CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in children 2 to <18 years of age at high risk of respiratory syncytial virus disease
Protocol Number:	mRNA-1345-P202
Amendment Number:	mRNA-1345-P202 Protocol Amendment 2
Date:	02 Oct 2024
Compound:	mRNA-1345
Brief Title:	A study to investigate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in children 2 to <18 years of age at high risk of respiratory syncytial virus
Study Phase:	2
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	325 Binney Street Cambridge, MA 02142
Regulatory Agency Identifier Number(s):	**Registry** **ID** IND 23342 EU CT 2023-506271-96-00
Pediatric Investigational Plan Number	EMEA-003309-PIP01-22

Sponsor Signatory:

See e-Signature and date signed on last page of the document.

Sponsor Signatory and Contact Information will be provided separately.

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in children 2 to <18 years of age at high risk of respiratory syncytial virus disease" dated 02 Oct 2024 and the most recent version of the mRNA-1345 Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current protocol, the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable local and country regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without IRB/IEC approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a Sub-Investigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study site staff and members of the IRB/IEC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, regulations, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator	**Date**
Printed Name of Principal Investigator	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History	
Document	**Date**
Amendment 2	02 Oct 2024
Amendment 1	18 Jun 2024
Original Protocol	29 Aug 2023

Amendment 2, 02 Oct 2024

This amendment is considered to be substantial because it impacts the overall design of the study.

Overall Main Rationale for the Amendment

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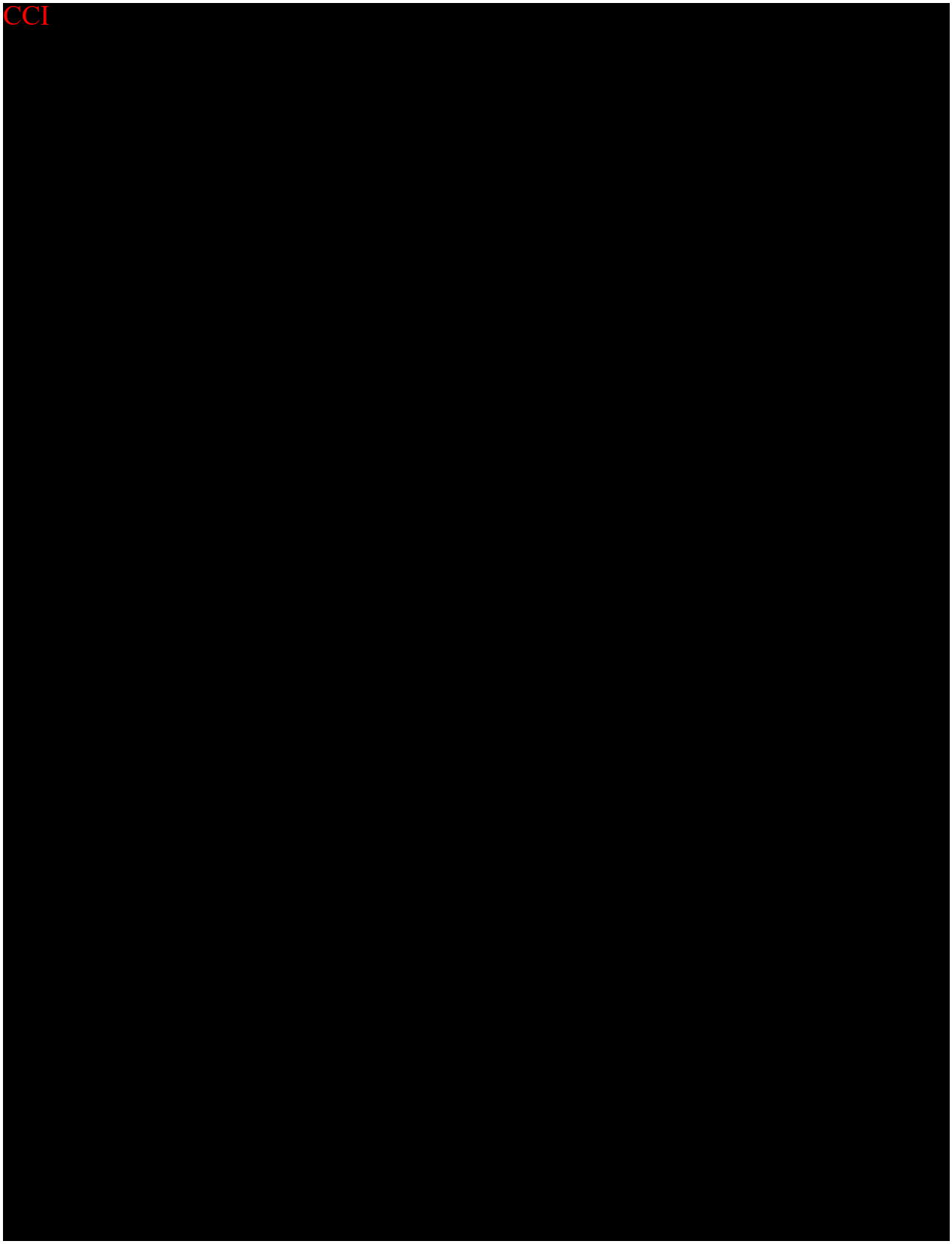

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
CDC	Centers for Disease Control and Prevention
CEAC	Cardiac Event Adjudication Committee
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CI	Confidence interval
CMI	Cell-mediated immunity
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CSR	Clinical study report
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EoS	End-of-study
ERD	Enhanced respiratory disease
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMFR	Geometric mean fold-rise
GMT	Geometric mean titer
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Definition
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IRB	Institutional Review Board
IRT	Interactive response technology
IST	Internal safety team
LAR	Legally authorized representative
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticle
LRTD	Lower respiratory tract disease
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mRNA	Messenger ribonucleic acid
nAb	Neutralizing antibody
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
POCBP	Person of childbearing potential
PP	Per Protocol
QTLs	Quality tolerance limits
RSV	Respiratory syncytial virus
RSV-A	Respiratory syncytial virus subtype A
RSV-B	Respiratory syncytial virus subtype B
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
UR	Uncertainty range
US	United States
VAERD	Vaccine-associated enhanced respiratory disease
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title:

A Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in children 2 to <18 years of age at high risk of respiratory syncytial virus disease

Brief Title:

A study to investigate the safety, reactogenicity, and immunogenicity of mRNA-1345, an mRNA vaccine targeting respiratory syncytial virus, in children 2 to <18 years of age at high risk of respiratory syncytial virus

Regulatory Agency Identifier Number(s):

Registry	**ID**
IND	23342
EU CT number	2023-506271-96-00

Pediatric Investigational Plan Number: EMEA-003309-PIP01-22

Rationale:

RSV is the leading cause of LRTD in children worldwide, with all children aged 2 to <5 years and children aged 5 to <18 with certain underlying conditions forming vulnerable subpopulations. Despite this significant disease burden, there are no approved vaccines for active immunization of children of any age for the prevention of LRTD due to RSV.

This study will be conducted with 2 parts:

Part A: The purpose of the study is to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345 in children 2 to <5 years of age (Cohort 1) and in children at high risk of RSV disease 5 to <18 years of age (Cohort 2) to inform the dose level selection for the next phase of development (Phase 3).

Part B was added after the important potential risk of VAERD has been identified for children 5 to <8 months old in another clinical study that administered mRNA-1345 in a subset of participants. While the risk was not seen in children >2 years of age, the mechanism behind VAERD may apply to all children who have not previously experienced any RSV infection (RSV-naïve children). There could be RSV-naïve children in the age group of 2 to <5 years of age (Cohort 1); therefore, observation of already dosed children during an additional RSV season after receiving mRNA-1345 or placebo is warranted. Part B includes safety follow-up and RSV surveillance for Cohort 1 participants from Part A for 6 months after re-enrollment, which will include the US RSV season (anticipated to last approximately from 01 Oct 2024 to 30 Apr 2025).

Part A: Objectives and Endpoints: Cohort 1 (2 to <5 years):

Objectives Cohort 1	Endpoints Cohort 1
Primary	
• To evaluate the safety and reactogenicity of a single study injection.	• Solicited local and systemic ARs through 7 days postinjection. • Unsolicited AEs through 28 days postinjection. • MAAEs from Day 1 to Month 6/EoS Visit. • AESIs from Day 1 to Month 6/EoS Visit. • SAEs from Day 1 to Month 6/EoS Visit. • AEs leading to discontinuation from Day 1 to Month 6/EoS Visit.
Secondary	
• To evaluate the immunogenicity of a single study injection.	• GMT of serum RSV neutralizing antibody at Day 1, Day 29, and Month 6/EoS Visit. • GMC of serum RSV prefusion F binding antibody at Day 1, Day 29, and Month 6/EoS Visit. • GMFR of Postbaseline/Baseline neutralizing antibody titers and binding antibody concentrations at Day 29 and Month 6/EoS Visit. • Percentage of participants with a seroresponse (defined as a postinjection titer >4-fold-rise if Baseline is >LLOQ or >4 × LLOQ if Baseline titer is <LLOQ) in the above immunogenicity measures.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end-of-study; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; GMT = geometric mean titer; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; SAE = serious adverse event

Part A: Objectives and Endpoints: Cohort 2 (5 to <18 years):

Objectives Cohort 2	Endpoints Cohort 2
Primary	
• To evaluate the safety and reactogenicity of a single study injection.	• Solicited local and systemic ARs through 7 days postinjection. • Unsolicited AEs through 28 days postinjection. • MAAEs from Day 1 to Month 6/EoS Visit. • AESIs from Day 1 to Month 6/EoS Visit. • SAEs from Day 1 to Month 6/EoS Visit. • AEs leading to discontinuation from Day 1 to Month 6/EoS Visit.

Objectives Cohort 2	Endpoints Cohort 2
Secondary	
• To evaluate the immunogenicity of a single study injection.	• GMT of serum RSV neutralizing antibody at Day 1 and Day 29. • GMC of serum RSV prefusion F binding antibody at Day 1 and Day 29. • GMFR of Postbaseline/Baseline neutralizing antibody titers and binding antibody concentrations at Day 29. • Percentage of participants with a seroresponse (defined as a postinjection titer >4-fold-rise if Baseline is >LLOQ or >4 × LLOQ if Baseline titer is <LLOQ) in the above immunogenicity measures.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end-of-study; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; GMT = geometric mean titer; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; SAE = serious adverse event.

Part B: Objectives and Endpoints: Cohort 1 (2 to <5 years):

Objectives Cohort 1	Endpoints Cohort 1
Primary	
• To evaluate the incidence of RSV-RTD during 6 months after re-enrollment.	From Part B Day 1 to Part B EoS: • RSV-RTD • RSV-LRTD • Severe RSV-LRTD • Very severe RSV-LRTD • RSV hospitalization
Secondary	
• To evaluate the safety of a single study injection administered in Part A during 6 months after re-enrollment.	• AESIs from Part B Day 1 to EoS Visit. • SAEs from Part B Day 1 to EoS Visit.
Exploratory[a]	
• To evaluate the persistence of the immunogenicity of a single study injection administered in Part A.	• GMT of serum RSV neutralizing antibody at Part B Day 1. • GMC of serum RSV prefusion F and postfusion F binding antibody at Part B Day 1.
• To explore immune response biomarkers.	• Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses, including cell-mediated immunogenicity.

Abbreviations: AESI = adverse event of special interest; EoS = end-of-study; GMC = geometric mean concentration; GMT = geometric mean titer; LRTD = lower respiratory tract disease; RSV = respiratory syncytial

virus; RSV-LRTD = respiratory syncytial virus— associated lower respiratory tract disease; RTD = respiratory tract disease; SAE = serious adverse event.

[a.] Immunogenicity assessments and immune response biomarker testing are optional for participants in Part B.

Overall Design Synopsis:

This is a Phase 2, randomized, observer-blind study to evaluate the safety, reactogenicity, and immunogenicity of a single injection of mRNA-1345, an mRNA vaccine targeting RSV, in children 2 to <5 years of age and children at high risk of RSV disease 5 to <18 years of age.

Part A:

In Cohort 1, approximately 160 participants who, at the time of randomization are 2 to <5 years of age, will be randomized (1:1:1:1 ratio) to receive either a single injection of mRNA-1345 (CCI µg, CCI µg, or CCI µg) or placebo (normal saline), with approximately 40 participants in each study group. Randomization and enrollment will be stratified by age categories (40%/60%; 2 to <3 years old and 3 to <5 years old). Approximately 60 of the estimated 160 participants will be 2 to <3 years of age.

In Cohort 2, approximately 180 participants who, at the time of randomization are 5 to <18 years of age, will be randomized (1:1:1 ratio) to receive a single injection of mRNA-1345 (CCI µg, CCI µg, or CCI µg), with approximately 60 participants in each study group. Randomization and enrollment will be stratified by age categories (50%/50%; 5 to <12 years old and 12 to <18 years old).

Brief Summary:

Part A of the study aims to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345 in children 2 to <5 years of age and in children at high risk for RSV disease 5 to <18 years of age.

Study details include:

- Cohort 1: There will be up to 4 in-person visits (Screening Visit, Days 1 and 29, and Month 6/EoS Visit) and 2 safety phone calls (Day 8 and Month 3) as specified in the SoA.
- Cohort 2: There will be up to 3 in-person visits (Screening Visit, Day 1, and Day 29) and 3 safety phone calls (Day 8, Month 3, and Month 6/EoS Visit) as specified in the SoA.
- The participant or participant's parent(s)/LAR(s) will be asked to complete an eDiary for solicited ARs for 7 days (ie, the day of the study injection and 6 subsequent days).
- Collection of unsolicited AEs will be from the study injection on Day 1 through 28 days after the study injection (ie, the day of study injection and 27 subsequent days).
- Collection of MAAEs, AESIs, and AEs leading to discontinuation will be from the study injection on Day 1 through Month 6/EoS Visit.
- Collection of SAEs will be from signing of the ICF through Month 6/EoS Visit.

- Blood samples to assess immunogenicity will be taken on Day 1 (all cohorts; prior to the study injection [ie, Baseline blood sample]), Day 29 (all cohorts), and Month 6/EoS Visit (Cohort 1 only).

Part B:

For Part B, all Cohort 1 participants (approximately 160) who were enrolled and dosed in Part A, will be offered to re-enroll into this safety follow-up study, in which surveillance for RSV disease will be conducted over a 6-month period. This will include the next RSV season in the US (approximately 01 Oct 2024 to 30 Apr 2025). RSV surveillance will be performed weekly during RSV season and monthly during RSV off season.

Part B of the study aims to provide surveillance for RSV disease for the next RSV season (6 months after re-enrollment) and safety follow-up for Cohort 1 participants that were enrolled and dosed in Part A.

Study details include:

- There will be no Screening Visit. The first visit will be the Part B Day 1, which is the day of re-enrollment of Cohort 1 participants into the study.
- No treatment will be administered to the participants in Part B of the study.
- There will be at least 1 in-person visit (Part B Day 1), weekly text messages during RSV season (from approximately 01 Oct 2024 to 30 Apr 2025), and 3 safety phone calls (Month 2, Month 4, and Month 6 [EoS]) as specified in the SoA. Additional unscheduled visits will occur if a participant experiences relevant RSV symptoms. Convalescent visits may occur after confirmed RSV-LRTD.
- Interim medical history: SAEs and AESIs that may have occurred subsequent to Part A EoS Visit/discontinuation until the time of signing the ICF for Part B will be collected.
- SAEs and AESIs will be collected from signing of the ICF for Part B through Month 6/EoS Visit.
- Subsequent sample collection and assessments will occur as per the SoA (Table 3)

Overall, the study will require up to 6 months of participation for each participant in Part A and up to an additional 6 months of participation for each participant in Part B.

Number of Participants:

Approximately 340 participants will be enrolled in the study.

Note: *Enrolled* means participants', or their legally authorized representatives', agreement to participate in a clinical study following completion of the informed consent process and Screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after Screening.

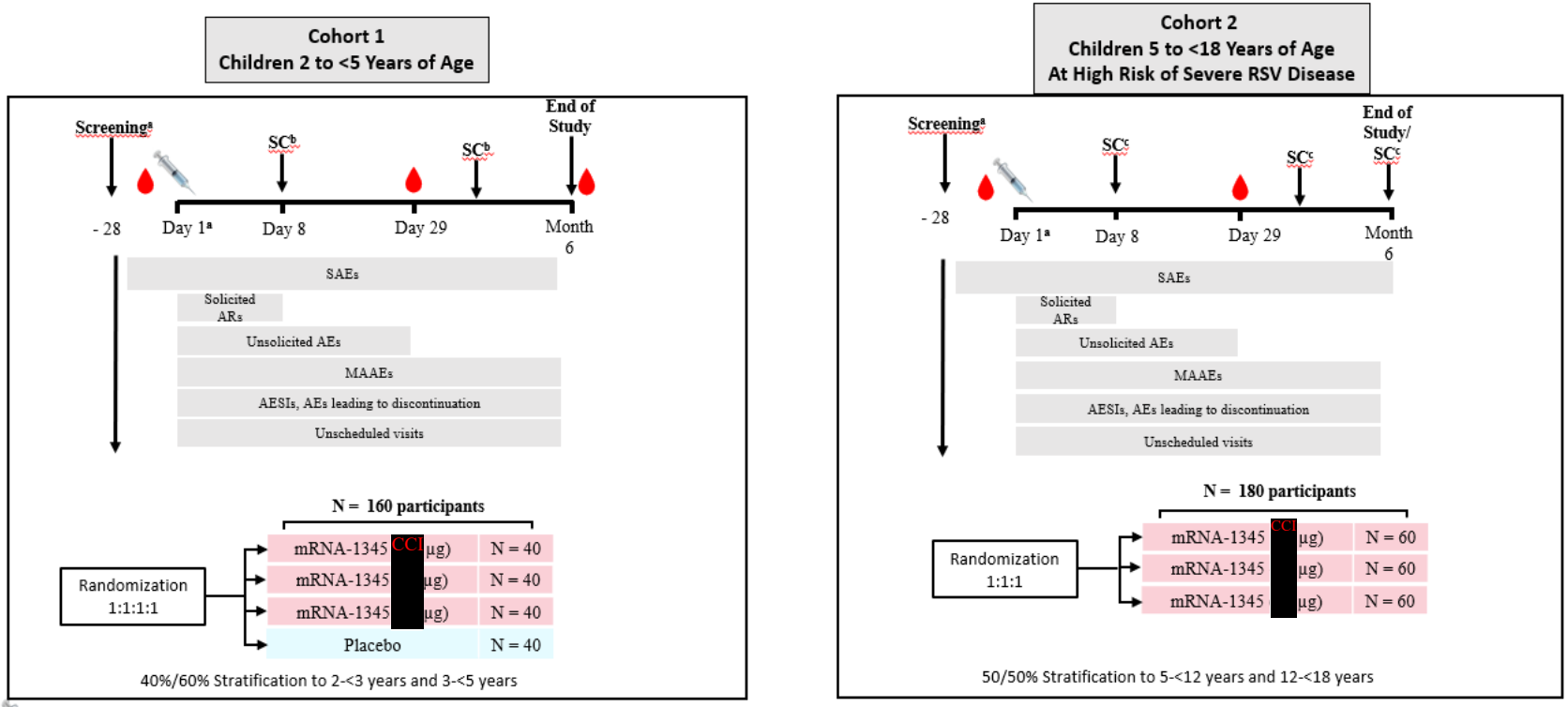
Participants enrolled in Part A Cohort 1 who opt to participate in Part B Cohort 1, will be re-enrolled into Part B.

Study Groups and Duration:

- Cohort 1 is comprised of 4 study groups: mRNA-1345 CCI µg, mRNA-1345 CCI µg, mRNA-1345 CCI µg, and placebo (normal saline).
- Cohort 2 is comprised of 3 study groups: mRNA-1345 CCI µg, mRNA-1345 CCI µg, and mRNA-1345 CCI µg.
- The study will require up to 6 months of participation in total for each participant in Part A.
- Part B will add up to an additional 6 months of follow-up for Cohort 1 participants only.

1.2. Schema

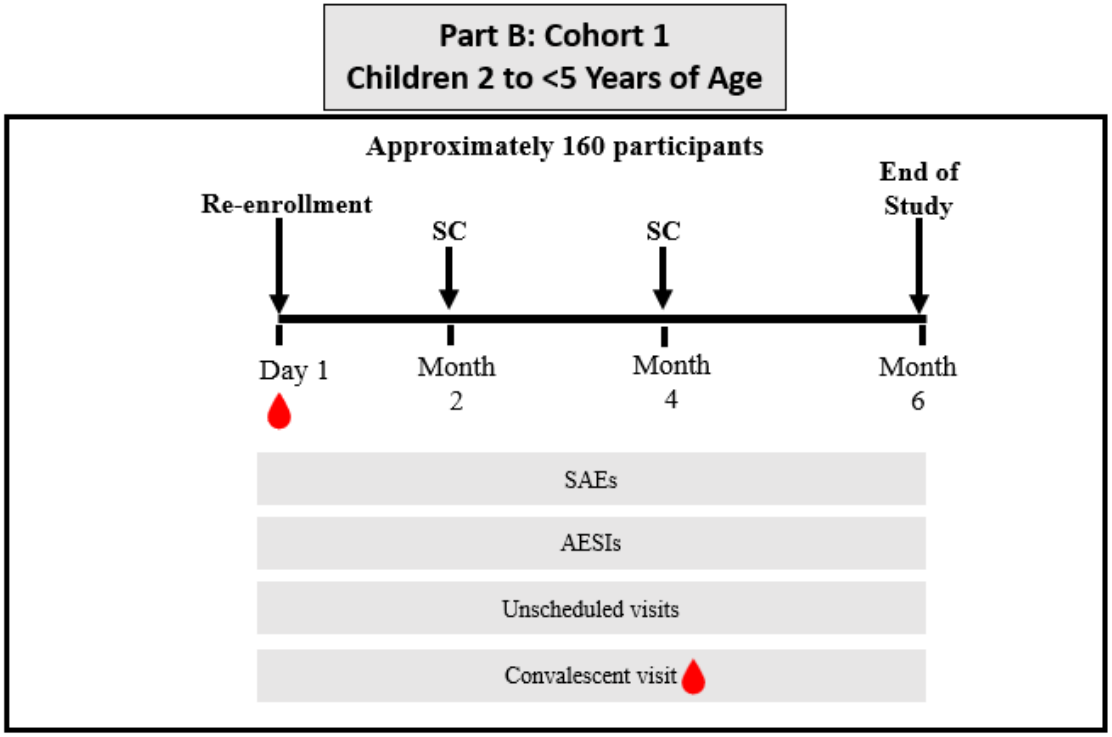
Figure 1: Schema– Part A



[a] Screening Visit and Day 1 Visit may occur on the same day
[b] A SC will be performed at Day 8, and Month 3.
[c] A SC will be performed at Day 8, Month 3, and Month 6/End of Study.

Abbreviations: AE=adverse event, AESI=adverse event of special interest; AR=adverse reaction; MAAE=medically attended adverse event; mRNA=messenger ribonucleic acid; RSV=respiratory syncytial virus; SAE=serious adverse event; SC = safety phone call

Figure 2: Schema– Part B



= Optional immunogenicity blood draw

Abbreviations: AE=adverse event, AESI=adverse event of special interest; SAE=serious adverse event; SC = safety phone call

1.3. Schedule of Activities

Table 1: Part A: Schedule of Activities for Cohort 1 (2 to Less than 5 Years)

Study Period	**SCR**	**Intervention**	**Follow-Up**					**Notes**
Visit Number		**1**	**2**	**3**	**4**	**5**	**USV[a]**	
Timepoint	**SCR**	**D1**	**D8**	**D29**	**M3**	**M6/ EoS Visit**		1 Month = 30 Days Screening Visit and D1 Visit may occur on the same day. Refer to Section 4.1
Window Allowance (Days)	**-28 before D1**		**+3**	**±4**	**±7**	**±7**		
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**V**	**V**	
Informed Consent	X							Refer to Section 10.1.3
Demographics and medical history	X							Refer to Section 8.1
Inclusion/exclusion criteria[b]	X	X						Refer to Section 5.1 and Section 5.2
Vital signs[b]	X	X					X	Refer to Section 8.3.4
Physical examination[b,c]	X	X		X		X	X	Refer to Section 8.3.3
Participants with CHD only: ECG (if not available within 6 months of Screening)	X							Refer to Section 8.3.5
Recording of concomitant medications and non-study vaccinations	X	X	X	X	X	X	X	Refer to Section 6.9
Randomization		X						Refer to Section 6.3
Study injection (including the 30-minute postdose observation period)[d]		X						Refer to Section 6.1

Study Period	**SCR**	**Intervention**	**Follow-Up**					**Notes**
Visit Number		**1**	**2**	**3**	**4**	**5**	**USV[a]**	
Timepoint	**SCR**	**D1**	**D8**	**D29**	**M3**	**M6/ EoS Visit**		1 Month = 30 Days Screening Visit and D1 Visit may occur on the same day. Refer to Section 4.1
Window Allowance (Days)	**-28 before D1**		**+3**	**±4**	**±7**	**±7**		
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**V**	**V**	
Blood for antibody-mediated immunogenicity		X[e]		X		X		Refer to Section 8 and Section 8.9
Blood for CMI (PBMC)[f]		X[e]		X		X		Refer to Section 8 and Section 8.9
eDiary activation for recording solicited ARs		X						Refer to Section 8.3.2
Review of solicited ARs eDiary[d]			X					Refer to Section 8.3.2
Follow-up safety phone call[g]			X		X			Refer to Section 8.3.1
Recording of unsolicited AEs		X	X	X				Refer to Section 10.3
MAAEs and concomitant medications associated with MAAEs[h]		X	X	X	X	X	X	Refer to Section 8.4.7
AESIs, AEs leading to discontinuation, and concomitant medications associated with these AEs[h]		X	X	X	X	X	X	Refer to Section 8.4.8 and Section 10.3
SAEs and concomitant medications associated with SAEs[h]	X[i]	X	X	X	X	X	X	Refer to Section 10.3
Study completion						X		

Note: If a participant cannot attend a scheduled in-person visit with the exception of the Screening Visit and Day 1, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service. If neither an in-person visit from the participant nor a home visit to the participant is possible (with the exception of the Screening Visit and Day 1), a safety phone call should be performed that includes the assessments scheduled for the safety phone calls.

Abbreviations: AE = adverse event; AESI = AE of special interest; AR = adverse reaction; CHD = congenital heart defect; CMI = cell-mediated immunity; D = day; eDiary = electronic diary; EoS = end-of-study; ICF = informed consent form; LAR = legally authorized representative; M = month (month = 30 days); MAAE = medically attended adverse event; PBMC = peripheral blood mononuclear cell; RSV = respiratory syncytial virus; SAE = serious adverse event; SC = safety phone call; SCR = Screening; USV = unscheduled visit; V = in-person visit.

a. Visit for participants who discontinue/withdraw from the study and unscheduled visits.
b. Vital sign measurements, check of inclusion/exclusion criteria, and physical examination do not need to be repeated if the Screening Visit and the Day 1 Visit occur on the same day. A complete physical examination will be performed at the Screening Visit.
c. A symptom-directed physical examination will be performed at in-person visits after the Screening Visit, at the discretion of the Investigator.
d. eDiary entries will be recorded by the participant's parent(s)/LAR(s) within approximately 30 minutes after study injection while at the clinic with instruction provided by the study site staff. Participant's parent(s)/LAR(s) will continue to record solicited ARs in the eDiary each day after they leave the clinic, on the day of study intervention and the subsequent 6 days following study intervention.
e. Prior to study intervention (ie, Baseline blood sample).
f. Blood for PBMC will be collected from a subset of participants at selected study sites for participants enrolled in Cohort 1 only.
g. Trained study site staff will remind the participant's parent(s)/LAR(s) to complete the eDiary and to collect information about any Grade 3 solicited ARs, any underarm/groin swelling or tenderness on same side as injection, any medications taken to prevent or treat pain or fever, and any medical visits, as applicable.
h. Trained study site staff will collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESI, and information on concomitant medications associated with those events, and any non-study vaccinations received.
i. After signing of the ICF.

Table 2: Part A: Schedule of Activities for Cohort 2 (5 to Less than 18 Years)

Study Period	**SCR**	**Intervention**	**Follow-Up**					**Notes**
Visit Number		**1**	**2**	**3**	**4**	**5**	**USV[a]**	
Timepoint	**SCR**	**D1**	**D8**	**D29**	**M3**	**M6/ EoS Visit**		1 Month = 30 Days Screening Visit and D1 Visit may occur on the same day. Refer to Section 4.1
Window Allowance (Days)	**-28 before D1**		**+3**	**±4**	**±7**	**±7**		
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**SC**	**V**	
Informed Consent	X							Refer to Section 10.1.3
Demographics and medical history	X							Refer to Section 8.1
Inclusion/exclusion criteria[b]	X	X						Refer to Section 5.1 and Section 5.2
Vital signs[b]	X	X					X	Refer to Section 8.3.4
Physical examination[b,c]	X	X		X			X	Refer to Section 8.3.3
Pregnancy test (urine)[d] prior to injection and IRT registration (POCBP)	X	X						Refer to Section 8.3.6
Participants with CHD only: ECG (if not available within 6 months prior to Screening)	X							Refer to Section 8.3.5

Study Period	**SCR**	**Intervention**	**Follow-Up**					**Notes**
Visit Number		**1**	**2**	**3**	**4**	**5**	**USV[a]**	
Timepoint	**SCR**	**D1**	**D8**	**D29**	**M3**	**M6/ EoS Visit**		1 Month = 30 Days Screening Visit and D1 Visit may occur on the same day. Refer to Section 4.1
Window Allowance (Days)	**-28 before D1**		**+3**	**±4**	**±7**	**±7**		
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**SC**	**V**	
Participants aged 12-<18 years only: 12-Lead ECG (predose) and collection of banked serum for potential cardiac biomarker testing		X						Refer to Section 8.3.5 and Section 8.8.
Recording of concomitant medications and non-study vaccinations	X	X	X	X	X	X	X	Refer to Section 6.9
Randomization		X						Refer to Section 6.3
Study injection (including the 30-minute postdose observation period)[e]		X						Refer to Section 6.1
Blood for antibody-mediated immunogenicity		X[f]		X				Refer to Section 8 and Section 8.9
eDiary activation for recording solicited ARs		X						Refer to Section 8.3.2
Review of solicited ARs eDiary[e]			X					Refer to Section 8.3.2
Follow-up safety phone call[g]			X		X	X		Refer to Section 8.3.1
Recording of unsolicited AEs		X	X	X				Refer to Section 10.3

Study Period	**SCR**	**Intervention**	**Follow-Up**					**Notes**
Visit Number		**1**	**2**	**3**	**4**	**5**	**USV[a]**	
Timepoint	**SCR**	**D1**	**D8**	**D29**	**M3**	**M6/ EoS Visit**		1 Month = 30 Days Screening Visit and D1 Visit may occur on the same day. Refer to Section 4.1
Window Allowance (Days)	**-28 before D1**		**+3**	**±4**	**±7**	**±7**		
Type of Visit	**V**	**V**	**SC**	**V**	**SC**	**SC**	**V**	
MAAEs and concomitant medications associated with MAAEs[h]		X	X	X	X	X	X	Refer to Section 8.4.7
AESIs, AEs leading to discontinuation, and concomitant medications associated with these AEs[h]		X	X	X	X	X	X	Refer to Section 8.4.8 and Section 10.3
SAEs and concomitant medications associated with SAEs[h]	X[i]	X	X	X	X	X	X	Refer to Section 10.3
Study completion						X		

Note: If a participant cannot attend a scheduled in-person visit with the exception of the Screening Visit and Day 1, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service. If neither an in-person visit from the participant nor a home visit to the participant is possible (with the exception of the Screening Visit and Day 1), a safety phone call should be performed that includes the assessments scheduled for the safety phone calls.

Abbreviations: AE = adverse event; AESI = AE of special interest; AR = adverse reaction; CHD = congenital heart disease;D = day; eDiary = electronic diary; ECG = electrocardiogram; EoS = end-of-study; ICF = informed consent form; IRT = Interactive Response Technology; LAR = legally authorized representative; M = month (month = 30 days); MAAE = medically attended adverse event; POCBP = person of childbearing potential; RSV = respiratory syncytial virus; SAE = serious adverse event; SC = safety phone call; SCR = Screening; USV = unscheduled visit; V = in-person visit;

a. Visit for participants who discontinue/withdraw from the study and unscheduled visits.
b. Vital sign measurements, check of inclusion/exclusion criteria, and physical examination do not need to be repeated if the Screening Visit and the Day 1 Visit occur on the same day. A complete physical examination will be performed at the Screening Visit.
c. A symptom-directed physical examination will be performed at in-person visits after the Screening Visit, at the discretion of the Investigator.
d. Applicable to female participants who have reached menarche only. Serum pregnancy test will be performed to confirm a positive result of a urine pregnancy test. Participants who become pregnant at any time should remain in the study and complete all study visits as scheduled.

[e.] eDiary entries will be recorded by the participant's parent(s)/LAR(s) or the participant within approximately 30 minutes after study injection while at the clinic with instruction provided by the study site staff. Participant's parent(s)/LAR(s) or the participant will continue to record solicited ARs in the eDiary each day after they leave the clinic, on the day of study intervention and the subsequent 6 days following study intervention.

[f.] Prior to study intervention (ie, Baseline blood sample).

[g.] Trained study site staff will remind the participant's parent(s)/LAR(s) and the participant to complete the eDiary and to collect information about any Grade 3 solicited ARs, any underarm/groin swelling or tenderness on same side as injection, any medications taken to prevent or treat pain or fever, and any medical visits, as applicable.

[h.] Trained study site staff will collect information relating to any MAAEs, AEs leading to study discontinuation, SAEs, AESI, and information on concomitant medications associated with those events, and any non-study vaccinations received.

[i.] After signing of the ICF.

Table 3: Part B: Schedule of Activities for Cohort 1 (2 to Less than 5 Years)

		RSV Surveillance					
Study Period	**Re-Enrollment**	**Follow-Up**					**Notes**
Visit Number	**1**	**2**	**3**	**4 (EoS Visit)**	**USV[a]** (RSV Surveillance)	**Convalescent Visit**	
Timepoint	**D1**	**M2**	**M4**	**M6**	Whenever experiencing respiratory symptoms	Following a confirmed RSV-LRTD	1 Month = 30 Days
Window Allowance (Days)	**-**	**±7**	**±7**	**±7**	**N/A**	**+3 to 24**	
Type of Visit	**V**	**SC**	**SC**	**SC**	**V**	**V**	
Informed Consent	X						Refer to Section 10.1.3
Demographics (age only)	X						Refer to Section 8.1
Interim SAE and AESI history from Part A EoS or discontinuation to signing of ICF for Part B	X						Refer to Section 8.3
Inclusion/exclusion criteria	X						Refer to Section 5.1 and Section 5.2
Vital signs[b]	X				X		Refer to Section 8.3.4
Physical examination[c]	X				X	X	Refer to Section 8.3.3
Follow-up safety phone calls[d]		X	X	X			Refer to Section 8.3.1
AESIs and concomitant medications associated with AESIs[e]	X	X	X	X	X		Refer to Section 8.4
SAEs and concomitant medications associated with SAEs[e]	X	X	X	X	X		Refer to Section 8.4
Blood for antibody-mediated immunogenicity (optional)[f]	X						

Study Period		RSV Surveillance					Notes
	Re-Enrollment	Follow-Up					
Visit Number	**1**	**2**	**3**	**4 (EoS Visit)**	**USV[a]** (RSV Surveillance)	**Convalescent Visit**	
Timepoint	**D1**	**M2**	**M4**	**M6**	Whenever experiencing respiratory symptoms	Following a confirmed RSV-LRTD	1 Month = 30 Days
Window Allowance (Days)	**-**	**±7**	**±7**	**±7**	**N/A**	**+3 to 24**	
Type of Visit	**V**	**SC**	**SC**	**SC**	**V**	**V**	
RSV surveillance[d, g]	Weekly during RSV season and monthly when not in RSV season						Refer to Section 8.3.7
Nasal or Nasopharyngeal Swab					X		
Blood for cell-mediated and antibody-mediated immunogenicity (optional)[h]						X	

Note: If a participant cannot attend a scheduled in-person visit with the exception of the Part B Day 1 visit, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service. If neither an in-person visit from the participant nor a home visit to the participant is possible (with the exception of the Part B Day 1 Visit), a safety phone call should be performed that includes the assessments scheduled for the safety phone calls.

Abbreviations: AE = adverse event; AESI = AE of special interest; AR = adverse reaction; CHD = congenital heart defect; CMI = cell-mediated immunity; D = day; EoS = end-of-study; ICF = informed consent form; LAR = legally authorized representative; M = month (month = 30 days); RSV = respiratory syncytial virus; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = safety phone call; USV = unscheduled visit; V = in-person visit.

a. Visit for participants who experience symptoms of RSV disease (USV for RSV surveillance) or discontinue/withdraw from the study.

b. Vital signs to be collected at USV include at minimum: temperature, respiratory rate, pulse oximetry (SpO_2), and heart rate.

c. A complete physical examination will be performed at the Re-enrollment Visit. A symptom-directed physical examination will be performed at unscheduled visits for RSV surveillance. Physical exam to be completed at RSV surveillance (unscheduled) visits include at minimum: Observation of breathing pattern and work of breathing, auscultation of the chest, hydration and perfusion status.

d. Trained study site staff will contact parent(s)/LAR(s) of all participants weekly via text message during the RSV season to remind the parent(s)/LAR(s) to call and report with any potential (any new or worsening) RSV-RTD symptoms.

e. Trained study site staff will collect information relating to any SAEs, AESI, and information on concomitant medications associated with those events, and any non-study vaccinations received.
f. Optional blood draw for antibody-mediated immunogenicity in participants with parent(s)/LAR(s) who have provided consent to the additional blood volume.
g. Participants will be followed from Part B Day 1 through EoS for RSV-suspected disease. Study staff will text parent(s)/LAR(s) weekly to remind them to call the site if child experiences any symptoms of an RSV-suspected disease (defined as congestion or runny nose for >24 hours, cough, difficulty breathing, or respiratory distress, including wheezing). Once the site is notified by parent(s)/LAR(s) of relevant symptoms, parent(s) or LAR(s) will be encouraged to bring the participant for an assessment visit, preferably within 5 days of symptom(s) onset for evaluation and respiratory specimen collection. For assessment visits, evaluation and sample collections will be conducted for RSV and potentially for other respiratory viruses, including SARS-CoV-2.
h. An optional blood draw will occur 3 to 24 days after a confirmation of RSV-LRTD (following the USV or date of hospitalization, whichever is earlier) for cell-mediated and antibody-mediated immunogenicity in participants with parent(s)/LAR(s) who have provided consent to the additional blood volume.

2. INTRODUCTION

mRNA-1345 is an investigational LNP-encapsulated mRNA-based vaccine encoding the membrane-anchored RSV fusion glycoprotein, derived from an RSV-A strain (RSV-A A2 strain), and stabilized in the prefusion conformation through structural engineering. The fusion protein exists in 2 primary conformational states; the prefusion state facilitates viral entry into the host cell through a conformational change to the postfusion state. The fusion protein was selected as the vaccine antigen due to its role in host cell entry and because it is highly conserved across RSV-A and RSV-B subtypes. The prefusion conformation was selected because it displays all the epitopes known to elicit neutralizing antibodies and is the primary target of the neutralizing antibody response following RSV exposure (McLellan et al 2013, Ngwuta et al 2015, Crank et al 2019, Graham 2019).

2.1. Study Rationale

RSV is the leading cause of LRTD in children worldwide, with children aged 2 to <5 years and children 5 to <18 years with underlying medical conditions forming vulnerable subpopulations. Despite this significant disease burden, there are no approved active vaccines for children of any age for the prevention of LRTD due to RSV (Path.org. 2023).

This study will be conducted with 2 Parts:

In Part A, the purpose of the study is to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1345 in children aged 2 to <5 years of age and in children at high risk of RSV disease 5 to <18 years of age to inform the dose level selection for the next phase of development (Phase 3).

Part B was added after the important potential risk of VAERD has been identified for children 5 to <8 months old in another clinical study that administered mRNA-1345 in a subset of participants. While the risk was not seen in children >2 years of age, the mechanism behind VAERD may apply to all children who have not previously experienced any RSV infection (RSV-naïve children). There could be RSV-naïve children in the age group of 2 to <5 years of age (Cohort 1); therefore, observation of already dosed children during an additional RSV season after receiving mRNA-1345 or placebo is warranted. Part B includes safety follow-up and RSV surveillance for Cohort 1 participants from Part A for 6 months after re-enrollment (anticipated to last approximately from 01 Oct 2024 to 30 Apr 2025.

2.2. Background

RSV is the leading cause of LRTD in children worldwide (Modjarrad et al 2016, Li et al 2022). Among children <5 years of age, an estimated 33.0 million (UR: 25.4 million to 44.6 million) episodes of RSV-LRTD and an estimated 3.6 million (UR: 2.9 million to 4.6 million) RSV-associated hospitalizations occurred globally in 2019 (Li et al 2022). Among children 2 to <5 years of age, the estimated annual incidence of medically attended RSV infection in the US is 110.9 per 1000 children (UR: 46.0 to 175.2) (Jackson et al 2021). A study between 2012 and 2014 in India suggested that the incidence of RSV-LRTD in children 2 to <5 years of age is around 20 per 1000 person-years (UR:10 to 40 per 1000 person-years), which translates to approximately 2 children out of 100 who develop RSV-LRTD every year (Krishnan et al 2019). Research in the Philippines between 2014 and 2016 has shown a similar disease burden of

RSV-LRTD, which ranged from 15.8 per 1000 person-years in children 3 to <4 years of age to 18.7 per 1000 person-years in children 4 to <5 years of age (Ueno et al 2019).

While RSV is well-known for its significant impact on infants and young children under the age of 5, it also represents a considerable disease burden in high-risk children aged 5 to <18 years, particularly in those with underlying health conditions such as asthma, cystic fibrosis, chronic respiratory diseases and malformations of the lung, trisomy 21, neuromuscular disease, cerebral palsy, and congenital heart disease (Manzoni et al 2017). A review suggested that RSV has been associated with 4% to 12% of acute asthma exacerbation in older children (Papadopoulos et al 2011). Studies in Brazil, Canada, and the US showed that RSV is frequently associated with pulmonary exacerbation or LRTD in children with cystic fibrosis under 18 years. Among patients with pulmonary exacerbation, 17% to 24% tested positive for RSV (Garcia et al 2007, Asner et al 2012, Somayaji et al 2017, Meyer et al 2020). In addition, RSV case-fatality rate is markedly high in children with chronic lung disease and congenital heart disease (Welliver et al 2010). A literature review reported a range of 3.5% to 23% and 2% to 37% RSV case-fatality rate in children under 18 years with chronic lung disease and with congenital heart disease, respectively (Welliver et al 2010). Extensive research has shown that children with trisomy 21 are at increased risk of severe RSV disease and mortality (Kristensen et al 2012, Zachariah et al 2012, Murray et al 2014, Stagliano et al 2015, Pisesky et al 2016, Sánchez-Luna M et al 2017). For example, a meta-analysis suggests that children with Down syndrome are associated with higher odds of RSV-associated hospitalizations (OR = 8.69, 95% CI 7.33-10.3) and mortality (OR = 9.4, 95% CI: 2.26–39.15) compared with children without Down syndrome (Beckhaus and Castro-Rodriguez 2018). In addition to the aforementioned comorbidities, children with neuromuscular disease experience elevated rates of RSV-associated LRTD hospitalizations than the general pediatric population (Wilkesmann et al 2007). A recent study (study period: 2006 to 2015) conducted by the US CDC reported that the RSV-related hospitalization rate was 7 (95% CI 6.9, 7.2) per 1000 person-years among children <19 years of age with any neurological condition and was 9.4 (95% CI 9.0, 9.9) per 1000 person-years among those with cerebral palsy (Rose et al 2021).

Given that most children have been infected with RSV at least once by 2 years of age (Glezen et al 1986, Nyiro et al 2017, Andeweg et al 2021), the substantial burden of RSV disease in children >2 years of age highlights that RSV infection-induced immunity is incomplete (Henderson et al 1979, Hall et al 1991, Walsh et al 2013).

While interventions such as RSV monoclonal antibodies (eg, nirsevimab) and maternal immunization against RSV offer the potential for disease reduction in the youngest pediatric cohorts, these interventions are directed at prevention of disease only during the child's first +/- second RSV season, and may potentially increase the burden of disease in children 2 to <5 years of age due to a delay in the age of the first RSV infection (Zheng et al 2022).

The Sponsor is developing the mRNA-1345 vaccine for the prevention of RSV-LRTD in all vulnerable age groups and populations. Presently, this vaccine has been administered to over 17,000 adults aged ≥60 years in an ongoing Phase 2/3 study (mRNA-1345-P301, NCT05127434) Results from this study show a single CCI-µg mRNA-1345 injection in adults ≥60 years of age demonstrates vaccine efficacy of 83.7% (95.88% CI: 66.1%, 92.2%) against RSV-LRTD defined by 2 or more symptoms and 82.4% (96.36% CI: 34.8%, 95.3%) against RSV-LRTD defined by

3 or more symptoms. The vaccine was also well tolerated with no safety concerns identified to date (Wilson et al, 2023).

In addition, mRNA-1345 was administered to 30 RSV-seropositive children aged 12 to 59 months in an ongoing Phase 1 safety and immunogenicity study (mRNA-1345-P101) (Snape et al 2023). The interim data from this study demonstrated:

- Up to 3 injections of the CCI-µg and CCI-µg dose level of mRNA-1345 administered on Day 1, Month 2, and Month 4 were generally well tolerated. There was no evidence of reactogenicity increasing with ascending number of injections, except for tenderness. The rates of any solicited ARs were comparable among participants receiving mRNA-1345 and placebo. Most solicited ARs were Grade 1 or Grade 2. Grade 3 local ARs were most frequently reported in participants in the mRNA-1345 CCI-µg group. A single participant in the CCI-µg group reported a Grade 4 fever as a solicited AR. No SAEs, deaths, AESIs, and no AEs leading to study discontinuation have been reported to date.
- A single injection of the CCI-µg or CCI-µg dose level of mRNA-1345 increased neutralizing antibody titers against RSV-A and RSV-B with minimal dose response. The limited available immunogenicity data after a second and third injection of mRNA-1345 at Months 2 and 4 suggest that sequential injections on this regimen did not substantially increase the neutralizing antibody titers any further in this Baseline RSV-seropositive population.

Based on these data, the Sponsor is also evaluating a 3-dose series of the mRNA-1345 vaccine in children 5 to <24 months of age without determining Baseline RSV-serostatus prior to enrollment in an ongoing Phase 1 safety and immunogenicity study (mRNA-1365-P101) with age de-escalation from children 8 to <24 months of age (fully enrolled, approximately 30 children dosed with CCI µg mRNA-1345) to infants 5 to <8 months of age who will be predominantly RSV-naïve. This study recently met a pause rule trigger and was put on clinical hold due to the important potential risk of VAERD identified for children 5 to <8 months of age.

In parallel, the Sponsor is evaluating in the present study the safety and immunogenicity of a single mRNA-1345 injection in children 2 to <5 years of age and children 5 to <18 years of age who are at high risk of RSV disease, given the considerable burden of disease in these populations as outlined above.

RSV vaccine-associated ERD was observed after natural RSV infection of previously naïve infants vaccinated with a formalin-inactivated RSV vaccine evaluated in clinical studies conducted in the 1960s (Chin et al 1969, Kim et al 1969). The etiology of RSV vaccine-associated ERD remains incompletely understood, but has been variously attributed to T helper cell type 2 polarization and associated infiltration of neutrophils and eosinophils into airways (Connors et al 1994, Prince 2001), failure to elicit cytotoxic CD8+ T cells (Srikiatkhachorn and Braciale, 1997), lack of antibody affinity maturation resulting in low avidity antibodies (Delgado et al 2009), immune complex deposition and complement activation (Polack et al 2002), or a combination of these mechanisms (Acosta et al 2015). Based on epidemiological data, the risk of vaccine-associated ERD is considered low in children ≥2 years of age and adults due to previous priming by natural RSV infection (Giersing et al 2019, Browne et al 2020).

However, another Sponsor clinical study (Study mRNA-1365-P101, where a subgroup of participants also received mRNA-1345) was recently put on clinical hold after 2 severe RSV LRTDs cases were reported in 5- to 8-month-olds. The Sponsor paused further dosing and enrollment in that study as a precautionary measure to ensure the safety and well-being of the clinical study participants. Following a review of RSV infections reported in the mRNA-1365-P101 study by Moderna's safety governance, RSV ERD in children 5 months to <8 months of age was categorized as an important potential risk associated with both mRNA-1345 and mRNA-1365. The above events were only noted in participants 5 months to <8 months of age and were not identified in the 2 to <5-year-old population.

Nonetheless, the US FDA subsequently put Study mRNA-1345-P202 on partial clinical hold and requested that no additional dosing occur in 2 to <5 years of age until the mRNA-1345-P202 protocol is amended to enhance safety assessments in this age group.

The Sponsor proceeded to remove Cohort 3 and add Part B to mRNA-1345-P202 protocol in order to follow Cohort 1 participants for their next RSV season and collect data on RSV surveillance in these children, to supplement the ongoing data collection in younger children in Study mRNA-1365-P101.

2.3. Benefit/Risk Assessment

mRNA-1345 is being evaluated in ongoing clinical studies and has shown a positive and favorable benefit/risk profile in clinical settings across different subpopulations.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of mRNA-1345 may be found in the IB.

2.3.1. Risk Assessment

Recent seroprevalence studies across countries of different demographic and socioeconomic background demonstrated that most children have been infected by RSV by 2 years of age (Glezen et al 1986, Lu et al 2011, Nyiro et al 2017, Andeweg et al 2021). A WHO expert committee agreed that the potential risk of vaccine-associated ERD is highest in (and perhaps confined to) RSV-naïve infants, and serological tests may underestimate the RSV-exposed population because of the lack of sensitivity (WHO 2019). The risk of vaccine-associated ERD is considered low in children ≥2 years of age due to previous priming by natural RSV infection and a more developed respiratory tract (Kapikian et al 1969, Acosta et al 2015, Giersing et al 2019, Browne et al 2020). Accordingly, it is reasonable to apply an age cut-off based on relevant epidemiological data to minimize the risk of ERD without determining Baseline RSV-serostatus prior to enrollment (WHO 2019). Furthermore, the Sponsor has conducted ERD de-risking nonclinical studies in support of development of mRNA-1345 in RSV-naïve children prior to this study. Preclinical rodent models support that mRNA-1345 did not trigger ERD and has the potential to be safe and effective at prevention of RSV disease. More details may be found in the IB.

As described in Section 2.2, the Sponsor recently paused another RSV vaccine study in younger children (mRNA-1365-P101).

A study pause was triggered on 17 Jul 2024 in the mRNA-1365-P101 clinical study, based on the per protocol pause rule #7 threshold of "Any severe LRTD with positive PCR for RSV in

≥2 participants" when 2 participants in the study experienced protocol defined severe RSV-LRTD. The mRNA-1365-P101 clinical study is a blinded placebo-controlled safety and immunogenicity study of mRNA-1345 and mRNA-1365 in participants aged 5 months to <24 months of age. Following the initiation of the study pause for Study mRNA-1365-P101, the Sponsor conducted a safety review analyzing all RSV infections identified in Study mRNA-1365-P101 and determined that RSV enhanced respiratory disease in 5- to <8-month-old children is an important potential risk associated with mRNA-1345 and mRNA-1365. Additional details on these events may be found in the mRNA-1345 IB.

While RSV ERD is a known potential risk with active immunization of RSV vaccines in RSV-naïve children, the risk of RSV ERD associated with mRNA-1345 is less likely in older pediatric populations that are not RSV infection naïve. Nonetheless, the Sponsor proceeded to remove Cohort 3 and add Part B to mRNA-1345-P202 protocol in order to follow Cohort 1 participants for their next RSV season and collect data on RSV surveillance in these children, to supplement the ongoing data collection in younger children in Study mRNA-1365-P101.

As with all injectable vaccines, immediate systemic allergic reactions, ranging from mild (eg, urticaria) to severe (eg, anaphylaxis) can occur. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection. Systemic ARs may also occur after vaccination, are usually mild to moderate in severity, and may include headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills, and fever. In most cases, these reactions resolve spontaneously within several days.

As with other IM injections, the study vaccines should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as hemophilia) because bleeding or bruising may occur following an IM injection in these individuals.

Local ARs are expected after IM injection. These typically include pain, erythema (redness), or swelling/induration (hardness) at the injection site, mostly mild to moderate in severity, generally occur within 24 hours of injection, and most often resolve within 3 to 4 days of onset.

There have been very rare (<1 in 10,000 recipients) reports of myocarditis and pericarditis occurring after vaccination with COVID-19 vaccines, including mRNA vaccines. The majority of these cases have been reported in adolescent and young adult males shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Investigators and participants should be alert to the signs and symptoms of myocarditis and pericarditis. The risk of myocarditis or pericarditis after administration of non-COVID mRNA vaccines is unknown (Appendix 6 [Gargano et al 2021]).

2.3.2. Benefit Assessment

Given that vaccine efficacy in adults aged ≥60 years was demonstrated in an ongoing Phase 2/3 study (mRNA-1345-P301, NCT05127434) (Section 2.2), it is anticipated that study participants receiving mRNA-1345 will likely benefit from this intervention.

All participants will be contributing to the process of developing a new potentially prophylactic measure in an area of unmet medical need (the prevention of LRTD due to RSV) among a subpopulation that is particularly vulnerable to this disease.

2.3.3. Overall Benefit/Risk Conclusion

As discussed in Section 2.2, interim data from the ongoing Phase 1 safety and immunogenicity study in RSV-seropositive children aged 12 to 59 months demonstrated that up to 3 injections of the CCI-µg and CCI-µg dose levels of mRNA-1345 were well tolerated (mRNA-1345-P101). A single CCI-µg mRNA-1345 injection in adults ≥60 years of age was also well tolerated with no safety concerns identified to date.

Appropriate eligibility criteria, as well as specific criteria for delaying the study intervention, are included in this protocol. The risk to participants in this study may be minimized by compliance with the eligibility criteria and study assessments and procedures.

All safety findings will be closely monitored by the study team and reviewed by an IST with a remit to escalate to an independent DSMB to evaluate the safety and vaccination status of all participants as needed. The DSMB will review safety data of the selected Phase 2 dose in each age group. The DSMB will review and assess the safety data as described in a separate charter.

The study team (including Sponsor Medical Monitor and Sponsor Safety Physician) will receive an alert whenever a participant reports any Grade 3 or Grade 4 reactogenicity event in their eDiary, or the site enters an SAE or AESI in EDC. The Sponsor Medical Monitor and Safety Physician will review blinded Grade 3+ reactogenicity events, SAEs, and AESIs weekly during active enrollment. In addition, the IST will review unblinded cumulative safety data including solicited ARs at regularly scheduled intervals during active enrollment. An IST review will occur once after approximately 40 participants in Cohort 1, and once after approximately 40 participants in Cohort 2, are enrolled and have reached Day 8. The frequency of subsequent reviews will be determined by the IST.

The roles of the IST and the DSMB will be described in separate charters.

Considering the measures used to minimize the risk to individuals participating in this study and oversight by an IST and an independent DSMB, the potential risks to the participants are justified by the potential benefits afforded by mRNA-1345 as seen in older adults, and those linked to the development of the mRNA-1345 vaccine.

Given the important potential risk of RSV enhanced respiratory disease associated with mRNA-1345, described above, in younger children (5 months to <8 months of age) who received mRNA-1345, the Sponsor has removed Cohort 3 (2 to <5 years of age) until more data becomes available. The benefit-risk for use of mRNA-1345 in older RSV experienced participants remains favorable.

3. OBJECTIVES AND ENDPOINTS

Table 4: Part A: Objectives and Endpoints: Cohort 1 (2 to <5 years)

Objectives Cohort 1	Endpoints Cohort 1
Primary	
• To evaluate the safety and reactogenicity of a single study injection.	• Solicited local and systemic ARs through 7 days postinjection. • Unsolicited AEs through 28 days postinjection. • MAAEs from Day 1 to Month 6/EoS Visit. • AESIs from Day 1 to Month 6/EoS Visit. • SAEs from Day 1 to Month 6/EoS Visit. • AEs leading to discontinuation from Day 1 to Month 6/EoS Visit.
Secondary	
• To evaluate the immunogenicity of a single study injection.	• GMT of serum RSV neutralizing antibody at Day 1, Day 29, and Month 6/EoS Visit. • GMC of serum RSV prefusion F binding antibody at Day 1, Day 29, and Month 6/EoS Visit. • GMFR of Postbaseline/Baseline neutralizing antibody titers and binding antibody concentrations at Day 29 and Month 6/EoS Visit. • Percentage of participants with a seroresponse (defined as a postinjection titer >4-fold-rise if Baseline is >LLOQ or >4 × LLOQ if Baseline titer is <LLOQ) in the above immunogenicity measures.
Exploratory (may be performed)	
• To further characterize the immune response to a single study injection.	• Transcriptome analysis may be conducted to further evaluate immune responses. • Frequency, magnitude, and/or phenotype of vaccine-specific T-cell and B-cell responses by flow cytometry or other methods may be evaluated. • Frequency, specificities, or other endpoints to be determined for the further characterization of immune responses.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end-of-study; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; GMT = geometric mean titer; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; SAE = serious adverse event.

Table 5: Part A: Objectives and Endpoints: Cohort 2 (5 to <18 years)

Objectives Cohort 2	Endpoints Cohort 2
Primary	
• To evaluate the safety and reactogenicity of a single study injection.	• Solicited local and systemic ARs through 7 days postinjection. • Unsolicited AEs through 28 days postinjection. • MAAEs from Day 1 to Month 6/EoS Visit. • AESIs from Day 1 to Month 6/EoS Visit. • SAEs from Day 1 to Month 6/EoS Visit. • AEs leading to discontinuation from Day 1 to Month 6/EoS Visit.
Secondary	
• To evaluate the immunogenicity of a single study injection.	• GMT of serum RSV neutralizing antibody at Day 1 and Day 29. • GMC of serum RSV prefusion F binding antibody at Day 1 and Day 29. • GMFR of Postbaseline/Baseline neutralizing antibody titers and binding antibody concentrations at Day 29. • Percentage of participants with a seroresponse (defined as a postinjection titer >4-fold-rise if Baseline is >LLOQ or >4 × LLOQ if Baseline titer is <LLOQ) in the above immunogenicity measures.
Exploratory (may be performed)	
• To evaluate immune response biomarkers as potential correlates of protection or risk of RSV disease.	• Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; EoS = end-of-study; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; GMT = geometric mean titer; MAAE = medically attended adverse event; RSV = respiratory syncytial virus; SAE = serious adverse event

Part B: Objectives and Endpoints: Cohort 1 (2 to <5 years):

Objectives Cohort 1	Endpoints Cohort 1
Primary	
• To evaluate the incidence of RSV-RTD during 6 months after re-enrollment.	From Part B Day 1 to Part B EoS: • RSV-RTD • RSV-LRTD • Severe RSV-LRTD • Very severe RSV-LRTD • RSV hospitalization
Secondary	
• To evaluate the safety of a single study injection administered in Part A during 6 months after re-enrollment.	• AESIs from Part B Day 1 to EoS Visit. • SAEs from Part B Day 1 to EoS Visit.
Exploratory[a]	
• To evaluate the persistence of the immunogenicity of a single study injection administered in Part A.	• GMT of serum RSV neutralizing antibody at Part B Day 1. • GMC of serum RSV prefusion F and postfusion F binding antibody at Part B Day 1.
• To explore immune response biomarkers.	• Frequency, specificities, or other endpoints to be determined, for the further characterization of immune responses, including cell-mediated immunogenicity.

Abbreviations: AESI = adverse event of special interest; EoS = end-of-study; GMC = geometric mean concentration; GMT = geometric mean titer; LRTD = lower respiratory tract disease; RSV = respiratory syncytial virus; RSV-LRTD = respiratory syncytial virus— associated lower respiratory tract disease; RTD = respiratory tract disease; SAE = serious adverse event.

[a] Immunogenicity assessments and immune response biomarker testing are optional for participants in Part B.

Primary and secondary estimands are provided in Section 9.6 and Section 9.7, respectively.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, observer-blind, study to evaluate the safety, reactogenicity, and immunogenicity of a single injection of mRNA-1345 vaccine in approximately 160 participants 2 to <5 years of age (Cohort 1) and 180 participants 5 to <18 years of age (Cohort 2). The study will be conducted in 2 Parts.

Part A:

In Cohort 1, approximately 60 of the estimated 160 participants will be 2 to <3 years of age. In Cohort 2, approximately 90 of the estimated 180 participants will be 5 to <12 years of age, and approximately 90 participants will be 12 to <18 years of age. The study will enroll a total of approximately 340 participants.

For Part A, study details include:

- Potential participants will have a Screening Visit for the purpose of determining eligibility for the study (Section 5).
- Cohort 1: The Immunization Visit (Day 1) will occur within 28 days of Screening. The Screening Visit and the Day 1 Visit may also occur on the same day. Enrolled participants will be randomized (1:1:1:1) on Day 1 to receive a single injection of mRNA-1345 (CCI µg, CCI µg, or CCI µg) or placebo (normal saline), with approximately 40 participants in each study group. Randomization and enrollment will be stratified by age categories at Day 1 (40%/60%; 2 to <3 years old and 3 to <5 years old). Blood samples to assess immunogenicity will be taken at timepoints specified in the SoA (Table 1).
- Cohort 2: The Immunization Visit (Day 1) will occur within 28 days of Screening. The Screening Visit and the Day 1 Visit may also occur on the same day. Enrolled participants will be randomized on Day 1 to receive a single injection of mRNA-1345 (1:1:1 randomization; CCI µg, CCI µg, or CCI µg), with approximately 60 participants in each study group. Randomization and enrollment will be stratified by age categories (50%/50%; 5 to <12 years old and 12 to <18 years old). Blood samples to assess immunogenicity will be taken at timepoints specified in the SoA (Table 2).
- Subsequent sample collection and assessments will occur as per the SoA (Table 1 and Table 2).

Part B:

For Part B, all Cohort 1 participants (approximately 160) who were enrolled and dosed in Part A, will be offered to re-enroll into this safety follow-up study, in which surveillance for RSV disease will be conducted over a 6-month period. This will include the next RSV season in the US (approximately 01 Oct 2024 to 30 Apr 2025). RSV surveillance will be performed weekly during RSV season and monthly during RSV off season.

Part B of the study aims to provide surveillance for RSV disease for the next RSV season (6 months after re-enrollment) and safety follow-up for Cohort 1 participants that were enrolled and dosed in Part A.

Study details include:

- There will be no Screening Visit. The first visit will be the Part B Day 1, which is the day of re-enrollment of Cohort 1 participants into the study.
- No treatment will be administered to the participants in Part B of the study.
- There will be at least 1 in-person visit (Part B Day 1), weekly text messages during RSV season (from approximately 01 Oct 2024 to 30 Apr 2025), and 3 safety phone calls (Month 2, Month 4, and Month 6 [EoS]) as specified in the SoA. Additional unscheduled visits will occur if a participant experiences relevant RSV symptoms. Convalescent visits may occur after confirmed RSV-LRTD.
- Interim medical history: SAEs and AESIs that may have occurred subsequent to Part A EoS Visit/discontinuation until the time of signing the ICF for Part B will be collected.
- SAEs and AESIs will be collected from signing of the ICF for Part B through Month 6/EoS Visit.
- Subsequent sample collection and assessments will occur as per the SoA (Table 3)

Overall, the study will require up to 6 months of participation for each participant in Part A and up to an additional 6 months of participation for each participant in Part B.

The study will be conducted with the oversight of an unblinded IST (Section 10.1.6.1) and DSMB (Section 10.1.6.2 and pause rules will be implemented (Section 7.4). An independent CEAC will review all reported suspected cases of myocarditis, pericarditis, and myopericarditis (Section 8.4.10 and Section 10.6).

The study schema is included in Section 1.2. Study visits and assessments are defined in the SoA (Part A; Table 1 for Cohort 1 and Table 2 for Cohort 2: Part B; Table 3 for Cohort 1). The maximum planned volumes of blood sampled at each visit (as indicated in the SoA) are summarized in Table 8.

4.2. Scientific Rationale for Study Design

Most children have been infected with RSV at least once by 2 years of age (Glezen et al 1986) and the substantial burden of RSV disease in children above 2 years of age highlights that RSV infection-induced immunity is incomplete (Andeweg et al 2021, Nyiro et al 2017). There are no approved active vaccines against RSV for children at any age (Path.org. 2023). Given the unmet global medical need for a prophylactic vaccine among subpopulations that are particularly vulnerable to RSV, the Sponsor is developing the mRNA-1345 vaccine.

4.3. Justification for Dose

The proposed dose levels of mRNA-1345 to be evaluated in this Phase 2 study (CCI µg, CCI µg, or CCI µg in children aged 2 to <5 years and CCI µg, CCI µg, or CCI µg in children aged 5 to <18 years) are based on several data sources, including nonclinical and clinical studies of mRNA-1345, and nonclinical and clinical studies of other Sponsor mRNA-based vaccines formulated in the same SM-102–containing LNPs. The proposed mRNA-1345 dose levels in this study are within the

range for which nonclinical and clinical safety and immunogenicity data have shown a favorable benefit/risk profile.

The Sponsor is conducting a mRNA-1345 Phase 1 safety and immunogenicity study (mRNA-1345-P101) in RSV-seropositive children aged 12 to 59 months who receive 3 injections of CCI µg or CCI µg mRNA-1345; an interim analysis demonstrated that both dose levels were tolerated and induced RSV neutralizing antibodies. Further, mRNA-1345 CCI µg has shown to be well tolerated with no safety concerns identified and highly efficacious in an ongoing pivotal Phase 2/3 study in adults ≥60 years of age (Section 2.2). Therefore, it is reasonable to assume that for mRNA-1345 in children 2 to <5 years, a dose in the range of CCI µg to CCI µg (approximately half of the adult dose) can both provide adequate efficacy against RSV disease and demonstrate an acceptable safety and reactogenicity profile in this age group. For children 5 to <18 years of age, the adult dose (CCI µg) may be tolerable, but CCI µg may not be sufficient; therefore, a different dose range of CCI µg to CCI µg is tested in this age group, approximately one-third of the adult dose to the full adult dose.

Also supportive of the proposed mRNA-1345 dose range, the Sponsor's vaccine against COVID-19 (mRNA-1273) was tested in children from 6 months to 17 years of age and demonstrated that for children 2 to 5 years of age, a quarter (CCI µg) of the adult dose (CCI µg) elicited noninferior levels of neutralizing antibodies against SARS-CoV-2 when compared to adults 18 to 25 years of age, along with an acceptable safety profile (Anderson et al 2022). The same study also showed that CCI µg given as 2 doses was well tolerated in children 6 to 11 years of age. In a separate study, adolescents (12 to 17 years of age) received the same dose as adults (CCI µg), and this was well tolerated in this age group (Ali et al 2021).

Justification for Parallel Dosing Design:

In the Phase 1 study for mRNA-1345 (mRNA-1345-P101), schedules with 3 injections (Days 1, 56, and 112) of CCI µg or CCI µg were tested in RSV-seropositive children 12 to 59 months in a dose escalation manner, including a DSMB review of safety prior to escalating from CCI µg to CCI µg. Both dosage levels were well tolerated in this age group. There was no evidence of reactogenicity increasing with ascending number of injections, except for tenderness. The rates of any solicited ARs were comparable among participants receiving mRNA-1345 and placebo. Most solicited ARs were Grade 1 or Grade 2. Grade 3 local ARs were most frequently reported in participants in the mRNA-1345 CCI µg group; only two Grade 3 reactions were reported after Dose 1 (one event of irritability in the CCI µg group and one event of tenderness in the CCI µg group). A single participant in the CCI µg group reported a Grade 4 fever (>40ºC) as a solicited AR. No SAEs, AESIs, and no AEs leading to study discontinuation and no deaths have been reported to date (for more details, see the IB).

For Cohort 1 (2 to <5 years) in this study, a single injection of the same doses of mRNA-1345 (CCI µg and CCI µg) already assessed in P101 will be tested, in addition to one lower dose (CCI µg) and placebo. Given that the Phase 1 study evaluated 3 injections of CCI µg and CCI µg in an age group that included even younger children (12 to 59 months in mRNA-1345-P101 vs 2 to <5 years in Cohort 1 in this study), and these doses were generally well tolerated (78% to 80% of children remaining afebrile after the first dose), parallel dosing of single injections of CCI µg, CCI µg, and CCI µg doses is planned.

In Cohort 2 (5 to <18 years) in this study, a single injection of a similar dose range of mRNA-1345 will be tested (CCI µg, CCI µg, and CCI µg). The reactogenicity profile of CCI µg and CCI µg of mRNA-1345 is expected to be the same or more benign in this age range (5 to <18 years) compared to the younger age range already studied in mRNA-1345-P101 (12 to 59 months), based on previous experience with the Sponsor's mRNA-based COVID-19 vaccine (Spikevax™) where younger children had slightly higher fever rates at the same dosage levels as older children (Anderson et al 2022, Creech et al 2022).

TheCCI µg dose of mRNA-1345 has been tested in 19 young adults 18 to 49 years in Study mRNA-1345-P101 and in over 17,000 participants in the older adult efficacy Study mRNA-1345-P301. This dose showed a favorable reactogenicity profile in both studies (eg, 10.5% fever rate overall, 0% Grade 3 fevers in young adults 18 to 49 years; for more details, see the IB). In addition, as of 17 Jun 2023, it is estimated that more than 4 million children 5 to 11 years of age have received the CCI µg Primary Series of Spikevax worldwide.

Given the existing data on the CCI µg and CCI µg doses of mRNA-1345 in young children, the reassuring reactogenicity and safety profile of the CCI µg dose of mRNA-1345 in younger and older adults and the extensive experience of the CCI µg dose of Spikevax in 6 to 11 year old children, this study design incorporates parallel testing of all 3 doses of mRNA-1345 CCI µg, CCI µg, and CCI µg) in the older age group of 5 to <18-year-old children.

Of note, solicited adverse reaction reporting by participants via eDiaries and SAE reporting by the Investigators will be monitored by the Sponsor Medical Monitoring team in real-time as described in Section 7.4.

Justification for Use of Placebo in Cohort 1:

Cohort 1 of the study will be conducted as a randomized, placebo-controlled, observer-blinded study, with a randomization ratio of 1:1:1:1 for mRNA-1345 (CCI µg, CCI µg,CCI µg) or placebo. Children aged 2 to <5 years can have a higher incidence of apparent ARs (eg, fever) due to intermittent illnesses (Anderson et al 2022). More importantly, the use of placebo in this age group may help prevent overestimation of reactogenicity events by causes other than study treatment. In addition, RSV-F binding, RSV neutralizing antibody concentrations increase via natural infection in children 2 to <5 years of age. Including a placebo comparator group in this study may help determine additional benefit of immunization over natural infection. This is less of a concern in older children.

Justification for Additional Safety Follow-up and RSV Surveillance of Cohort 1 Through the Next RSV Season:

Cohort 1 includes children who may now be 2 to <5 years of age (inclusive), and this cohort was enrolled from Oct 2023 to Jan 2024. Children in this age group can be RSV-naïve and may not have gone through a full RSV season after receipt of mRNA-1345. In light of the important potential risk of ERD identified for 5- to 8-month-old children who received mRNA-1345 or mRNA-1365 (see Section 2.3.1), children enrolled in Cohort 1 should be monitored for the next RSV season (approximately 01 Oct 2024 to 30 Apr 2025) and assessed for any evidence of RSV-related LRTDs. This may help to further characterize the important potential risk of ERD in children 2 to 5 years of age.

4.4. EoS Definition

The Sponsor would expect the end of the study to be declared only once final analysis of study samples has been completed.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure at the final visit (EoS Visit) as shown in the SoA (Table 1, Table 2, and Table 3).

Participants who have reached EoS for Part A of Cohort 1 or were dosed and subsequently discontinued from Part A for various reasons will be re-enrolled into Part B if they opt to participate in Part B.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria (Part A: Cohort 1)

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

Age

1. 2 to <5 years of age at Day 1.

Type of Participant and Disease Characteristics

2. Healthy, or with stable chronic conditions increasing the risk of RSV disease, per the clinical judgment of the Investigator.

Relevant chronic conditions include:

a. Medically treated asthma.

b. Cystic fibrosis

c. Chronic respiratory diseases and malformations of the lung.

d. Trisomy 21.

e. Neuromuscular disease.

f. Cerebral palsy.

g. Hemodynamically significant or symptomatic congenital heart disease.

h. Sickle cell disease without the need for any blood transfusions in the 3 months prior to enrollment.

Informed Consent

3. Participant's parent(s)/LAR(s) has provided written informed consent for participation in this study.

5.1.2. Inclusion Criteria (Part A: Cohort 2)

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

Age

1. 5 to <18 years of age at Day 1.

Type of Participant and Disease Characteristics

2. Participants with stable chronic conditions increasing the risk of RSV disease. Participants must have one of the following relevant chronic conditions:

a. Medically treated asthma.

b. Cystic fibrosis.

c. Chronic respiratory diseases and malformations of the lung.

d. Trisomy 21.

e. Neuromuscular disease.

f. Cerebral palsy.

g. History of hemodynamically significant or symptomatic congenital heart disease (stable at Screening).

h. Sickle cell disease without the need for any blood transfusions in the 3 months prior to enrollment.

Sex and Contraceptive/Barrier Requirements

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

   a. Has a negative pregnancy test at the Screening Visit and on the day of injection (Day 1).

   b. Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to Day 1.

   c. Has agreed to continue adequate contraception through 90 days following injection. Adequate female contraception is defined as consistent and correct use of a local health authority approved contraceptive method in accordance with the product label (see Section 10.4).

   d. Is not currently breastfeeding.

Informed Consent

4. Participant's parent(s)/LAR(s) has provided written informed consent for participation in this study. Depending on local regulations, participants aged 16 years and over may self-consent.

Informed Assent

5. Verbal or written assent for study participation (according to local practice) or written assent for study participation (if not self-consenting).

5.1.3. Inclusion Criteria (Part B: Cohort 1 Re-enrollment)

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

1. Enrolled and dosed in Part A of Cohort 1; either reached EoS for Part A or were dosed and subsequently discontinued from study for various reasons. This includes participants who were lost to follow-up, if they can be re-engaged.
2. Participant's parent(s)/LAR(s) has provided written informed consent for participation in this study.

5.2. Exclusion Criteria

5.2.1. All Cohorts (Part A Only)

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

Medical Conditions

1. Acutely ill or febrile (temperature ≥38.0°C [100.4°F]) within 72 hours prior to or at the Screening Visit or Day 1. A participant meeting either of these criteria may be rescheduled for enrollment if the event resolves within the 28-day Screening window. See Section 5.3 for guidance on rescreening.
2. History of a diagnosis or condition that, in the judgment of the Investigator, may affect study assessment or compromise participant safety, specifically:
   a. Congenital or acquired immunodeficiency, including human immunodeficiency virus infection.
   b. Chronic hepatitis or suspected active hepatitis.
   c. Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy.
   d. Clinically significant thrombocytopenia.
   e. Dermatologic conditions that could affect local solicited AR assessments.
   f. History of allergic or anaphylactic reactions following a vaccination that required medical intervention.
   g. Active autoimmune disease treated with immunosuppressive therapy. (Note: hypothyroidism treated with thyroid hormone replacement and celiac disease treated with gluten avoidance are allowed.)
   h. History of myocarditis, pericarditis, or myopericarditis.
   i. Confirmed RSV infection within the last 3 months.
   j. Epilepsy (history of single febrile seizure allowed).

Prior/Concomitant Therapy

3. Has received or plans to receive any licensed or authorized vaccine ≤14 days prior to the study vaccine injection (Day 1) or plans to receive a licensed or authorized vaccine within 14 days after the study vaccine injection. Approved non-study vaccines included in the routine immunization schedule should not be delayed and, if received ≤14 days prior to Day 1, participants may be rescheduled for enrollment.
4. Receipt of:
   a. Any prior systemic immunosuppressants. Short courses (<7 days) of oral corticosteroids are allowed if completed at least 3 months prior to enrollment. Participants may be rescheduled for enrollment if they no longer meet this criterion within the Screening window. Inhaled, nasal, and topical steroids are allowed, as is topical tacrolimus.

b. Intravenous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment.

c. Receipt of RSV monoclonal antibodies within 6 months prior to enrollment in the study.

Prior/Concurrent Clinical Study Experience

5. Participated in an interventional clinical study within 28 days (6 months for a study assessing a product unlicensed/unauthorized in this age group in country of residence at time of enrollment) prior to the day of enrollment or plans to do so while enrolled in this study.

Other Exclusion Criteria

6. Has a family member or household contact who is an employee of the research center or otherwise involved with the conduct of the study.
7. A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government, or a government body, acting in accordance with powers conferred on them by laws and regulation (eg, foster care). Does not include a child who is adopted or has an appointed legal guardian.

5.2.2. Exclusion Criteria (Part B: Cohort 1 Re-enrollment)

1. Participant is currently enrolled in another interventional clinical study

5.3. Screen Failures

A screen failure occurs when a participant or participant's parent(s)/LAR(s) has consented to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once within the 28-day Screening window.

Rescreening may be performed outside the 28-day Screening period (eg, if study pause occurs [Section 7.4] or exclusion criteria are resolved). In this instance, a new participant number will be assigned.

5.4. Criteria for Temporarily Delaying Administration of Study Injection

Body temperature (axillary preferred) must be measured on the dosing visit before vaccine administration. The following events constitute criteria for delay of injection, and if any of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date at the discretion of the Investigator, but as soon as possible; or the participant may be discontinued from dosing at the discretion of the Investigator (Section 7.2):

- Acute moderate or severe infection with or without fever at the time of dosing.

- Fever, defined as body temperature ≥38.0°C/≥100.4°F within 72 hours prior to dosing.

Participants with a minor illness without fever, as assessed by the Investigator, can be vaccinated.

Participants with a fever of ≥38.0°C/≥100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the Investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled as soon as possible after the participant has recovered.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified, investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1. Study Intervention(s) Administered (Part A)

mRNA-1345 is comprised of a single mRNA sequence that encodes the RSV fusion glycoprotein stabilized in the prefusion conformation formulated in LNPs. mRNA-1345 will be administered IM as a single injection at either a CCI µg, CCI µg, CCI µg, or CCI µg dose. Normal saline (0.9% sodium chloride) will be used as placebo (Table 6).

Table 6: Study Intervention(s) Administered

Intervention Name	mRNA-1345	mRNA-1345	mRNA-1345	mRNA-1345	Placebo
Dose Level	CCI µg	CCI µg	CCI µg	CCI µg	0.9% sodium chloride
Dose Form	Injection	Injection	Injection	Injection	Injection
Route of Administration	IM	IM	IM	IM	IM

Abbreviations: IM = intramuscular; mRNA = messenger ribonucleic acid.

Study Intervention Packaging and Labeling:

The investigational products (mRNA-1345 and placebo) used in this study will be prepared, packaged, and labeled in accordance with the standard operating procedures of the Sponsor or those of its designee, CFR Title 21, Good Manufacturing Practice guidelines, ICH guidance for industry, GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

Note: No investigational product will be administered in Part B follow-up of Cohort 1.

6.2. Preparation, Handling, Storage, and Accountability (Part A)

The Investigator or designee must confirm appropriate conditions (eg, temperature) 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 study site staff may supply, prepare, 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 study site staff.

The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention (Part A)

In Cohort 1, approximately 160 participants will be randomized (1:1:1:1 ratio) to receive a single injection of mRNA-1345, CCI µg (N=40), CCI µg (N=40), CCI µg (N=40), or placebo (N=40). Randomization and enrollment will be stratified by age categories (40%/60%; 2 to <3 years old and 3 to <5 years old). Approximately 60 of the estimated 160 participants will be 2 to <3 years of age.

In Cohort 2, approximately 180 participants will be randomized (1:1:1 ratio) to receive a single injection of mRNA-1345, CCI µg (N=60), CCI µg (N=60), or CCI µg (N=60). Randomization and enrollment will be stratified by age categories (50%/50%; 5 to <12 years old and 12 to <18 years old).

6.4. Blinding

As the appearance of the study interventions may differ, enrollment will be observer blinded as to treatment assignment.

Dose preparation, administration, and accountability of study intervention will be performed by designated unblinded study site staff who will not participate in any of the clinical study evaluations and assessments of any study endpoints. They will not reveal the identity of the study intervention to either the participant, participant's parents(s)/LAR(s) or the blinded study site staff involved in the conduct of the study unless this information is necessary in the case of an emergency. The unblinded study site staff will prepare the study intervention out of view of the participant, the participant's parent(s)/LAR(s), and the blinded study site staff. The syringe used for administration will be masked to maintain the blind at the time of study intervention administration.

The laboratory personnel in charge of immunogenicity testing will be blinded to the treatment assignment of the samples tested throughout the course of the study.

Unblinded site monitors, not involved in other aspects of monitoring, will be assigned as the study intervention accountability monitors. They will have responsibilities to ensure that sites are following all proper study intervention accountability, preparation, and administration procedures.

Neither the participant, the participant's parent(s)/LAR(s) nor the Investigator nor study site staff responsible for study assessments/safety will have access to the treatment assignment during the conduct of the study.

6.4.1. Unblinding

This is a blinded study in which the Investigators are blinded to study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may contact the Sponsor to discuss the situation prior to unblinding a participant's intervention

assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.5. Study Intervention Compliance (Part A)

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

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention after the End of the Study

Continued access to the study intervention will not be available after the end of the study.

6.8. Treatment of Overdose (Part A)

As the study intervention is to be administered by a healthcare provider, it is unlikely that an overdose will occur.

Any dose of mRNA-1345 that is greater than the participant's assigned dose (Section 6.1) will be considered an overdose.

In the event of an overdose, the Investigator/treating physician should:

- Contact the Medical Monitor.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Document the quantity of the excess dose in source documents.

6.9. Prior and Concomitant Therapy

Medications administered within the period starting 28 days before the study intervention must be recorded in the eCRF.

Any medications (including any prescription or over-the-counter medications, vaccines, or blood products) that the participant is receiving at the time of enrollment or receives during the study must be recorded, with the exception of dietary supplements (eg, vitamins) and nonsteroidal topical therapy. Information regarding any prior history of mRNA vaccination will be documented.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Prohibited Therapy

There are no prohibited therapies other than those listed under the exclusion criteria for study participation (Section 5.2).

6.9.2. Concomitant Medications and Vaccines That May Lead to the Elimination of a Participant from the Per Protocol Analyses

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's evaluability in the PP analysis (analysis sets are described in Section 9.4):

- Any investigational or nonregistered product (drug or vaccine) other than the study intervention used during the study period.
- Immunosuppressants administered during the study period. Inhaled, nasal, and topical steroids are allowed.
- Immunoglobulins and/or any blood products administered during the study period.
- A vaccine not foreseen by the study protocol administered during the period from 14 days before through 14 days after the study injection.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.10.

7.1. Discontinuation of Study Intervention

Not applicable as participants will only receive 1 study injection.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant or participant's parent(s)/LAR(s) may withdraw themselves/the child from the study at any time by their own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an unscheduled visit should be conducted, as shown in the SoA (Table 1, Table 2, and Table 3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- A participant who withdraws from the study after enrollment will not be replaced.
- If the participant or participant's parent(s)/LAR(s) withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant or participant's parent(s)/LAR(s) may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

From an analysis perspective, a "withdrawal" from the study refers to a situation wherein a participant or participant's parent(s)/LAR(s) does not return with the participant for the final visit foreseen in the protocol. All data collected until the date of withdrawal or last contact of the participant will be used for the analysis. A participant is considered a "withdrawal" from the study when no study procedure has occurred, no follow-up has been performed, and no further information has been collected for that participant from the date of withdrawal or last contact.

Information relative to the withdrawal will be documented in EDC. The Investigator will document whether the decision to withdraw a participant from the study was made by a

participant or participant's parent(s)/LAR(s), or by the Investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Adverse event
- Death
- Lost to follow-up
- Noncompliance with study intervention
- Physician decision
- Protocol deviation
- Screen failure
- Study terminated by Sponsor
- Withdrawal by participant or participant's parent(s)/LAR(s)
- Withdrawal due to serious adverse reaction/reactogenicity
- Pregnancy
- Other

Participants who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow-up with participants or parent(s)/LAR(s) of participants who are withdrawn from the study because of an SAE or AE until resolution of the event.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant or participant's parent(s)/LAR(s) repeatedly fails to return with the participant for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant or participant's parent(s)/LAR(s) fails to return with the participant to the clinic for a required study visit:

- The site must attempt to contact the participant or participant's parent(s)/LAR(s) and reschedule the missed visit as soon as possible, counsel the participant or participant's parent(s)/LAR(s) on the importance of maintaining the assigned visit schedule and ascertain whether the participant or participant's parent(s)/LAR(s) wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant or participant's parent(s)/LAR(s) (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's parent[s]/LAR[s] last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant or participant's parent(s)/LAR(s) continue to be unreachable, the participant will be considered to have withdrawn from the study.
- A participant should not be considered lost to follow-up until due diligence has been completed.

7.4. Pause Rules

The study team (including Sponsor Medical Monitor and Sponsor Safety Physician) will receive an alert whenever a participant reports any Grade 3 or Grade 4 reactogenicity event in their eDiary, or the site enters an SAE or AESI in EDC. The Sponsor Medical Monitor and Safety Physician will review blinded Grade 3+ reactogenicity events, SAEs, and AESI weekly during active enrollment. In addition, the IST will review unblinded cumulative safety data including solicited adverse reactions at regularly scheduled intervals during active enrollment. An IST review will occur once after approximately 40 participants in Cohort 1, and once after approximately 40 participants in Cohort 2, are enrolled and have reached Day 8. The frequency of subsequent reviews will be determined by the IST.

Study pause rules, events, and thresholds are described in Table 7. The Investigators, study Medical Monitor, and Sponsor will monitor for events that could trigger a study pause.

Table 7: Pause Rules Assessed by the Investigator (Blinded Data)

Pause Rule	Event	Threshold for Triggering Study Pause
1	Any SAE that cannot be reasonably attributed to a cause other than study intervention.	≥1 participant
2	Any local or systemic solicited AR that leads to hospitalization that cannot be reasonably attributed to a cause other than study intervention.	≥1 participant
3	Any case of myocarditis/pericarditis that cannot be reasonably attributed to a cause other than study intervention.	≥1 participant

Abbreviations: AR = adverse reaction; SAE = serious adverse event.

Any safety concerns raised by the IST following safety reviews (or throughout the study) will be referred to the DSMB. If a potential pause rule trigger occurs, it will initially be reviewed by the IST, and if confirmed as meeting criteria for a pause rule, it will be referred to the DSMB. If any of the thresholds for a study pause are met, the Sponsor will immediately suspend further enrollment and/or study dosing in the affected cohort, and younger cohorts, by notifying all Investigators.

The Investigator or designee is responsible for reporting to the Sponsor each event that potentially meets any pause rule criterion within 24 hours of observation. If an SAE assessed as related to study intervention by the Investigator is reported at any point, the Sponsor's Medical Monitor is responsible for a rapid assessment of whether the pause rule for SAEs has been met; the Sponsor's medical personnel may consult with the IST to make that determination, as described in the IST charter. The Sponsor will inform the IST of any event that meets any pause rule criterion. The IST will review all relevant available study data to help adjudicate such events and if it determines a pause rule has been met, the Sponsor will inform the DSMB. The Sponsor

will notify the appropriate health authority within 48 hours in the event of a study pause. If study pause occurs during a participant's Screening period such that the 28-day Screening period window is exceeded, the participant may be rescreened for study eligibility as long as the participant or participant's parent(s)/LAR(s) continues to provide consent to participate in the study.

If any of the study pause rules are met and the IST requests that the study be paused due to a safety concern, further study vaccination will be suspended, but all other planned procedures relating to safety, reactogenicity, and immunogenicity assessments will continue as described in the SoA (Table 1 and Table 2).

Should recruitment and further dosing be paused pending an IST or DSMB review following triggering of the predefined pause requirements, this will not be considered a halt to the study and would not necessitate a substantial amendment to either stop or resume recruitment.

If, after this safety review, the IST or DSMB advises that further recruitment/dosing should remain paused, then the study will be temporarily halted, and the regulatory authorities will be notified of a study pause according to local requirements. In this instance, recruitment/dosing will only be resumed once the DSMB approves a resumption of recruitment/dosing and any required appropriate regulatory approvals for this resumption amendment have been obtained.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1, Table 2, and Table 3).
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- 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.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed blood limits specified by local regulations.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Further details are provided in both the ICF and Laboratory Reference Manual.

The approximate amount of blood by study visit is summarized in Table 8.

Table 8: Maximum Planned Blood Sampling Volumes per Participant by Visit

	Collection Timepoints	Blood for Serum (Prioritized)	Blood for PBMC[a] (if Volume for Serum is Achieved at the Visit)	Total Blood Collection
Cohort 1 (2 to <5 years)	Part A: Day 1[b], Day 29, and M6/EoS Visit	Approximately 5 mL	Approximately 8 mL	Approximately 13 mL
	Part B: Day 1 (optional)	Approximately 5 mL	N/A	Approximately 5 mL
	Part B: Convalescent Visit (optional)	N/A	Approximately 8 mL [Plasma to be used for antibody testing]	Approximately 8 mL
	Total per participant over course of study	Up to 20 mL	Up to 32 mL	Up to 52 mL
Cohort 2 (5 to <12 years)	Day 1[b] and Day 29	Approximately 8 mL	N/A	Approximately 16 mL
Cohort 2 (12 to <18 years)	Day 1 (Baseline for banking)[c]	Approximately 4 mL	N/A	Approximately 4 mL
	Day 1[b] and Day 29	Approximately 12 mL	N/A	Approximately 24 mL
	Total over course of study	Approximately 16 mL	N/A	Approximately 28 mL

Abbreviations: AE= adverse event; EoS = end-of-study; M = month; N/A = not applicable; PBMC = peripheral blood mononuclear cell

a. Blood for PBMC will be collected from a subset of participants at selected study sites for participants enrolled in Part A for Cohort 1 only; optional for all participants in Cohort 1 Part B.
b. Prior to study intervention (ie, Baseline blood sample).
c. Baseline serum for storage only; may be used for Baseline testing of cardiac markers in case of cardiac AE occurring later in the study.

8.1. Demography

Demographic information relating to the participant's sex, age, ethnicity, and race will be recorded at Screening in EDC.

Medical history of each participant will be collected and recorded in EDC. Significant findings that were present prior to the signature of the informed consent will also be included in EDC.

8.2. Efficacy and Immunogenicity Assessments

Planned timepoints for all immunogenicity assessments are provided in the SoA (Table 1, Table 2, and Table 3).

Efficacy will not be evaluated in this study.

8.3. Safety Assessments

Safety assessments will include monitoring and recording of the following for each participant; according to the SoA (Table 1, Table 2, and Table 3).

Part A:

- Solicited local and systemic ARs that occur immediately after and during the 7 days following the study injection (ie, the day of injection and 6 subsequent days).
- Unsolicited AEs observed or reported during the 28 days following the study injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are AEs that are not included in the protocol defined solicited ARs.
- AEs leading to discontinuation from study participation from Day 1 through Month 6/EoS Visit.
- MAAEs from Day 1 through Month 6/EoS Visit .
- SAEs from signing of the ICF through Month 6/EoS Visit for Part A.
- AESIs from Day 1 through Month 6/EoS Visit.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medications and non-study vaccinations.
- ECG (participants aged 12 to <18 years and participants with CHD without an ECG within 6 months prior to Screening; for storage of baseline comparison in case of future cardiac event only).

Part B:

- For participants from Cohort 1 Part A who are re-enrolled into Cohort 1 Part B, any SAEs or AESIs that occurred subsequent to Part A EoS Visit/discontinuation until the time of signing the ICF for Part B (re-enrollment date) should be reported on the interim medical history page for the respective participant.
- SAEs from signing of the ICF through EoS Visit.
- AESIs from signing of the ICF through EoS Visit.

  Note: A healthcare encounter form should be completed for all RSV-related SAEs and AESIs in Part B.
- Vital sign measurements.
- Physical examination findings.
- Concomitant medication and non-study vaccinations.

The AESIs that will be monitored are listed in Table 13 in Appendix 5.

8.3.1. Safety Phone Calls

A safety phone call is a telephone call made to the participant or participant's parent(s)/LAR(s) by trained site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety phone calls will follow a schedule for each participant, as shown in the SoA (Table 1, Table 2, and Table 3). The participant or participant's parent(s)/LAR(s) will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESIs, AEs leading to discontinuation from study participation, concomitant medications associated with those events, and any non-study vaccinations. All safety information collected from the phone call must be documented in the source documents as described by the participant or participant's parent(s)/LAR(s) and not documented on the script used for the phone call. An unscheduled follow-up safety phone call may be triggered if an eDiary record results in identification of a relevant safety event. A safety phone call may trigger an unscheduled visit.

8.3.2. Use of Electronic Diaries

At the time of consent, the participant or participant's parent(s)/LAR(s) must confirm they will be willing to complete an eDiary (for 7-day reactogenicity). The local and systemic ARs that will be solicited by the eDiary are described in Table 12 for participants 2 to <18 years of age.

Solicited local and systemic reactogenicity ARs will be collected on the day of the study injection and during the 7 days after study injection (ie, the day of dosing and 6 subsequent days). Details on the recording of local and systemic ARs are included in Section 8.4.6.

At the dosing visit, the participant or participant's parent(s)/LAR(s) will record data into the eDiary starting approximately 30 minutes after dosing under supervision of the study site staff to ensure successful entry of assessments. The 30-minute observation period is an opportunity for study site staff to train the participant or participant's parent(s)/LAR(s) on eDiary completion requirements. The study site staff will perform any retraining as necessary.

At the dosing visit, the participant or participant's parent(s)/LAR(s) will be instructed on thermometer usage to measure body temperature, ruler usage to measure injection site erythema (redness) and swelling/induration (hardness), and self-assessment for localized axillary (underarm) swelling or tenderness ipsilateral (on the same) side as the injection arm(s) during the 7 days after study injection(s). Daily axillary temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site staff.

The participant or participant's parent(s)/LAR(s) will be trained on how to complete the eDiary questions according to the SoA (Table 1 and Table 2).

The study site staff will review eDiary data with the participant or participant's parent(s)/LAR(s) as indicated in the SoA (Table 1 and Table 2).

8.3.3. Physical Examinations

Physical examinations will be performed at the timepoints indicated in the SoA (Table 1, Table 2, and Table 3).

- A complete physical examination will be performed at the Screening Visit (Part A) and Re-enrollment Visit (Part B) and will include, at a minimum, assessments of the skin, lungs, heart, abdomen, lymph nodes, and musculoskeletal system/extremities,

with further examination (eg, head, ears, eyes, nose, throat, neck) as directed by the medical history. Height and weight will also be measured and recorded.

- A symptom-directed physical examination will be performed at in-person visits after the Screening Visit, at the discretion of the Investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- On the day of study intervention administration, before administration, the arm(s) receiving the injection(s) should be examined and the associated lymph node(s) should be evaluated.
- During Unscheduled Visits for RSV surveillance, respiratory auscultation and assessment of signs of respiratory distress (eg, wheezing, lower chest wall in-drawing) and assessment of hydration status and mental status will be performed.

8.3.4. Vital Signs

Vital signs will be measured at the timepoints indicated in the SoA (Table 1, Table 2, and Table 3). On the study injection days, axillary temperature, pulse rate, respiratory rate, and blood pressure will be recorded before the study vaccine injection. If vital signs are clinically concerning, participant should not be dosed. When applicable, vital sign measurements should be performed before blood collection. Postinjection vital signs should only be obtained if the participant is showing concerning signs or symptoms (eg, signs of anaphylaxis). At subsequent scheduled visits, vital signs should only be obtained if necessary for the evaluation of an AE.

Febrile participants on the study injection day (fever is defined as a body temperature ≥38.0°C/100.4°F within 72 hours prior to dosing) may be rescheduled within the relevant window period. Criteria for delay of study vaccine are provided in Section 5.4.

An abnormal vital sign measurement should be assessed to determine if it meets AE reporting criteria per protocol and reported as an AE in EDC, if appropriate. The Investigator will continue to monitor the participant with additional assessments until the vital sign value has reached the reference range, returns to the vital sign value at Baseline, is considered stable, or until the Investigator determines that follow-up is no longer medically necessary.

During unscheduled visits for RSV surveillance, the following vital signs will be recorded for every visit: temperature, respiratory rate, heart rate, oxygen saturation (SpO_2).

8.3.5. Electrocardiogram (Part A Only)

A Baseline 12-lead ECG will be obtained at Screening (prior to study injection on Day 1) for participants aged 12 to <18 years in Cohort 2 after 10 minutes of supine rest. The purpose of the ECG is to serve as a stored baseline comparison, should it be necessary, for subsequent clinical evaluation if a case of suspected myocarditis/pericarditis occurs within the study. The ECG output should be filed in the participant's binder, and the Investigator will not be expected to document an ECG reading. Central reading of the ECG will also not be performed. Abnormal ECG findings, if incidentally observed by the Investigator, may contribute to the Investigator's assessment of eligibility at their discretion, as per the general Exclusion Criterion 2.

For all cohorts, participants with CHD must have a Baseline ECG performed if one is not available within 6 months prior to Screening.

8.3.6. Pregnancy Testing (Part A Only)

Refer to Section 5.1.2 (Inclusion Criteria [Cohort 2]) for the pregnancy testing entry criteria.

Additional serum or urine pregnancy tests also be performed if required by local regulatory requirements.

8.3.7. Surveillance for RSV

To timely detect and capture RSV-RTD cases by study sites all children 2 to <5 years of age who were enrolled and dosed in Part A of Cohort 1 and opted for re-enrollment in Part B will be closely monitored for respiratory illnesses, by RSV surveillance, from Part B Day 1 until Part B EoS.

RSV Surveillance: Parent(s)/LAR(s) will be instructed to contact the Investigator/study site staff when the participant experiences new RTD symptoms defined as congestion or runny nose for >24 hours, cough, difficulty breathing, or respiratory distress, including wheezing; or worsening of RTD symptom(s); or in case of difficulty in breathing or wheezing, as soon as possible. Parent(s)/LAR(s) of all the participants will be contacted by the Investigator/study staff weekly via text message during the RSV season to remind them to report any new or worsening of RTD symptoms.

The Investigator/study site staff will contact the participant's parent(s)/LAR(s) within the next working day of being alerted of a participant's symptoms and schedule an RSV surveillance visit within 5 days of onset of RSV-RTD symptoms, if presence of qualifying RSV-RTD symptoms is confirmed.

- All RSV surveillance contacts will be documented in the source.
- All conversations between the participant's parent(s)/LAR(s) and study site staff regarding a report of RSV-RTD symptom(s) should be documented in the source.

Unscheduled Visit for RSV Surveillance: The purpose of the unscheduled visit for RSV surveillance is to objectively document signs and symptoms by an appropriately qualified person (ie, physician or nurse) and take a nasal and/or nasopharyngeal swab for detection of RSV infection.

- RSV surveillance visits may take place in the participant's home or other locations, where approved by local regulations, the Investigators clinical facility, or a medical facility, as appropriate to the circumstances in the judgment of the Investigator.
- If the reported symptoms are already of a level of severity that urgent care is indicated, the parent(s)/LAR(s) should be redirected to the proper location with the participant to receive this care (eg, urgent care or emergency department), and an RSV surveillance visit could be scheduled to take place at urgent care visit or emergency care department at a suitable time, if feasible.
- During the RSV surveillance visit, the Investigator/study site staff will evaluate clinical symptoms (eg, congestion, cough, runny nose, difficulty breathing).

Examination will include, at a minimum, body temperature, respiratory rate, heart rate, blood oxygen saturation, respiratory auscultation, and assessment of signs of respiratory distress (eg, wheezing, lower chest wall in-drawing, mental status). Signs and symptoms to be recorded in the eCRF.

- A nasal or nasopharyngeal swab will be taken for testing of RSV (and/or other viruses, per local practice) at a local routine laboratory for participants who have symptoms of RTD, when available.
- A nasal swab will be collected for analysis to be performed at the Sponsor-designated laboratory for all participants who have symptoms of an RTD.
- Parent(s)/LAR(s) will be instructed to contact the study site staff if the severity of the already-existing symptoms increases or if the participant develops difficulty in breathing or wheezing, and this may lead to a repeat RSV surveillance visit upon the judgment of the Investigator. If possible, additional nasal samples should be collected within 5 days of worsening RTD symptoms.
- During subsequent surveillance contacts after an RSV surveillance visit, the status and evolution of the case will be followed until case resolution.
- Each RSV surveillance visit will be recorded in eCRF.
- If presence of RSV-LRTD (of any severity) or RSV hospitalization is confirmed and the parent(s)/LAR(s) agree to the optional Convalescent Visit, a blood sample for exploratory CMI and antibody assessment will be drawn 3 to 24 days after the initial unscheduled visit or from date of hospitalization, whichever occurred earlier.

Every effort should be made to collect swab samples within 5 days of RTD symptom onset (or of symptom worsening). However, if this is not possible, then swab samples may still be collected at the discretion of the Investigator up to10 days after symptom onset and this would not be considered a protocol deviation.

For any respiratory symptoms, if the caregiver is concerned regarding the child's health (eg, with difficulty breathing or respiratory distress) they should be advised to contact the emergency services before contacting the study site.

Case Definition

All cases identified during the surveillance of RSV-RTD will be definitively classified as either RTD, LRTD, severe LRTD, very severe LRTD, or hospitalization according to the modified case definitions based on the available WHO case definitions for RSV. Case definitions are presented in Table 9. Classification will be made by the Clinical Assessment Team of the Sponsor.

Table 9: Case Definitions for RSV for Data Analysis

RSV-RTD	Runny nose **OR** blocked nose **OR** cough AND Confirmed RSV infection[a]
RSV-LRTD	Cough **OR** difficulty breathing[b] AND SpO_2 <95%[c], **OR** RR increase[d] AND Confirmed RSV infection[a]
RSV Severe-LRTD	Meeting the case definition of RSV-LRTD AND SpO_2 <93%[c], **OR** lower chest wall in-drawing
RSV Very Severe LRTD	Meeting the case definition of RSV-LRTD AND SpO_2 <90%[c], **OR** failure to respond/unconscious
RSV Hospitalization	Confirmed RSV[a,e] AND Hospitalized for acute medical condition[f]
For each of 'RSV-RTD,' 'RSV-LRTD,' 'RSV severe-LRTD,' and 'RSV very severe LRTD,' an additional category of 'Medically attended RSV-RTD (MA-RSV-RTD), MA-RSV-LRTD,' etc, will be created to include the subset of participants that meet these definitions that attended a health care consultation.	

Abbreviations: BPM = beats per minute; LRTD = lower respiratory tract disease; RT-PCR = reverse transcription polymerase chain reaction; RR = respiratory rate; RSV = respiratory syncytial virus; RTD = respiratory tract disease; SpO_2 = blood oxygen saturation.

a. RSV infection confirmed on nasal swab positive by positive RT-PCR or other local laboratory tests.
b. Based on observation by Investigator; difficulty breathing includes signs of wheezing, stridor, tachypnoea, chest in-drawing or subcostal or intercostal retractions.
c. For SpO2, the lowest stable value monitored will be used.
d. RR increased defined as >38 BPM for 2- to <3-year-olds, >33 BPM for -3 to <4-year-olds, and >29 BPM for ≥4-year-olds per 99th percentiles for age (Fleming et al 2011).
e. RSV sampling and testing is based on medical judgment of medical practitioner or driven by algorithm.
f. Hospitalization is defined as a medical decision in which the participant requires overnight admission for observation or treatment.

8.4. AEs, SAEs, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

The definitions of unsolicited and solicited AEs can be found in Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (Section 7). This includes events reported by the participant or participant's parent(s)/LAR(s).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period and frequency for collecting AEs and SAEs is provided in the SoA (Table 1, Table 2, and Table 3) and Section 8.3.Nonserious medical occurrences that begin before the start of the study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs; however, if the condition worsens at any time after the study intervention, it will be recorded and reported as an AE.

All SAEs occurring after signing the ICF will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

For participants from Cohort 1 Part A who are re-enrolled into Cohort 1 Part B, any SAEs or AESIs that occurred between EoS for Part A and signing of ICF for Part B (re-enrollment date) should be reported on the interim medical history page for the respective participant.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE or death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant or participant's parent(s)/LAR(s) is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE, including those considered to be a SUSAR, is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators. For example, for reports that are required to be submitted to the EU, individual case

safety reports, will be submitted via the EudraVigilance Clinical Trials Module Gateway.

- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- For expedited reporting purposes, the expectedness of SAEs will be assessed against the investigational treatment regimen the participant is receiving at the time of the event. AE terms not listed as expected events in the IB will be considered unexpected.
- Investigator safety reports must be prepared for SUSARs and undergo expedited reporting according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.4.5. Pregnancy

- Details of all pregnancies in female participants will be collected through 90 days after the last study intervention is administered.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE (refer to Section 10.3).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such (refer to Section 10.3).
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Solicited Adverse Reactions

Solicited ARs are a subset of AEs consisting of selected signs and symptoms that the participant or participant's parent(s)/LAR(s) are asked to record/report. In this study, the solicited ARs are reactogenicity events. The term "reactogenicity" refers to the occurrence of transient adverse effects associated with vaccine administration. The eDiary will solicit daily participant/participant's parent(s)/LAR(s) reporting of ARs using a structured checklist. The participant or participant's parent(s)/LAR(s) will record such occurrences in the eDiary on the day of the study vaccine injection and 6 subsequent days.

Severity grading of reactogenicity will occur automatically based on the participant or participant parent(s)/LAR(s) entry into the eDiary according to the grading scales presented in Appendix 3, which are modified from the Toxicity Grading Scales for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007). All solicited ARs (local and systemic) will be considered causally related to dosing.

If a participant or participant's parent(s)/LAR(s) reports a solicited AR with onset during the solicited period, but they did not record the event in the eDiary, then the event should be recorded by study site staff in EDC.

If the event starts during the solicited period, but continues beyond 7 days after dosing, the participant or participant's parent(s)/LAR(s) should notify the site to provide an end date and close out the event in EDC.

If the participant or participant's parent(s)/LAR(s) reported an event that started after the solicited period (ie, beyond 7 days after dosing), it should be recorded as an AE in EDC. Causality for these events will be determined per assessment by the Investigator.

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff in EDC:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (MAAE).
- Solicited local or systemic AR leading to the participant being withdrawn from the study by the participant or participant's parent(s)/LAR(s) or the participant being withdrawn from the study by the Investigator (AE leading to discontinuation).
- Solicited local or systemic AR lasting beyond 7 days postinjection.
- Solicited local or systemic AR that leads to participant discontinuation from study.
- Solicited local or systemic AR that otherwise meets the definition of an SAE.

8.4.7. Medically Attended Adverse Events (Part A Only)

A MAAE is an AE that leads to an unscheduled visit to a healthcare practitioner. This would include visits to a study site for unscheduled assessments (eg, rash assessment, abnormal laboratory follow-up) and visits to healthcare practitioners external to the study site (eg, emergency room, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAEs. Unsolicited AEs will be captured in EDC.

8.4.8. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor are required. Such events may require further investigation to characterize and understand them.

AESI for this protocol are listed in Appendix 5.

Investigators should report all events which fall into the following categories as an AESI per the reporting processes specified in Appendix 3 (Reporting of SAEs).

8.4.9. Anaphylaxis

All suspected cases of anaphylaxis associated with study intervention administration should be recorded as an AESI and reported as an SAE (Appendix 3 [Reporting of SAEs]), based on criteria for a medically important event, unless the event meets other serious criteria. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity reaction with multiorgan system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involving 2 or more organ systems, as follows:
  - **Skin/mucosal:** urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes.
  - **Cardiovascular:** measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation.
  - **Respiratory:** bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea.
  - **Gastrointestinal:** diarrhea, abdominal pain, nausea, vomiting.

8.4.10. Myocarditis and/or Pericarditis

A case of suspected, probable, or confirmed myocarditis, pericarditis, or myopericarditis should be reported as an AESI, even if it does not meet criteria per the CDC case definition. The event should also be reported as an SAE if it meets seriousness criteria (Section 10.3.2). Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings.

An independent CEAC will review all suspected cases of myocarditis, pericarditis, and myopericarditis, which are reported in ongoing interventional clinical studies per the CEAC charter, to determine if they meet CDC criteria for “probable” or “confirmed” events (Section 10.6).

The CDC Working Case Definitions are provided in Appendix 6 as guidance.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genomics are not evaluated in this study.

8.8. Biomarkers

A blood sample for storage and potential future cardiac biomarker testing will be collected from participants aged 12 to <18 years of age in Cohort 2 at Baseline according to the schedule described in the SoA (Table 2) and as detailed in the Laboratory Manual provided separately to the sites. The Sponsor may store samples for the time period specified in the ICF to achieve study objectives. These samples would only need to be tested in case of a future cardiac AE and serve as a baseline comparison.

8.9. Immunogenicity Assessments

Immunogenicity assessments will include the following:

- RSV-A and RSV-B neutralizing antibody as measured by microneutralization assay.
- RSV prefusion binding antibody measurements.

Exploratory assays to further characterize the immune response to mRNA-1345, or infection with RSV or other respiratory viruses, may be performed and may include the following:

- CMI assessments in a subset of participants at selected study sites in Cohort 1, Part A only; optional at all sites in Part B.
- System serology, humoral immunity profiling, and antibody effector function assessment may be performed.

Sample aliquots will be designed to ensure that backup samples are available and vial volumes are likely to be adequate for future testing needs. The actual date and time of each sample will be noted. Unique sample identification will be utilized to maintain the blind at the laboratory at all times and allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate Laboratory Manual.

Measurement of antibody levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 10.1.3), biological samples from blood collected for cellular and antibody immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to study vaccines and/or other respiratory viruses and to support assay development.

8.10. Health Economics

Health economics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of the statistical analyses will be provided in the SAP, which will be finalized before the clinical database lock for the study and treatment unblinding. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary objectives/hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or CSR for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

9.1. Blinding and Responsibility for Analyses

This is an observer-blind study. The Investigator, study site staff, study participants, participant's parent(s)/LAR(s), site monitors, and Sponsor personnel (or its designees) will be blinded to the study intervention administered until the study database is locked and unblinded, with the following exceptions:

- An independent unblinded statistical and programming team will perform the preplanned IA (Section 9.8.1).
- An IST with prespecified Sponsor subject matter experts not involved in other aspects of the study/monitoring will review unblinded cumulative safety data at prespecified frequency as outlined in the IST charter. The IST members will not communicate the results to the blinded Investigators, study site staff, clinical monitors, or participant's parent(s)/LAR(s). Section 10.1.6.1 and the IST charter provide additional information on IST and safety review. Roles and responsibilities will be clearly outlined in the IST charter.
- The DSMB will also review unblinded statistical outputs for ad hoc safety reviews triggered by pause rules, should this occur, or other safety concerns raised by the IST. Section 10.1.6.1 and the DSMB charter provide additional information on DSMB and safety review. Roles and responsibilities will be clearly outlined in the DSMB charter.

9.2. Statistical Hypothesis

There is no formal statistical hypothesis testing planned for the study. All statistical analyses will be descriptive in nature.

9.3. Sample Size Determination

As shown in Table 10, a sample size of 60 or 40 participants in each study group has approximately 95% or 87% probability, respectively, to observe at least 1 participant with an AE given the true underlying incidence rate of 5%, which should allow for a preliminary assessment of the reactogenicity profile for each dose level.

Placebo is used in Cohort 1, but not for Cohort 2 due the likely higher background rate of serious ARs expected to be reported for the youngest age group (based on experience with the Sponsor's COVID-19 vaccines; Anderson et al 2022), which could confound tolerability assessment.

Table 10: Probability of AEs Based on Sample Size

Sample Size Per Group (n)	True AE Rate	Probability of at Least 1 AE Observed
60	2%	70%
60	3%	84%
60	4%	91%
60	5%	95%
60	10%	>99%
40	2%	55%
40	3%	70%
40	4%	80%
40	5%	87%
40	10%	99%

Abbreviations: AE = adverse event; n = number of participants

9.4. Analysis Sets

The analysis sets are presented in Table 11.

Table 11: Analysis Sets

Analysis Sets	Description
Randomization Set	All participants who are randomized in the study, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All participants who are randomly assigned and receive the study injection and have a Baseline and at least 1 postinjection antibody assessment. Participants will be analyzed according to the group to which they are randomized.
Per Protocol (PP) Set	All participants in the FAS who receive the planned dose of the study intervention, comply with the immunogenicity testing schedule, have a Baseline and Day 29 assessment, and have no important protocol deviations that affect the immune response. The PP Set will be used as the primary analysis set for analyses of immunogenicity unless otherwise specified. Participants will be analyzed according to the group to which they are randomized.
Safety Set	All participants who are randomly assigned and receive the study intervention. The Safety Set will be used for all analyses of safety, except for the solicited ARs. Participants will be included in the group corresponding to what they actually received.

Analysis Sets	Description
Solicited Safety Set	All participants in the Safety Set who contribute any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs, and participants will be included in the group corresponding to what they actually received.

Abbreviations: AR = adverse reaction; RSV = respiratory syncytial virus; RT-PCR = reverse transcription polymerase chain reaction

9.5. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the preplanned statistical analysis details/data derivations, the participant populations to be included in the analyses, and procedures for accounting for missing and/or unused data.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Immunogenicity Analyses (Part A)

The primary immunogenicity analysis will be performed using the PP Set. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

All the immunogenicity analyses will be provided by treatment group and by cohort, unless otherwise specified.

For the serum RSV neutralizing antibody titers, GMT with corresponding 95% CI will be provided at each timepoint by treatment group and by cohort.

For the serum RSV binding antibody concentrations, GMC with corresponding 95% CI will be provided at each timepoint by treatment group and by cohort.

GMFR and corresponding 95% CI of RSV neutralizing and binding antibody titers at each individual postinjection timepoint over preinjection (eg, Baseline) will be provided at each Postbaseline timepoint by treatment group and by cohort.

The number and percentage of participants with a seroresponse will be provided with a 2-sided 95% CI using the Clopper-Pearson method at each Postbaseline timepoint by treatment group and by cohort.

9.5.2. Efficacy Analyses

Not applicable for this study.

9.5.3. Safety Analyses

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety set. All safety analyses will be provided by treatment group and by cohort unless otherwise specified.

Part A:

Safety and reactogenicity will be assessed by clinical review of all relevant parameters, including solicited ARs (local and systemic ARs), unsolicited AEs (including any clinical safety laboratory abnormalities), treatment-related AEs, severe AEs, SAEs, MAAEs, AEs leading to discontinuation from study participation, AESIs, vital sign measurements, and physical examination findings.

The number and percentage of participants with any solicited local AR or solicited systemic AR during the 7-day follow-up period after the study injection will be summarized. A 2-sided 95% CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, treatment-related AEs, severe AEs, SAEs, AESIs, MAAEs, and AEs leading to discontinuation from study participation will be summarized.

Solicited ARs will be coded according to the MedDRA for AR terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials modified for participants 2 to <18 years of age will be used in this study (DHHS 2007). Unsolicited AEs will be coded according to the MedDRA and presented by MedDRA system organ class and preferred term.

The number of events of unsolicited AEs/SAEs, AESIs, MAAEs, and AEs leading to discontinuation will be reported in summary tables accordingly.

Part B:

The number and percentage of participants with RSV-RTD, RSV-LRTD, RSV severe-LRTD, RSV very severe LRTD, RSV hospitalization, MA-RSV-RTD, MA-RSV-LRTD, MA-RSV severe-LRTD, and MA-RSV very severe LRTD from Part B Day 1 to Part B EoS will be summarized by treatment group and by cohort.

The primary analysis of the above RSV case classification summary will be based on the assessment results from Clinical Assessment Team of the Sponsor.

The number and percentage of participants with, and the number of events of, SAEs and AESIs will be summarized. For all other safety parameters, descriptive summary statistics will be provided. Further details will be described in the SAP.

9.5.4. Exploratory Analyses

Exploratory analyses will be described in the SAP as appropriate.

9.6. Primary Estimand(s)

Part A: Cohort 1 and Cohort 2:

- The number and percentage of participants with any solicited local AR or solicited systemic AR during the 7-day follow-up period after the study injection.
- The number and percentage of participants with unsolicited AEs through 28 days after the study injection.

- The number and percentage of participants with MAAEs from Day 1 to Month 6/EoS Visit.
- The number and percentage of participants with AESIs from Day 1 to Month 6/EoS Visit.
- The number and percentage of participants with SAEs from Day 1 to Month 6/EoS Visit.
- The number and percentage of participants with AEs leading to discontinuation from Day 1 to Month 6/EoS Visit.

Part B: Cohort 1

- RSV-RTD, RSV-LRTD, severe RSV-LRTD, RSV very severe LRTD, and RSV hospitalization.

9.7. Secondary Estimand(s)

Part A:

Cohort 1:

- GMT of serum RSV neutralizing antibody at Day 1, Day 29, and Month 6/EoS Visit.
- GMC of serum RSV prefusion F binding antibody at Day 1, Day 29, and Month 6/EoS Visit.
- GMFR of Postbaseline/Baseline neutralizing antibody titers and binding antibody concentrations at Day 29 and Month 6/EoS Visit.
- Seroresponse rates (percentage of participants) at Day 29 and Month 6/EoS Visit in the above immunogenicity measures. Seroresponse rate is defined as a postinjection titer >4-fold-rise if Baseline is >LLOQ or >4 × LLOQ if Baseline titer is <LLOQ.

Cohort 2:

- GMT of serum RSV neutralizing antibody at Day 1 and Day 29.
- GMC of serum RSV prefusion F binding antibody at Day 1 and Day 29.
- GMFR of Postbaseline/Baseline neutralizing antibody titers and binding antibody concentrations at Day 29.
- Seroresponse rates (percentage of participants) at Day 29 in the above immunogenicity measures. Seroresponse rate is defined as a postinjection titer >4-fold-rise if Baseline is >LLOQ or >4 × LLOQ if Baseline titer is <LLOQ.

Part B: Cohort 1

- The number and percentage of participants with AESIs from Part B Day 1 to Part B EoS Visit.
- The number and percentage of participants with SAEs from Part B Day 1 to Part B EoS Visit.

9.8. Planned Analyses

9.8.1. Interim Analysis

Interim analyses of reactogenicity, safety and immunogenicity data may be performed at the specified timepoint. The IAs will be performed by a separate team of unblinded programmers and statisticians. The unblinded biostatistics team will not be involved in either study design or regular study conduct. These analyses will be conducted on cleaned data and may be combined depending on study timelines. A limited number of preidentified Sponsor team members will review unblinded treatment study groups, results, and individual listing, and will remain unblinded as described in the data blinding plan. The participant's parent(s)/LAR(s), participants, and all study site staff will remain blinded throughout the study.

An IA of reactogenicity, safety, and immunogenicity will be performed for each cohort after all participants in the cohort have completed the Day 29 Visit.

Additional interim analyses may be performed as needed. Final analysis will be performed after all participants have completed the study and all data are available.

9.8.2. Multiplicity

This study is descriptive, and no multiplicity adjustments will be applied.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH GCP guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are at minimum responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or parent(s)/LAR(s) of the potential participant and answer all questions regarding the study.
- Potential participant or parent(s)/LAR(s) of potential participants must be informed that the participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained from the participant or parent(s)/LAR(s) before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participant or parent(s)/LAR(s) must reconsent to the most current version of the ICF(s) during the child's participation in the study.
- A copy of the ICF(s) must be provided to the participant or participant's parent(s)/LAR(s).

Participant or parent(s)/LAR(s) of a participant who is rescreened are not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

Future Research using leftover samples: The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant or participant's parent(s)/LAR(s) the objectives of the exploratory research. Participants or participant's parent(s)/LAR(s) will be told that they are free to refuse the participation of the child and may withdraw their consent at any time and for any reason during the storage period. The ICF will require the participant or participant's parent(s)/LAR(s) to clearly indicate whether or not they agree to allow any remaining specimens to be used for exploratory research.

10.1.4. Recruitment Strategy

Enrollment targets will be established to ensure the participant population reflects those that are most at risk for the condition, or those that are most reflective of the general population, if appropriate.

Participant recruitment and retention initiatives will be incorporated into the study. These include, but are not limited to, services that provide a means to identify potential participants and direct them to participating clinical study sites, participant support services such as concierge, and study information and support collateral for both the participant and the site. Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant or participant's parent(s)/LAR(s) should be submitted to the Sponsor for approval. All documents must be approved by the IRB/IEC.

10.1.5. 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 which would make the participant identifiable will not be transferred.
- The participant or participant's parent(s)/LAR(s) must be informed that the participant's 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 or participant's parent(s)/LAR(s) who will be required to give consent for the child's data to be used as described in the informed consent.
- The participant or participant's parent(s)/LAR(s) must be informed that the participant's 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.
- The contract between the Sponsor or designee and the study sites may specify responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committee Structures

An unblinded IST and external DSMB will be convened to oversee the safety of this study.
Internal Safety Team

The IST charter will provide additional information on IST safety reviews.

10.1.6.1. Independent Internal Safety Team

An IST will be formed to review interim and cumulative blinded safety data on a regular basis with a remit to escalate concerns to the DSMB.

Safety monitoring for this clinical study will include the blinded study team members, inclusive of at a minimum, the Sponsor's Medical Monitor and a CRO Medical Monitor and an unblinded IST. The IST is comprised of the Sponsor's physicians, who will not otherwise be involved in the conduct of the clinical study. The study team will conduct ongoing blinded safety reviews during the clinical study and will be responsible for notifying the IST of potential safety signal events or the triggering of pause rules. An unblinded statistician will support the determination if study pause rules have been met.

An IST will be formed to review cumulative unblinded safety data at regularly scheduled intervals, and in case of an emerging safety concern, and with a remit to escalate concerns to the DSMB. An IST review will occur once after approximately 40 participants in Cohort 1, and once after approximately 40 participants in Cohort 2, are enrolled and have reached Day 8. The frequency of subsequent reviews will be determined by the IST.

10.1.6.2. Data Safety Monitoring Board

An independent DSMB will review blinded and unblinded data, at the scheduled data review meeting following the IA. The DSMB will review safety of the selected Phase 2 dose in each age group. For Part B Cohort 1, an additional safety data review for RTD cases will be completed by the Sponsor and DSMB at the end of Part B. Any emerging safety concerns from IST safety reviews or in case of pause rule trigger confirmed by the IST will be referred to the DSMB.

After each data review meeting, the DSMB will make a recommendation to the Sponsor to take one of the following courses of action:

- Stop further enrollment due to a safety concern.
- Pause enrollment and consider a change in study design.
- Continue enrollment and/or study conduct as planned.

The Sponsor may also request that the DSMB conduct ad hoc reviews of safety events from this study or other data, including new nonclinical or clinical information related to mRNA-1345 external to this study. The DSMB will review all available study data to adjudicate such events in accordance with the DSMB charter. Refer to the DSMB charter for additional details.

The DSMB composition, its remit and frequency of data review will be further defined in the DSMB charter.

10.1.6.3. Cardiac Event Adjudication Committee

An independent CEAC comprised of medically qualified personnel, including cardiologists, will review all suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet CDC criteria for “probable” or “confirmed” events, which are reported in ongoing clinical studies per the CEAC charter (Gargano et al 2021). Any cases that the CEAC assesses as representing probable or confirmed cases of myocarditis, pericarditis, or myopericarditis will be referred to the Sponsor, who will then determine if additional action is needed. The CEAC will operate under the rules of the approved charter that will be written and reviewed at the organizational meeting of the CEAC. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the charter.

10.1.7. Dissemination of Clinical Study Data

The Sponsor shares information about clinical studies and results on publicly accessible websites, based on international and local legal and regulatory requirements and other clinical study disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register, and some national registries.

In addition, results from clinical studies are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available, the privacy of participants in

clinical studies sponsored by the Sponsor is ensured. Details on data sharing criteria and the process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.8. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in Data Agreements and the Monitoring Plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF 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.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment, also referred to as 'first site active (FSA)' is the first site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant or participant's parent(s)/LAR(s) and should assure appropriate participant therapy and/or follow-up.

10.1.11. 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- The Investigator agrees to provide any manuscripts, posters, or abstracts that are in any way related to this study to the Sponsor for Sponsor review and agreement before submission. This allows the Sponsor to protect proprietary information and to provide comments.

10.2. Appendix 2: Clinical Laboratory Tests

Local clinical laboratory tests are not performed in this study with the exception of:

1. Local urine and/or serum pregnancy test in participants who are of childbearing potential and have reached menarche (Part A Cohort 2)
2. Nasal or nasopharyngeal swab for detection of RSV infection or other respiratory pathogen in participants who have RSV-RTD symptoms during RSV surveillance (Part B)

10.3. Appendix 3: AEs and SAEs: 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 study intervention.

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 (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant or participant's parent(s)/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant or participant's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant or participant's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant or participant's parent(s)/LAR(s) will be collected during an interview with the participant's parent(s)/LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant or participant's parent(s)/LAR(s) in the participant's diary.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

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

Note: Not applicable for this study.

f. Other situations:

- Medical or scientific judgment should be exercised by the Investigator 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 one 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, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.2.1. Suspected Unexpected Serious Adverse Reaction

A SUSAR is an AE that occurs in a clinical study participant, which is assessed by the Sponsor and/or the Investigator as being unexpected, serious, and having a reasonable possibility of a causal relationship with the study intervention.

10.3.3. Recording and Follow-Up of AE and/or 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 reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the eCRF/required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each unsolicited AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs) observed during this study. The intensity grading scales used in this study are presented in Table 12.

Table 12: Participants 2 to Less Than 18 Years Solicited Adverse Reactions and Grades

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Local					
Injection site pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5.0 cm	51-100 mm/ 5.1-10.0 cm	>100 mm/ >10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	<25 mm/ <2.5 cm	25-50 mm/ 2.5-5.0 cm	51-100 mm/ 5.1-10.0 cm	>100 mm/ >10 cm	Necrosis

Reaction	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Some interference with activity	Prevents daily activity	Emergency room visit or hospitalization
Systemic					
Headache	None	No interference with activity	Some interference with activity	Significant; Prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity	Requires emergency room visit or hospitalization for hypotensive shock
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever	<38.0°C <100.4°F	38.0-38.4°C 100.4-101.1°F	38.5-38.9°C 101.2-102.0°F	39.0-40.0°C 102.1-104.0°F	>40.0°C >104.0°F

Abbreviation: EDC = electronic data capture
Note: Events listed above but starting >7 days post study injection will be recorded in EDC. Causality for each event will be determined per assessment by the Investigator.
Modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS 2007).

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- **Not related:** There is not a reasonable possibility of a relationship to the study intervention. Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention.
- **Related:** There is a reasonable possibility of a relationship to the study intervention. There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. 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 or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee 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.
- If a participant dies during participation in the study, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs Including SUSARs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection tool (ie, EDC).
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- 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 electronic data collection tool will be taken offline 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 electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to the Sponsor or Designee via Paper Data Collection Tool

- Initial notification via email or fax does not replace the need for the Investigator to complete and sign the electronic SAE data collection tool within the designated reporting timeframes.
- SAE reports should be emailed to drugsafety@modernatx.com.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Person of Childbearing Potential

People in the following categories are considered POCBP (fertile):

Following menarche

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy.
  - Documented bilateral salpingectomy.
  - Documented bilateral oophorectomy.
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.4.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c].
• IUD.
• IUS[c].
• Bilateral tubal occlusion.
• Azoospermic partner (vasectomized or due to a to medical cause). *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the person of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]. – oral. – intravaginal. – transdermal. – injectable.
Progestogen-only hormone contraception associated with inhibition of ovulation[c]. – oral. – injectable.
Sexual abstinence. *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant).*
[a.] Contraceptive use by participants should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. [b.] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. [c.] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

Abbreviations: IUD = intrauterine device; IUS = intrauterine hormone-releasing system; LAM = lactational amenorrhea method.

[a.] Contraceptive use by participants should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b.] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c.] Considered effective, but not highly effective-failure rate of ≥1% per year.

10.5. Appendix 5: Adverse Event of Special Interest Terms

Investigators should report all events that fall into the categories presented in Table 13 as an AESI per the reporting processes in Section 10.3.4. These AESIs are medical concepts that are generally of interest in vaccine safety surveillance as per the Brighton Collaboration and Safety Platform for Emergency Vaccines.

Table 13: Adverse Events of Special Interest

Medical Concept	Additional Notes
Thrombocytopenia	• Platelet counts <125 × 10^9/liter. • Including but not limited to immune thrombocytopenia, platelet production decreased, thrombocytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or HELLP syndrome.
New onset of or worsening of the following neurologic diseases:	• Guillain-Barre Syndrome. • Acute disseminated encephalomyelitis. • Idiopathic peripheral facial nerve palsy (Bell's palsy). • Seizures including but not limited to febrile seizures and/or generalized seizures/convulsions.
Anaphylaxis	• Anaphylaxis as defined per protocol (Section 8.4.9). • Follow reporting procedures are in Section 10.3.4.
Myocarditis/Pericarditis	• Myocarditis. • Pericarditis. • Myopericarditis.
Diseases caused by RSV	• LRTD, defined as per Table 9 ('Cough OR difficulty breathing,' AND 'SpO_2 <95%, OR RR increased' AND 'Confirmed RSV infection'[a]). • Acute otitis media (with examination evidence of an inflamed tympanic membrane), confirmed with RSV infection[a]. • Pharyngitis (with examination evidence of an inflamed pharynx), confirmed with RSV infection[a].

Abbreviation: HELLP = hemolysis, elevated liver enzymes, low platelet count; LRTD = lower respiratory tract disease; RR = respiratory rate; RT-PCR = reverse transcription polymerase chain reaction; RSV = respiratory syncytial virus; SpO_2 = blood oxygen saturation.

a. RSV infection confirmed on nasal or nasopharyngeal swab positive by positive RT-PCR or other local laboratory tests.

10.6. Appendix 6: CDC Working Case Definitions of Pericarditis, Myocarditis, and Myopericarditis Occurring After Receipt of COVID-19 mRNA Vaccines

The CDC Working Case Definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis (Gargano et al 2021) are provided in Table 14 as guidance.

Table 14: Case Definitions of Probably and Confirmed Myocarditis, Pericarditis, and Myopericarditis

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms:[*] • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope	Presence of ≥1 new or worsening of the following clinical symptoms:[*] • Chest pain, pressure, or discomfort • Dyspnea, shortness of breath, or pain with breathing • Palpitations • Syncope
	OR Infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability • Vomiting • Poor feeding • Tachypnea • Lethargy	**OR** Infants and children aged <12 years might instead have ≥2 of the following symptoms: • Irritability • Vomiting • Poor feeding • Tachypnea • Lethargy
	AND ≥1 new finding of: • Troponin level above upper limit of normal (any type of troponin) • Abnormal ECG or rhythm monitoring findings consistent with myocarditis[§] • Abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis	**AND** ≥1 new finding of: • Histopathologic confirmation of myocarditis[†] • cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	AND • No other identifiable cause of the symptoms and findings	**AND** • No other identifiable cause of the symptoms and findings

<table>
<tr><th>Condition</th><th colspan="2">Definition</th></tr>
<tr><td rowspan="2">Acute pericarditis**</td><td colspan="2">Presence of ≥2 new or worsening of the following clinical features:
• Acute chest pain††
• Pericardial rub on examination
• New ST-elevation or PR-depression on ECG
• New or worsening pericardial effusion on echocardiogram or MRI</td></tr>
<tr><td>OR
Infants and children aged <12 years might instead have ≥2 of the following symptoms:
• Irritability
• Vomiting
• Poor feeding
• Tachypnea
• Lethargy</td><td>OR
Infants and children aged <12 years might instead have ≥2 of the following symptoms:
• Irritability
• Vomiting
• Poor feeding
• Tachypnea
• Lethargy</td></tr>
<tr><td>Myopericarditis</td><td colspan="2">This term may be used for patients who meet criteria for both myocarditis and pericarditis.</td></tr>
</table>

Abbreviations: CDC = Centers for Disease Control and Prevention; CEAC = Cardiac Event Adjudication Committee; cMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram; MRI = magnetic resonance imaging.

Note: An independent CEAC comprised of medically qualified personnel, including cardiologists, will review suspected cases of myocarditis, pericarditis, and myopericarditis to determine if they meet Center for Disease Control and Prevention criteria for "probable" or "confirmed" events, (Gargano et al 2021), and provide the assessment to the Sponsor. The CEAC members will be blinded to study treatment. Details regarding the CEAC composition, responsibilities, procedures, and frequency of data review will be defined in the CEAC charter.

* Persons who lack the listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed).

† Using the Dallas criteria (Aretz et al 1987). Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause.

§ To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias; or 3) atrioventricular nodal conduction delays or intraventricular conduction defects.
Using either the original or the revised Lake Louise criteria.
https://www.sciencedirect.com/science/article/pii/S0735109718388430?via%3Dihub

** https://academic.oup.com/eurheartj/article/36/42/2921/2293375

†† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

10.7. Appendix 6: Protocol Amendment History

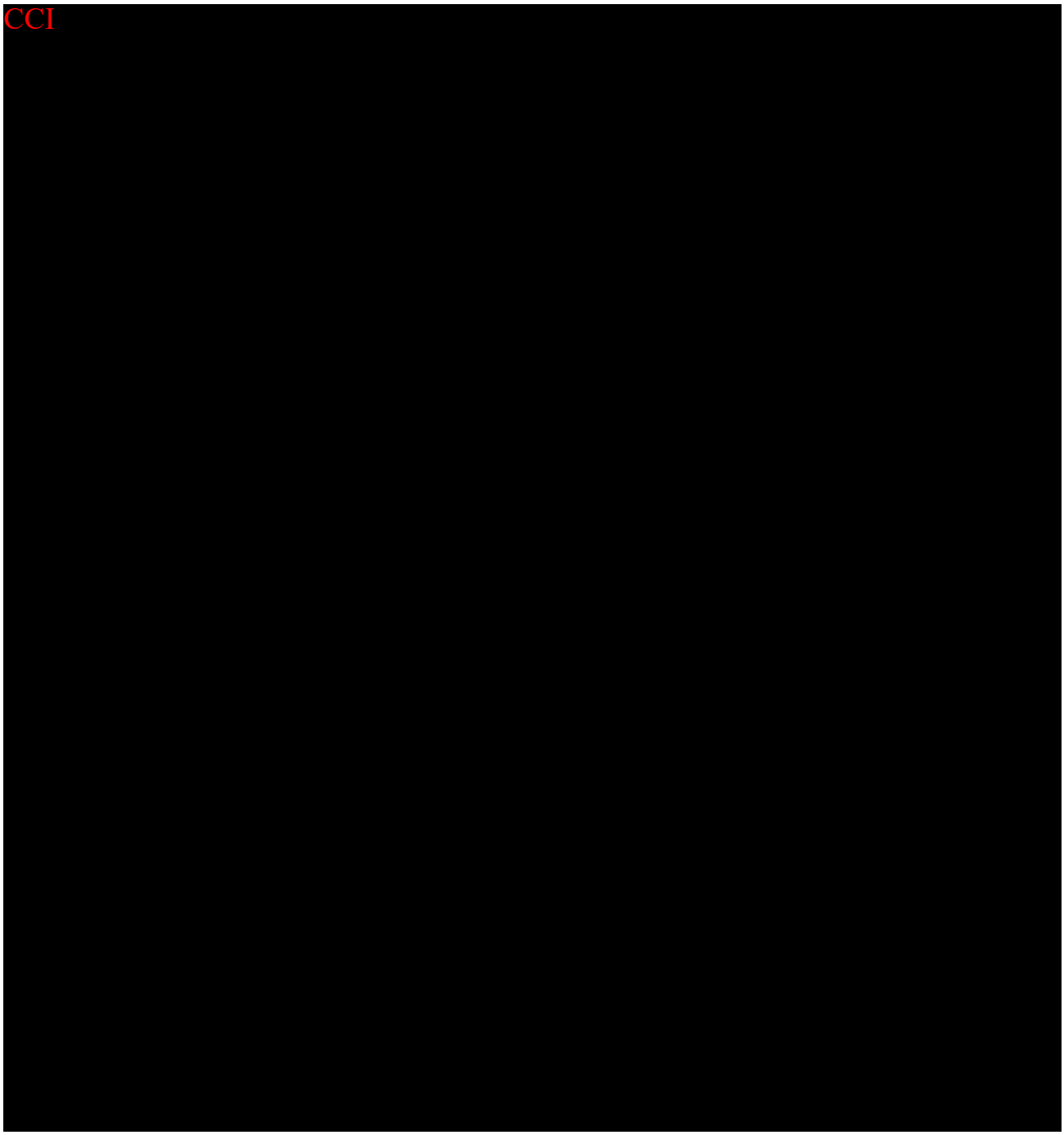
The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1, 18 Jun 2024

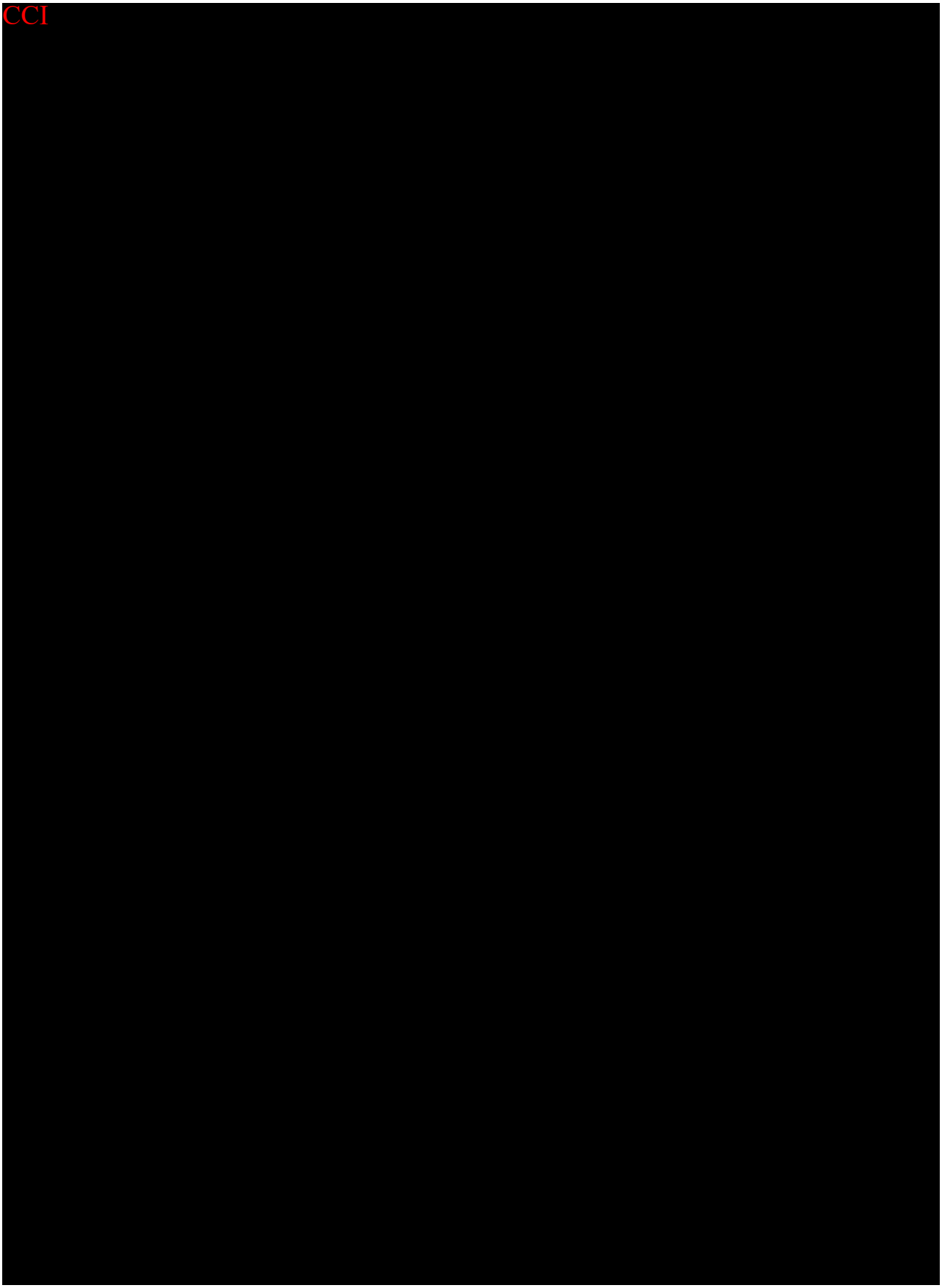
This amendment is considered to be substantial because it impacts the overall design of the study due to addition of Cohort 3.

Overall Main Rationale for the Amendment

CCI



CCI



11. REFERENCES

Acosta, PL, Caballero MT, Polack FP. Brief history and characterization of enhanced respiratory syncytial virus disease. Clin Vaccine Immunol. 2015;23(3):189-95.

Ali K, Berman G, Zhou H, Deng W, Faughnan V, et al.Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. N Eng J Med. 2021;85(24):2241-51.

Anderson EJ, Creech CB, Berthaud V, Piramzadian A, Johnson KA, Zervos M, et al; KidCOVE Study Group. Evaluation of mRNA-1273 vaccine in children 6 months to 5 years of age. N Engl J Med. 2022;387(18):1673-87.

Andeweg SP, Schepp RM, van de Kassteele J, Mollema L, Berbers GM, van Boven, Michel. Population-based serology reveals risk factors for RSV infection in children younger than 5 years. Sci Rep. 2021;11(1):8953.

Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr., et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1(1):3-14.

Asner S, Waters V, Solomon M, Yau Y, Richardson SE, et al. Role of respiratory viruses in pulmonary exacerbations in children with cystic fibrosis. J Cyst Fibros. 2012;11(5):433-9.

Beckhaus AA and Castro-Rodriguez JA. Down syndrome and the risk of severe RSV infection: a meta-analysis. Pedatrics. 2018;142(3):e20180225.

Browne SK, Beeler JA, Roberts JN. Summary of the Vaccines and Related Biological Products Advisory Committee meeting held to consider evaluation of vaccine candidates for the prevention of respiratory syncytial virus disease in RSV-naïve infants. Vaccine. 2020;38(2):101-6.

Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol. 1969;89(4):449-63.

ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT05127434. A study to evaluate the safety and efficacy of mRNA-1345 vaccine targeting respiratory syncytial virus (RSV) in adults ≥60 years of age. 2021 Nov 19 [updated 2023 Jan 31, cited 2023 Jun 6]. Available from https://clinicaltrials.gov/ct2/show/NCT05127434.

Connors M, Giese NA, Kulkarni AB, Firestone CY, Morse HC 3rd, Murphy BR. Enhanced pulmonary histopathology induced by respiratory syncytial virus (RSV) challenge of formalin-inactivated RSV-immunized BALB/c mice is abrogated by depletion of interleukin-4 (IL-4) and IL-10. J Virol. 1994;68(8):5321-5.

Crank MC, Ruckwardt TJ, Chen M, Morabito KM, Phung E, Costner PJ, et al. A proof of concept for structure-based vaccine design targeting RSV in humans. Science. 2019;365(6452):505-9.

Creech CB, Anderson E, Berthaud V, Yildirim I, Atz AM, et al. Evaluation of mRNA-1273 Covid-19 vaccine in children 6 to 11 years of age. N Eng J Med. 2022;386(21):2011-23.

Delgado MF, Coviello S, Monsalvo AC, Melendi GA, Hernandez JZ, Batalle JP, et al. Lack of antibody affinity maturation due to poor Toll-like receptor stimulation leads to enhanced respiratory syncytial virus disease. Nat Med. 2009;15(1):34-41.

Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-8.

Food and Drug Administration, DHHS, 2007. Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." [Cited 2023 Jun 6]. Available from: https://www.fda.gov/media/73679/download.

Garcia DF, Hiatt PW, Jewell A, Schoonover SL, Cron SG, et al. Human metapneumovirus and respiratory syncytial virus infectiosns in older children with cystic fibrosis. Pediatr Pulmonol. 2007;42(1):66-74.

Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID 19 vaccine after reports of myocarditis among vaccine recipients: update from the Advisory Committee on Immunization Practices – United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977-82.

Giersing BK, Karron RA, Vekemans J, Kaslow DC, Moorthy VS. Meeting report: WHO consultation on respiratory syncytial virus (RSV) vaccine development, Geneva, 25-26 April 2016. Vaccine. 2019;37(50):7355-62.

Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child. 1986;140(6):543-6.

Graham BS. Immunological goals for respiratory syncytial virus vaccine development. Curr Opin Immunol. 2019;59:57-64.

Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis. 1991;163(4):693-8.

Henderson FW, Collier AM, Clyde WA Jr, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. N Engl J Med. 1979;300(10):530-4.

Jackson ML, Scott E, Kuypers J, Nalla AK, Roychoudury P, Chu HY. Epidemiology of respiratory syncytial virus across five influenza seasons among adults and children one year of age and older-Washington State, 2011/2012-2015/2016. J Infect Dis. 2021;223(1):147-56.

Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol. 1969;89(4): 405-21.

Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969;89(4):422-34.

Krishnan A, Kumar R, Broor S, Gopal G, Saha S, Amarchand R, et al. Epidemiology of viral acute lower respiratory infections in a community-based cohort of rural north Indian children. J Glob Health. 2019;9(1):010433.

Kristensen K, Hjuler T, Ravn H, Simões EA, and Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis. 2012;54(6):810-7.

Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340): 2047-64.

Lu G, Gonzalez R, Guo L, Wu L, Wu C, Vernet G, Paranhos-Baccala G, et al. Large-scale seroprevalence analysis of human metapneumovirus and human respiratory syncytial virus infections in Beijing, China. Virol J. 2011;8:62.

Manzoni P, Figueras-Aloy J, Simoes EA, Checchia PA, Faroux B, et al. Defining the incidence and associated morbidity and mortality of severe respiratory synctytial virus infection among children with chronic diseases. Infect Dis Ther. 2017;6(3):383-411.

Meyer VM, Sequeira MM, Costa PF, Caetano BC, Lopes JC, et al. Clinical impact of respiratory virus in pulmonary exacerbations of children with cystic fibrosis. PLoS One. 2020;15(10):e0240452.

McLellan JS, Chen M, Joyce MG, Sastry M, Stewart-Jones GB, Yang Y, et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. Science. 2013;342(6158): 592-8.

Modjarrad K, Giersing B, Kaslow DC, Smith PG, and Moorthy VS et al. WHO consultation on respiratory syncytial virus vaccine development report from a World Health Organization meeting held on 23-24 March 2015. Vaccine. 2016; 34(2):190-7.

Murray J, Bottle A, Sharland M, Modi N, Aylin P, et al. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PLoS One. 2014;9(2):e89186.

Ngwuta JO, Chen M, Modjarrad K, Joyce MG, Kanekiyo M, Kumar A, et al. Prefusion F-specific antibodies determine the magnitude of RSV neutralizing activity in human sera. Sci Transl Med. 2015;7(309):309ra162.

Nyiro JU, Kombe IK, Sande CJ, Kipkoech J, Kiyuka PK, Onyango CO. Defining the vaccination window for respiratory syncytial virus (RSV) using age-seroprevalence data for children in Kilifi, Kenya. PLoS One. 2017;12(5):e0177803.

Papadopoulos NG, Christodoulou I, Rohde G, Agache I, Almqvist C et al. Viruses and bacteria in acute asthma exacerbations – a GA^2 LEN-DARE systematic review. Allergy. 2011;66(4):458-68.

Path.org. RSV Vaccine and mAb Snapshot. Path.org. 2023. [Cited 2023 Jun 6]. Available from: https://www.path.org/resources/rsv-vaccine-and-mab-snapshot.

Pisesky A, Benchimol EI, Wong CA, Hui C, Crowe M, et al. Incidence of hospitalization for respiratory syncytial virus infection amongst children in Ontario, Canada: a population-based study using validated health administrative data. PLoS One. 2016;11(3):e0150416.

Polack FP, Teng MN, Collins PL, Prince GA, Exner M, Regele H, et al. A role for immune complexes in enhanced respiratory syncytial virus disease. J Exp Med. 2002;196(6):859-65.

Prince GA, Curtis SJ, Yim KC, Porter DD. Vaccine-enhanced respiratory syncytial virus disease in cotton rats following immunization with Lot 100 or a newly prepared reference vaccine. J Gen Virol. 2001;82(Pt 12):2881-8.

Rose EB, Dahl RM, Havers FP, Peacock G, and Langley GE. Respiratory syncytial virus-associated hospitalizations in children with neurological disorders, 2006-2015. J Pediatric Infect Dis Soc. 2021;10(10):951-7.

Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al; Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

Sánchez-Luna M, Medrano C, and Lirio J. Down syndrome as a risk factor for respiratory syncytial virus hospitalization: a prospective multicenter epidemiology study. Influenza Other Respir Viruses. 2017;11(2):157-64.

Snape M, Ghamloush SS, Chen GL, Dhar R, Mithani R, et al. Safety/immunogenicity of 2 investigational mRNA vaccines, a respiratory syncytial virus and a human metapneumovirs and parainfluenza virus type 3 combination vaccine in young children. ESPID 2023; #837 [Abstract].

Somayaji R, Goss CH, Khan U, Neradilek M, Neuzil KM, et al. Cystic fibrosis pulmonary exacerbations attributable to respiratory syncytial virus and influenza: a population-based study. Clin Infect Dis. 2017;64(12):1760-7.

Srikiatkhachorn A and Braciale TJ. Virus-specific CD8+ T lymphocytes downregulate T helper cell type 2 cytokine secretion and pulmonary eosinophilia during experimental murine respiratory syncytial virus infection. J Exp Med. 1997;186(3):421-32.

Stagliano DR, Nylund CM, Eide MB, and Eberly MD. Children with Down syndrome are high-risk for severe respiratory syncytial virus disease. J Pediatr. 2015;166(3):703-9.e2.

Ueno, F, Tamaki R, Saito M, Okamoto, M, Saito-Obata M, Kamigaki T, et al. Age-specific incidence rates and risk factors for respiratory syncytial virus-associated lower respiratory tract illness in cohort children under 5 years old in the Philippines. Influenza Other Respir Viruses. 2019;13(4): 339-53.

Walsh EE, Peterson DR, Kalkanoglu AE, Lee FE, Falsey AR. Viral shedding and immune responses to respiratory syncytial virus infection in older adults. J Infect Dis. 2013;207(9):1424-32.

Welliver RC, Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, et al. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. Curr Med Res Opin. 2010;26(9):2175-81.

WHO. Guidelines on the quality, safety and efficacy of respiratory synctial virus vaccines. Geneva, Switzerland: WHO; 2019. [Cited 2023 Jun 6]. Available from: https://www.who.int/docs/default-source/biologicals/ecbs/rsv-guidelines-post-ecbs.pdf?sfvrsn=e9176411_2.

Wilkesmann A, Ammann RA, Schildgen O, Eis-Hübinger AM, Müller A, et al. Hospitalized children with respiratory synctytial virus infection and neuromuscular impairment face an increased risk of complicated course. Pediatr Infect Dis J. 2007;26(6):485-91.

Wilson E, Goswami J, Stoszek SK, Mithani R, Mehta S, et al. Safety and efficacy of mRNA-1345, an mRNA-based vaccine against repiratory syncytial virus, in adults 60 years and older. 2023; Presented at the RSVVW 2023 Conference.

Zachariah P, Ruttenber M, and Semões EAF. Down syndrome and hospitalizations due to respiratory syncytial virus: a population-based study. J Pediatr. 2012;160(5):827-31.e1.

Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations—a post-marketing surveillance review. Eur J Pediatr. 2002;161(1):21-5.

Zheng, Z, Weinberger DM, and Pitzer VE. Predicted effectiveness of vaccines and extended half-life monoclonal antibodies against RSV hospitalizations in children. NPJ Vaccines. 2022;7(1):127.

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