women who are pregnant or trying to become pregnant.

8.12.4 Discontinued Participants Continuing to be Monitored in the Study

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

8.12.5 Poststudy

Participants will be required to return to clinic approximately 28 days after the RSV inoculation on Day 57 for the poststudy visit. If the poststudy visit occurs less than 28 days (± 4 days) after the RSV inoculation, a subsequent follow-up telephone call should be made at 28 days (± 2 days) post the RSV inoculation to determine if any AEs have occurred since the poststudy clinic visit. In addition, two follow-up phone calls will be made approximately 33 days (Day 90 ±5 days) and 123 days (Day 180 ±7 days) after the poststudy visit to determine if any adverse events have occurred since the poststudy clinic visit.

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

This protocol is written with some flexibility to accommodate the inherent dynamic nature of early phase clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Repeat of or decrease in the dose of the study intervention administered in any given dose
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data
- IV infusions may be administered at a similar or lower infusion rate
- In the case where there are more than 70 subjects available for inoculation, the study statistician, who is unblinded, may direct the investigator via a PCL those subjects which are to be inoculated to help preserve the balance across the study groups.

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available data. These collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information.

- Additional blood or urine samples may be taken for laboratory safety tests or other tests, such as measurement for PK analysis. Any additional urine collections may include continuous, total collections, if necessary. Up to an additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Section 8).
- Additional noninvasive, painless procedures that are already specified in this protocol may be done based on newly available data.
- An additional 24 hours residence in the ward and up to 2 additional outpatient visits per period will be permitted, in the event of a technical failure, and/or if extra blood or urine samples, or extra pharmacodynamic measurements, are needed.

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

9 STATISTICAL ANALYSIS PLAN

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 exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Participants Inoculated with Experimental Respiratory Syncytial Virus
Intervention Assignment	Participants will be randomized to receive a single dose of MK-1654 100, 200, 300 or 900 mg or placebo in a 1:1:1:1:1 ratio.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint	Area Under the Viral Load-time Curve (VL-AUC) determined by RT-qPCR from Day 2 through Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40)
Key Secondary Endpoints	• Symptomatic RSV infection between Day 2 and Day 11 (inclusive) after viral inoculation (Study Day 31 through Day 40) • Adverse Events (AEs) and serious AEs (SAEs)
Statistical Methods for Key Efficacy Analyses	<u>Primary</u> VL-AUC between Day 2 and Day 11 after intranasal inoculation (study Day 31 through Day 40) will be analyzed using a linear model with treatment group as a fixed categorical effect. The mean VL-AUC in each group and the differences in mean VL-AUC between each MK-1654 dose group and placebo and the corresponding two-sided 90% confidence intervals (CI) will be computed based on the model. The primary hypothesis will be tested using a closed stepwise procedure where the testing starts with comparing the highest MK-1654 dose to placebo and the testing continues with the next lowest dose only if a statistically significant result is obtained at the previous dose. <u>Secondary</u> The proportion of participants with symptomatic RSV infection between Day 2 and Day 11 after intranasal inoculation (study Day 31 through Day 40) will be computed along with exact 95% CIs for each treatment group. Exact 95% CIs will be computed for the difference in proportions between each MK-1654 dose and placebo [Chan, I. S. F. and Zhang, Z. 1999].
Statistical Methods for Key Safety Analyses	Descriptive summaries (point estimates) by MK-1654 dose group and placebo will be provided for all safety parameters. In addition, within-group 95% confidence intervals (based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934]) will be provided for the following safety endpoints for each MK-1654 dose group and placebo: proportion of participants with any AE, a drug-related AE, a SAE, a death, an AE which is both drug-related and serious, and an AE which leads to discontinuation.

Interim Analyses	An interim analysis will be performed when all participants have completed the 11 day follow up post viral inoculation and efficacy data are available including symptoms of RSV infection and RSV viral load by qPCR from nasal wash samples. The SNA results from samples collected at baseline (prior to study drug administration) will be required for this analysis. The analysis of the primary and secondary efficacy endpoints will be conducted and all available PK and SNA data will be summarized. If the rate of enrollment is slower than expected, an earlier interim analysis may be conducted at the discretion of the sponsor when at least 35 participants have completed the 11 day follow up post viral inoculation and efficacy data are available. If the earlier interim analysis is conducted, the interim analysis when all participants have completed the 11 day follow up post viral inoculation may still be conducted. The purpose of these interim analyses is to make scientific decisions for future studies.
Multiplicity	The study has only 1 primary hypothesis which will be addressed using a closed step-wise testing procedure that preserves the overall alpha level at 0.05 1-sided (assuming a monotonic dose-response); therefore, there is no need for a multiplicity adjustment.
Sample Size and Power	For the primary hypothesis, with an evaluable sample size of 13 per dose group, there is ~80% power to detect a decrease in viral load AUC of 70% in the highest MK-1654 dose group vs. the placebo group assuming a coefficient of variation (CV) in viral load AUC of 0.7 with a 1-sided alpha=0.05 test.

9.2 Responsibility for Analyses

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, i.e., the investigators and participants will be blinded to the intervention assignments of the participants. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

The primary efficacy endpoint is the Area Under the Viral Load-time Curve (VL-AUC) between Day 2 and Day 11 after intranasal inoculation. Nasal wash samples will be collected twice daily from Day 2 through Day 11 (morning only on Day 11) after intranasal inoculation and viral load will be measured using a quantitative PCR assay.

The secondary efficacy endpoint is the number of participants with symptomatic RSV infection after intranasal inoculation. Symptomatic RSV infection is defined as presence of at least two quantifiable RT-qPCR at two or more consecutive days, plus symptoms of either any grade from two different symptoms from the subject symptom card (SSC) or at least one Grade 2 symptom from one or more respiratory categories.

9.4.2 Safety Endpoints

Refer to Section 4.2.1.2 for the description of the safety measures in this study. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), physical examinations, vital signs (VS) and laboratory safety tests. All AEs will be assessed for intensity. The following safety endpoints will be assessed:

1. Non-serious AEs throughout the study duration;
2. Serious AEs throughout the study duration.

9.4.3 Other Endpoints

1. MK-1654 serum concentration;
2. RSV A serum neutralizing antibody titers;
3. Mucus weight;
4. Daily symptom scores after viral inoculation;
5. Total symptom scores after viral inoculation;
6. RSV nasal viral load determined by quantitative culture;
7. D25 competing antibody titers to RSV F protein;
8. ELISPOT to measure T cell responses;
9. MK-1654 concentration in nasal mucosal fluid;
10. Anti-RSV F antibody (IgA or IgG) concentrations and RSV neutralizing activity in nasal mucosal fluid.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

Full Analysis Set (FAS) Population

The FAS will serve as the primary population for the evaluation of efficacy. The FAS population consists of all randomized participants who received 1 dose of the correct clinical material corresponding to the treatment group the participants were randomized into and who received the viral inoculation.

9.5.2 Safety Analysis Population

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

9.5.3 PK Analysis Population

The PK analysis population consists of all randomized participants who received 1 dose of the correct clinical material corresponding to the treatment group the participants were randomized into. Participants with major deviations from the protocol that may substantially affect the results of the PK endpoints will be excluded, or their specific data values will be excluded from the PK analysis population. The final determination on major protocol deviations, and thereby the composition of the PK analysis population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

9.6 Statistical Methods

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

9.6.1 Statistical Methods for Efficacy Analyses

VL-AUC between Day 2 and Day 11 after intranasal inoculation (study Day 31 through Day 40) will be computed for each participant and will be analyzed using a linear model with treatment group as a fixed categorical effect. The mean VL-AUC in each group and the differences in mean VL-AUC between each MK-1654 dose group and placebo and the corresponding two-sided 90% confidence intervals (CI) will be computed based on the model.

The primary hypothesis will be tested using the following stepwise procedure with an assumption that there is an increasing relationship between viral load reduction and MK-1654 doses. The primary hypothesis will be supported if the upper limit of the 90% confidence interval (equivalent to the upper bound of a one-sided 95% confidence interval)

for the difference in mean VL-AUC between the highest MK-1654 dose and placebo is <0 (indicating a reduction). If the hypothesis is supported in the previous step, then the same procedure will be applied to the next lowest dose. The procedure continues in this stepwise fashion until the upper limit of the 90% confidence interval at a particular dose is >0. For estimation purposes, 90% confidence intervals will also be constructed for all doses at which the true mean difference in VL-AUC between MK-1654 and placebo is not statistically significantly different from 0.

A supportive analysis will be conducted in which the VL-AUC endpoint will be analyzed using a non-parametric rank-sum test.

The relationship between VL-AUC and MK-1654 dose will be displayed graphically and modeling may be used to estimate the relationship. Other continuous efficacy endpoints will be analyzed in a similar manner.

The proportion of participants with symptomatic RSV infection between Day 2 and Day 11 after intranasal inoculation (study Day 31 through Day 40) will be computed along with exact 95% CIs for each treatment group. Exact 95% CIs will be computed for the difference in proportions between each MK-1654 dose and placebo [Chan, I. S. F. and Zhang, Z. 1999]. Additionally, the presence of symptomatic RSV infection will be modeled using a 3-parameter sigmoidal (logistic) function with treatment group as a fixed effect. Other discrete efficacy endpoints will be analyzed in a similar manner.

9.6.2 Statistical Methods for PK Analyses

The following (non-model-based) descriptive statistics will be provided for all PK parameters: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt($\exp(s^2) - 1$), where s^2 is the observed variance on the natural log-scale).

9.6.3 Statistical Methods for SNA Analyses

The SNA titers to RSV A will be summarized by time point and treatment group. The titers will be natural log-transformed and geometric means with corresponding 95% confidence intervals (CI) for each treatment group and time point will be reported. Geometric mean fold increases (GMFI) from baseline and corresponding 95% CIs will also be reported.

Similar summaries will be provided for the other immunogenicity assays.

Relationships between the SNA assay, PK parameters and efficacy endpoints will be explored graphically and modeling techniques may be applied.

9.6.4 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events and vital signs. Summary statistics and plots will be generated for vital signs as well as for change from baseline, as deemed clinically appropriate.

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

- The proportion of participants with non-serious AEs throughout the study duration;
- The proportion of participants with serious AEs throughout the study duration;
- The proportion of participants with any AE, a drug-related AE, a SAE, a death, an AE which is both drug-related and serious, and an AE which leads to discontinuation.

The proportion of participants with specific AEs or SOCs will be summarized using point estimates only.

9.7 Interim Analyses

An interim analysis will be performed when all participants have completed the 11 day follow up post viral inoculation and efficacy data are available including symptoms of RSV infection and RSV viral load by qPCR from nasal wash samples. The SNA results from samples collected at baseline (prior to study drug administration) will be required for this analysis. The analysis of the primary and secondary efficacy endpoints will be conducted and all available PK and SNA data will be summarized. If the rate of enrollment is slower than expected, an earlier interim analysis may be conducted at the discretion of the sponsor when at least 35 participants have completed the 11 day follow up post viral inoculation and efficacy data are available. If the earlier interim analysis is conducted, the interim analysis when all participants have completed the 11 day follow up post viral inoculation may still be conducted. The purpose of these interim analyses is to make scientific decisions for future studies.

9.8 Multiplicity

The study has only 1 primary hypothesis which will be addressed using a closed step-wise testing procedure that preserves the overall alpha level at 0.05 1-sided (assuming a monotonic dose-response); therefore, there is no need for a multiplicity adjustment.

9.9 Sample Size and Power Calculations

Up to 80 participants will be randomized and dosed with MK-1654 or placebo. Assuming an attrition rate of ~12% between dosing with MK-1654 or placebo and RSV A Memphis 37b inoculation, up to 70 participants will be administered the intranasal RSV A Memphis 37b

inoculation. The evaluable sample size for analysis is assumed to be 65, assuming that 65 out of the 70 participants administered the intranasal RSV A Memphis 37b inoculation complete the follow-up and sample collection through Day 11 post inoculation.

For the primary hypothesis, with a sample size of 13 per dose group, there is ~80% power to detect a decrease in viral load AUC of 70% in the highest MK-1654 dose group vs. the placebo group assuming a coefficient of variation (CV) in viral load AUC of 0.7 with a 1-sided alpha=0.05 test. The assumed CV in viral load AUC of 0.7 was obtained from the placebo group of prior publications of RSV challenge studies.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), 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 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 (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

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

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

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

Not applicable.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of 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 Studies.

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase Creatine kinase (CK) Troponin T C-Reactive Protein (CRP) Uric acid (screening only)	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Urine and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable. • Serum β human chorionic gonadotropin (β hCG) will be carried out on Day 27/28. At all other timepoints urine pregnancy test will be carried out (as needed for WOCBP) (Serum β hCG pregnancy test will be carried out if there is a positive urine test) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			
NOTES: The investigator (or medically qualified designee) must document their review of each laboratory safety report.				

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

10.3.1 Definition of AE

AE definition

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

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

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

Events meeting the AE definition

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

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

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

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

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

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

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

d. **Results in persistent or significant disability/incapacity**

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

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

e. **Is a congenital anomaly/birth defect**

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

f. **Other important medical events**

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

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

10.3.3 Additional Events Reported

Additional events which 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 new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

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

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

Assessment of intensity

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

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

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the 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 initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

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

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

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

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

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

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up of AE and SAE

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

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

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

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

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

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Refer to Section 1.3 Schedule of Activities for pregnancy testing and Section 5.1 Inclusion Criteria for contraceptive guidance.

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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

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

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a

particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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

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10.7 Appendix 7: Country-specific Requirements

This appendix is not applicable for this study.

10.8 Appendix 8: Blood Volume Table

Samples	Screening	Treatment and Inoculation Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Screening & Admission Safety Laboratory Test	1	1		2	7 mL	14 mL
Routine Safety Laboratory Test		5	1	6	5.5 mL	33 mL
Blood for Planned Genetic Analysis		1		1	8.5 mL	8.5 mL
Blood for serum MK-1654		8	1	9	3 mL	27 mL
Blood for serum ADA		1	1	2	3 mL	6 mL
Blood for RSV Serologies		4	1	5	3 mL	15 mL
Blood for PBMC		2	1	3	48 mL	144 mL
Blood for mRNA		3	1	4	5 mL	20 mL
					Total Blood Volume per Participant [a]	267.5 mL

[a] If additional serology, PBMC or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

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

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

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

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

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

   1. The participant may be excluded from the study;

   2. The participant may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

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

      OR

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

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

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

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

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADL	activities of daily living
AE	adverse event
BDS	blood drug screen
BID	two times a day
CAC	Clinical Adjudication Committee
CNS	central nervous system
CPE	complete physical examination
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
eCTA	exploratory Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPE	directed physical examination
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LRTI	lower respiratory tract infection
MTD	maximum tolerated dose
NDA	New Drug Application
NOAEL	no observed adverse effect level
NPS	Nasopharyngeal swab
PCL	Protocol clarification letter
PET	positron emission tomography
PK	pharmacokinetic
QP2	department of quantitative pharmacology and pharmacometrics
Qic-PCR	Qualitative integrated cycler polymerase chain reaction
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
siDMC	Standing Internal Data Monitoring Committee
SoA	schedule of activities

Abbreviation	Expanded Term
tds	three times a day
SUSAR	suspected unexpected serious adverse reaction
UDS	urine drug screen
URT	upper respiratory tract
WOCBP	woman/women of childbearing potential

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