NCT #: NCT06602531

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A Phase 1, First-in-human, Randomized, Observer-blind, Parallel design, Controlled, Dose Level and Schedule-finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of a Self-Amplifying mRNA Pandemic Influenza Vaccine (ARCT-2304) When Administered to Healthy Adults.

Protocol Number:	ARCT-2304-01
Protocol Version:	1.0
Protocol Date:	29 August 2024

STATISTICAL ANALYSIS PLAN

Version 2.0

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STATISTICAL ANALYSIS PLAN

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CTI Author	[redacted] CTI Signing on behalf of [redacted]	[redacted]	
CTI Biostatistics Reviewer	[redacted]		
Sponsor Approval	[redacted] Arcturus Therapeutics, Inc.		
Sponsor Approval	[redacted] Arcturus Therapeutics, Inc.		

Note that the last signature date is the effective date of the plan.

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SAP REVISION HISTORY

The following table details the revisions made to the SAP.

SAP Revision History		
SAP Version #	**Description of Changes**	**Superseded SAP Version #**
1.0	N/A: First version of SAP	N/A
2.0	• Updated endpoint for Serum MN antibody titers against the HA glycoprotein through Day 240. • Updated known ULOQ information for HAI and ELLA assays and updated "LLoQ" and "ULoQ" to "LLOQ" and "ULOQ" for consistency purposes in Section 7. • Added additional antibody titer thresholds for descriptive statistics in Section 7.2. • Removed broken hyperlink to Table 3 in Section 4.2. • Removed laboratory tabulation for abnormal clinical significance in Section 8.4, as data are not available in the data transfer from the laboratory. • Updated date and time display conventions in Section 4 to align with current TLF display conventions.	1.0

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical, Therapeutic, and Chemical
BMI	Body Mass Index
BS	Blood Sample
BUN	Blood Urea Nitrogen
CCAC	Central Cardiac Adjudication Committee
CI	Confidence Interval
CK-MB	Creatine kinase myocardial band
CMI	Cell Mediated Immunogenicity
CRF	Case Report Form
CS	Clinically Significant
DP	Drug Product
DS	Drug Substance
DSMB	Data Safety Monitoring Board
ECG	Electrocardiography
EDC	Electronic Data Capture
ELLA	Enzyme-linked lectin assay
FDA	Food and Drug Administration
GM	Geometric Mean
GMFR	Geometric Mean Fold Rise
GMP	Good Manufacturing Practice
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination inhibition
ICF	Informed Consent Form
IFN-γ	Interferon-Gamma

Abbreviation	Definition
IL-13	Interleukin 13
IL-2	Interleukin 2
IL-4	Interleukin 4
IM	Intramuscular
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ITT	Intent to Treat
LLOQ	Lower limit of quantification
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MN	Microneutralization
mRNA	Messenger ribonucleic acid
NA	Neuraminidase
NCS	Not Clinically Significant
PBMC	Peripheral blood mononuclear cell
PD	Protocol Deviation
PI	Principal Investigator
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Seroconversion
SCR	Seroconversion Rate
SD	Standard Deviation
SoA	Schedule of Assessments
SOC	System Organ Class
TNF-α	Tumor Necrosis Factor Alpha
ULOQ	Upper Limit of Quantification

Abbreviation	Definition
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

1. INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol number ARCT-2304-01 titled, "A Phase 1, First-in-human, Randomized, Observer-blind, Parallel design, Controlled, Dose Level and Schedule-finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of a Self-Amplifying mRNA Pandemic Influenza Vaccine (ARCT-2304) When Administered to Healthy Adults." version 1.0, dated 29 August 2024. See the study protocol for full details.

This document details the statistical methods planned to perform the final analyses. The results of this study may be released sequentially in two separate final analyses. If so, the first final analysis will include all data associated with primary endpoints. The second final analysis will include analysis of safety and immunogenicity data associated with all endpoints up to study end.

The study will include the use of an independent Data Safety Monitoring Board (DSMB) to evaluate participants' safety. See the DSMB Charter for more details. A Central Cardiac Adjudication Committee (CCAC) will meet to evaluate any potential myocarditis/pericarditis cases. Further details are provided in the CCAC charter.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

1. To evaluate the safety and reactogenicity of different dose levels of ARCT-2304.
2. To describe the hemagglutination inhibition (HAI) antibody responses against the hemagglutinin (HA) glycoprotein through 28 days after the second vaccination.
3. To describe the neuraminidase enzyme-linked lectin assay (ELLA) antibody responses against the neuraminidase (NA) glycoprotein, through 28 days after the second vaccination.

2.1.2 Secondary Objectives

1. To evaluate the safety of different dose levels of ARCT-2304 through the entire study period.
2. To describe the persistence of humoral immune response, following ARCT-2304, as measured by HAI and ELLA assays, throughout the entire study period.
3. To describe serum neutralizing microneutralization (MN) antibody titer against the HA glycoprotein through 28 days after the second vaccination.

2.1.3 Exploratory Objectives

1. To describe HA and NA-specific CD4+ and CD8+ T-cell responses elicited by the different dose levels of ARCT-2304.

2.2 Endpoints

2.2.1 Primary Endpoints

Endpoints for primary objective 1 (safety and reactogenicity):

- Local and systemic adverse events (AEs) reported within 7 days after each vaccination
- Unsolicited AEs reported within 28 days after each vaccination
- Any laboratory abnormalities on Days 1, 8, 29, and 36 (Cohort D1,29) or Days 1, 8, 57, and 64 (Cohort D1,57)
- Any clinically significant abnormal vital signs on Days 1, 8, 29, 36 and 57 (Cohort D1,29) or Days 1, 8, 57, 64 and 85 (Cohort D1,57)
- Serious Adverse Events (SAEs), Medically Attended AEs (MAAEs), AEs of Special Interest (AESIs), and AEs leading to early termination reported from Day 1 up to Day 57 (Cohort D1,29) and Day 1 up to Day 85 (Cohort D1,57) in:
    - ARCT-2304 recipients (by dose level)
    - Control/placebo vaccine recipients

Endpoints for primary objective 2 (immunogenicity):

- Serum HAI antibody titers against the H5N1 HA glycoprotein on Days 1, 29, 36 and 57 (Cohort D1,29) and on Days 1, 57, 64 and 85 (Cohort D1,57), in:
    - ARCT-2304 recipients (by dose level)
    - Historical control vaccine recipients

Endpoints for primary objective 3 (immunogenicity):

- Serum ELLA antibody titers against the H5N1 NA glycoprotein on Days 1, 29, 36, and 57 (Cohort D1,29) and on Days 1, 57, 64, and 85 (Cohort D1,57), in:
    - ARCT-2304 recipients (by dose level)

2.2.2 Secondary Endpoints

Endpoints for secondary objective 1 (safety):

- SAEs, MAAEs, AESIs, and AEs leading to early termination from the study, from Day 1 through Day 240, in:
    - ARCT-2304 recipients (by dose level)
    - Control/placebo vaccine recipients

Endpoints for secondary objective 2 (immunogenicity):

- Serum HAI and ELLA antibody titers against the HA and the NA glycoproteins on Days 1, 29, 36, 57, and 240 (Cohort D1,29) and Days 1, 57, 64, 85, and 240 (Cohort D1,57), in:
    - ARCT-2304 recipients (by dose level)

Endpoints for secondary objective 3 (immunogenicity):

- Serum MN antibody titers against the HA glycoprotein on Days 1, 29, 36, 57, and 240 (Cohort D1,29) and on Days 1, 57, 64, 85, and 240 (Cohort D1,57), in:
    - ARCT-2304 recipients (by dose level)
    - Historical control vaccine recipients

2.2.3 Exploratory Endpoints

Endpoints for exploratory objective 1 (immunogenicity):

- Expression of activation markers and subset-specific markers by ELISpot following HA and NA peptide pool stimulation on Days 1, 8, 29 and 36 (Cohort D1,29) and Days 1, 8, 57 and 64 (Cohort D1,57), in:
    - ARCT-2304 recipients (by dose level)

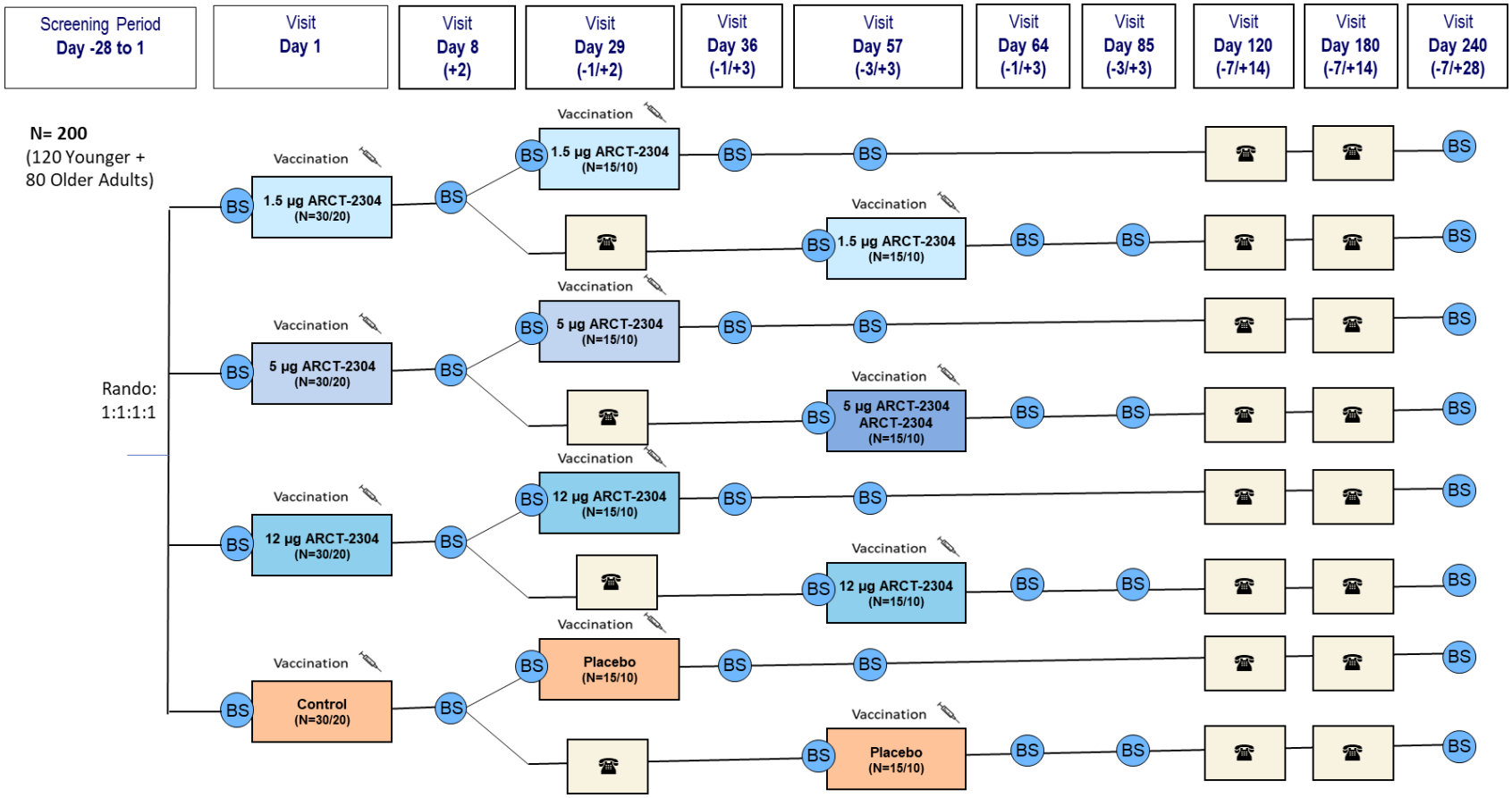
3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a Phase 1, first-in-human, randomized, observer-blind, parallel design, controlled, dose level and schedule-finding study to evaluate the safety, reactogenicity, and immunogenicity of a self-amplifying messenger ribonucleic acid (mRNA) pandemic influenza (H5N1) vaccine (ARCT-2304), when administered as a 2-dose vaccination series to healthy adults.

Approximately 200 evaluable participants (120 participants in age group 18-59 years and 80 participants in age group 60-80 years) are planned to be enrolled in this study; 150 participants receiving ARCT-2304 (different dose levels) and 50 participants receiving the control vaccine. The overall study design is provided in Figure 1.

Figure 1. Overall design of study ARCT-2304-01



BS: Blood Sample (for immunogenicity evaluation); Rando: Randomization; Control = seasonal influenza vaccine
Note: Control vaccine for participants 18-59 years of age is Flucelvax Trivalent®; control vaccine for participants 60 – 80 years of age is Fluad Trivalent®.

All participants will receive two intramuscular (IM) doses of either one of the three dose levels of the ARCT-2304 vaccine, or control vaccine (first vaccination) and placebo (second vaccination), and will follow one of the two different vaccination schedules (Days 1, 29 or Days 1, 57), according to Table 1.

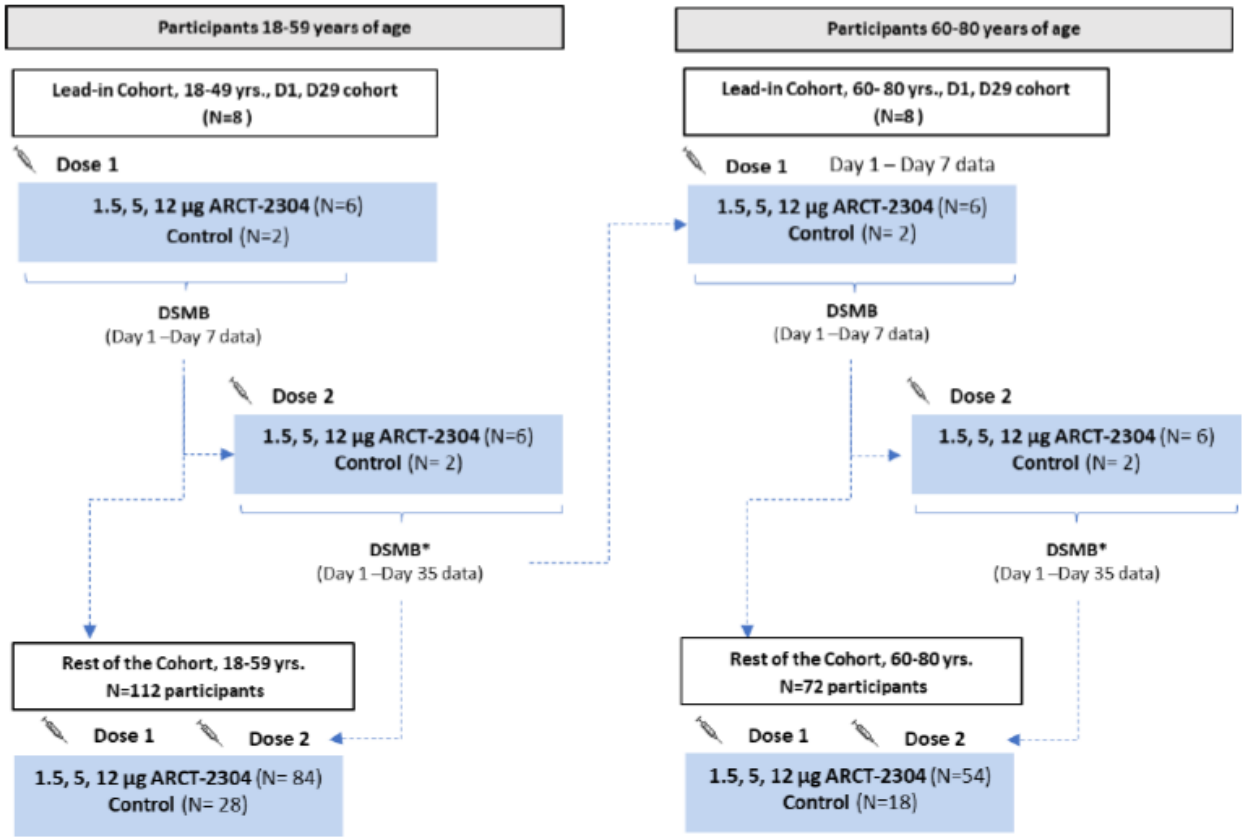
Table 1. Study Cohorts and Treatment Arms

Cohort	Treatment Arm	Schedule of Vaccine Administration	Total Enrolled	Enrollment by Age Group	
				18≤Age≤59	60≤Age≤80
D1,29	1.5 µg ARCT-2304	Day 1, Day 29	25	15	10
	5 µg ARCT-2304	Day 1, Day 29	25	15	10
	12 µg ARCT-2304	Day 1, Day 29	25	15	10
	Control vaccine/placebo	Day 1, Day 29	25	15	10
D1,57	1.5 µg ARCT-2304	Day 1, Day 57	25	15	10
	5 µg ARCT-2304	Day 1, Day 57	25	15	10
	12 µg ARCT-2304	Day 1, Day 57	25	15	10
	Control vaccine/placebo	Day 1, Day 57	25	15	10

As ARCT-2304 will be administered for the first time to humans in this study, a staggered enrollment approach will be taken as safety precaution. The study will be enrolled in four sequential phases as described below, and as visualized in Figure 2:

1. Lead-in Cohort 1 (18 – 49 years): Enrollment will start with 8 participants, 18 – 49 years of age, that will be assigned to the D1,29 vaccination schedule cohort and will be randomized to one of 4 treatment arms (1.5 µg, 5 µg or 12 µg of ARCT-2304 or control/placebo vaccine).
2. Expansion age group 18 – 59 years: The rest of the participants in the 18 – 59 years of age group will be randomized into one of eight arms – they will be assigned to one of two vaccine schedule cohorts (D1,29 or D1,57) and into one of the 4 treatment arms with that cohort (three dose levels of ARCT-2304 or control/placebo vaccine).
3. Lead-in Cohort 2 (60 – 80 years): Eight participants in the 60 – 80 years of age group will be enrolled, assigned to the D1,29 vaccination schedule cohort, and will be randomized to one of the 4 treatment arms, similar to the lead-in Cohort 1 (18 – 49 years).
4. Expansion age group 60 – 80 years: The rest of the participants in the 60 – 80 years of age group will be randomized into one of eight arms – they will be assigned to one of two vaccine schedule cohorts (D1,29 or D1,57) and into one of the 4 treatment arms within that cohort (three dose levels of ARCT-2304 or control/placebo vaccine).

Figure 2. Staggered Enrollment Plan



* Will include also all available safety data from the rest of cohort.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of assessments (SoA, Appendices A and B) for the last participant in the study. The duration of participation will be approximately 9 months for each participant.

3.2 Treatment

The details about the investigational ARCT-2304 vaccine are presented in Table 2.

Participants receiving the control/placebo treatment arm will get an age-appropriate comparator influenza vaccine for the first vaccination and placebo for the second vaccination. Participants aged 18-59 will receive a licensed cell-culture based inactivated influenza vaccine (Flucelvax Trivalent®) for the control and 0.9% saline for the placebo. Participants aged 60 – 80 will receive an adjuvanted inactivated influenza vaccine (Fluad Trivalent®) for the control and 0.9% saline for the placebo.

Table 2. Study Vaccine Details - ARCT-2304

Intervention Name	ARCT-2304 vaccine
Formulation	ARCT-2304 Drug Product (DP) contains one Drug Substance (DS): mRNA-2320 (A/Indonesia/05/2005 mRNA) encoding for HA and NA of Indonesia strain. mRNA construct encapsulated in the lipid nanoparticle
Presentation	Multi-dose vial, lyophilized powder to be reconstituted
Manufacturer	Designated manufacturer: Arcturus Therapeutics, Inc.
Route of Administration	IM in the deltoid region of the upper arm
Volume (after preparation)	0.5 mL and 0.25 mL
Content/vial	mRNA-2320: 320 µg
IMP	Yes
Packaging	The study vaccines will be packaged and labeled according to GMP and local regulations. The study vaccine will not be packed in individual participant kits; one kit may be used for multiple participants.

Abbreviations: GMP, Good Manufacturing Practice; HA, hemagglutinin, IM, intramuscular; IMP, investigational medicinal product, NA, neuraminidase.

3.2.1 Randomization Scheme and Treatment Arm Assignment

Participants will be randomized to receive:

- One of the 3 dose levels of investigational vaccine, administered as a 2-dose vaccination series (on Days 1, 29 or Days 1, 57), or
- Control/Placebo vaccine, administered as a 2-dose vaccination series (on Days 1, 29 or Days 1, 57) where the control is given for the first vaccination and the placebo is given for the second vaccination.

The randomization will be stratified according to enrollment phase (Lead-in Cohort 1 (18-49 years), Expansion age group (18-59 years), Lead-in Cohort 2 (60-80 years), or Expansion age group (60-80 years)).

3.2.2 Blinding

This study will be observer-blind.

After signing the informed consent form (ICF), each participant will be given a number (Subject ID) according to the screening order. On Day 1, following confirmation of eligibility, a randomization number will be assigned, and participants will be allocated to treatment using an interactive response technology (IRT) system.

An unblinded dosing team, not involved with study participant's evaluation, will prepare and administer the study vaccine doses. The study vaccine syringe will be opacified/masked to avoid unblinding of the participant. The administration of the study vaccine will also be performed in an area outside of the view of blinded team members to ensure that the other blinded staff members do not become unblinded. The investigative study center personnel, as well as the sponsor personnel involved in the monitoring or conduct of the study, will be blinded to the study treatment arm.

The treatment arm should be broken only if the investigator/physician in charge of the participant feels that the case cannot be treated without knowing the identity of the study vaccine.

Except in cases of medical necessity, a participant's treatment should not be unblinded without the approval of the sponsor. If unblinding should occur (by either accidental unblinding or emergency unblinding) before completion of the study, the investigator must promptly contact the sponsor or designee and document the date and reason that the blind was broken in the source documentation and case report form (CRF). Instructions regarding emergency unblinding will be provided to the investigator.

3.2.3 Dosing Schedule

Participants assigned to ARCT-2304 will receive the vaccine (one of the three dose levels they were randomized to) for the first and second vaccination, based on their vaccination schedule (Days 1, 29 or Days 1, 57).

Participants assigned to control/placebo will have a first vaccination of control and a second vaccination of placebo, based on their vaccination schedule (Days 1, 29 or Days 1, 57).

3.2.4 Participant Withdrawal

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn, at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant 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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study center study records and inform sponsor's representative.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

For this study, statistical analysis will be primarily descriptive, and a 95% confidence interval (CI) may be provided whenever applicable. No formal multiple comparison adjustments will be employed for multiple safety, immunogenicity, or exploratory endpoints. Nominal p-values and CIs may be computed for immunogenicity data analyses without controlling for multiplicity.

All descriptive summaries will be presented for each vaccination schedule cohort by treatment arm and nominal visit/time point (where applicable). Participant data will be listed by vaccination schedule cohort and sorted by treatment arm, participant number, and visit.

Analyses will be performed using SAS® statistical software, version 9.4 (SAS Institute Inc., Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Covington, KY) will perform all immunogenicity and safety statistical analyses.

Continuous variables:

Descriptive statistics will be summarized by presenting the number of non-missing observations

(n), arithmetic mean, standard deviation (SD), median, minimum, and maximum values.

The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD, and median values will be displayed to one more decimal than the source data for the specific variable.

The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the above-mentioned rules.

For source data with > 5 decimals, rounding to a maximum of 3 decimals will be performed.

Categorical variables:

Descriptive statistics will be summarized by presenting the number of participants and percentage for each category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place. Proportions will be displayed to 3 decimal places.

Repeat/unscheduled assessments:

Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point (early termination visits will not be summarized). All collected data will be included in the data listings.

Date and time display conventions:

The following displays conventions will be applied in all outputs where dates and/or times are displayed:

- Date: YYYY-MM-DD
- Time: hh:mm

Any incomplete dates and times will be imputed in the following manner:

- Missing day: YYYY-MM
- Missing day and month: YYYY
- Missing minutes: hh

4.1 Analysis Quality Control Procedures

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis. If the results are released sequentially in two separate final analyses, the data will be cleaned and frozen prior to the first final analysis and cleaned and locked prior to the second final analysis.

Data may be pulled by CTI Biostatistics for the DSMB analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis datasets, tables, and listings are independently

programmed by two members of the CTI Biostatistics team. The SAS outputs will be compared, and the programs will be updated until the outputs match.

4.2 Analysis Sets

The analysis sets are defined in Table 3.

In addition to information collected in the case report forms, the Protocol Deviation Specifications and Other Analysis Exclusionary Criteria document will also be used to determine which participants will be included in each analysis set.

Table 3. Analysis Sets

Analysis Set	Description
Enrolled Set	All screened participants who provided informed consent, received a participant ID, and were randomized.
Exposed Set / Intent to Treat (ITT) Analysis Set	All participants who received at least one dose of study vaccine. The ITT Analysis Set will be analyzed according to the vaccine assigned.
Modified ITT (mITT) Analysis Set*	All participants who are randomized, received at least one dose of study vaccine, and provided at least one post-baseline immunogenicity assessment. The mITT Analysis Set will be analyzed according to vaccine assigned.
Per Protocol (PPS) Analysis Set*	Participants in the mITT Analysis Set who correctly received the assigned protocol-required dose of study vaccine and had no protocol deviations impacting the analysis of immunogenicity data are included in the PPS Analysis Set.
Historical Control Set	Random Samples (sample size approximately 30-40 study participants) from the Per Protocol Set from the study V89P1. Study arms 7.5 micrograms and 15 micrograms with full dose (100%) of MF59; Day 1 and Day 43 samples.
Safety (SAF) Analysis Set	All participants in the Exposed Set who provide any evaluable post-vaccination reactogenicity and/or safety data. Should there be an error in administration where the actual study vaccine that the participant received was different than the one to which he/she was assigned, the Safety Analysis Set will be analyzed according to the vaccine actually received.

*Participants included in analysis set determined at Day 57/85 for the First Analysis and at Day 240 for the Second Analysis.

4.3 Assessment Windows

Table 4 shows the assessment windows for ARCT-2304 study. For the purpose of listing and summarizing data, the time-in-study for each participant observation will be defined using study days. Such days will be measured relative to Day 1, the day of study vaccine administration (there will be no Day 0).

All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.

Table 4. Assessment Windows for ARCT 2304-01

Visit Type	Visit Name	Target Study Day and Window	
		Cohort 1,29	Cohort 1,57
Screening Visit	-	Day -28 to Day 1	Day -28 to Day 1
Clinic Visit	V1	Day 1	Day 1
Clinic Visit	V2	Day 8 (+2)	Day 8 (+2)
Phone Call	-	-	Day 29 (-1/+2)
Clinic Visit	V3	Day 29 (-1/+2)	Day 57 (-1/+2)
Clinic Visit	V4	Day 36 (-1/+3)	Day 64 (-1/+3)
Clinic Visit	V5	Day 57 (-3/+3)	Day 85 (-3/+3)
Phone Call	-	Day 120 (-7/+14)	Day 120 (-7/+14)
Phone Call	-	Day 180 (-7/+14)	Day 180 (-7/+14)
Clinic Visit	V6	Day 240 (-7/+28)	Day 240 (-7/+28)

4.4 Handling of Dropouts or Missing Data

Any participant who withdraws/discontinues after randomization but prior to the first study vaccination will be replaced. Any participant from the Lead-in Cohort 1 or 2 who drops out within the first 7 days (from Day 1 to Day 7) of the study will be replaced to ensure eight evaluable participants are included in each Lead-in Cohort. Replacement of participants who withdraw/discontinue post dose(s) will be at the discretion of the Sponsor.

Missing data will not be imputed for immunogenicity, safety, or exploratory analyses.

Missing solicited AE diary and AE data will not be imputed.

For the calculation of geometric mean titer (GMT) and geometric mean fold rise (GMFR), imputation will be applied when applicable. Antibody titer values above the upper limit of quantitation (ULOQ) will be set to ULOQ, while antibody titer values below the lower limit of quantitation (LLOQ) will be imputed as ½ LLOQ (i.e., 0.5*LLOQ).

4.5 Multiple Comparisons

No multiple comparisons adjustments will be made.

4.6 Data Derivations and Transformations

The following derivations and definitions will be used in this study:

Study Day:

The study day of events occurring before the first study vaccine administration will be calculated as:

- Study Day = (Date of Event - Date of First Study Vaccine Administration)

For events occurring on or after Day 1, study day will be calculated as:

- Study Day = (Date of Event - Date of First Study Vaccine Administration) + 1

Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the time of analysis.

Study Day Relative to the First Dose is the same as the Study Day calculation above.

Study Day Relative to the Second Dose is the same as the Study Day calculation above, but utilizes the Date of Second Study Vaccination Administration instead of the Date of First Study Vaccination Administration.

Baseline:

The baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each participant prior to first study vaccine administration. If an assessment is taken on the day of first study vaccine administration, but the time is not available, this assessment will be considered for baseline assessment. Repeat and unscheduled assessments will be included in the derivation of the baseline values.

Change from Baseline:

The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

Change from Baseline Value = Result at Visit/Time Point – Baseline Value

The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.

Time to Onset of Event:

The time between the vaccination and the first event occurrence after each dose.

Duration of an Event:

For solicited AEs, the maximum duration for those events that have no interruptions during the 7 days. For example, if the event occurs on Day 1, Day 3, Day 4, and Day 5, the duration would be 3 days. Duration will be calculated considering the stop date from the Adverse Event CRF page for those events that last beyond day 7.

Conversion of Categorical Values:

In some safety assessments, continuous variables are expressed as a range (i.e., < 10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). As an example, a value of <10 may be converted to 10. Such substitutions will be clearly documented in the footnotes of relevant outputs.

5. STUDY PARTICIPANTS

5.1 Disposition of Participants

Participant disposition will include the number of participants who complete the full course of study treatment, participants who did not complete treatment, reason treatment was not completed, participants who completed the study, participants withdrawn from the study, as well as the primary reason for early discontinuation. Participant disposition will be summarized descriptively by vaccine schedule cohort and treatment arm for the Enrolled Set. This summary will include the number of participants enrolled but not treated.

A by-participant listing will be provided by vaccine schedule cohort and sorted by treatment arm and participant number for the Enrolled Set.

5.2 Analysis Sets

The number of participants included in each analysis set will be summarized descriptively overall, and by treatment arm and vaccine schedule cohort.

Reasons for exclusions from mITT Analysis Set, PPS Analysis Set, and Safety Analysis Set, including corresponding exclusionary protocol deviations, will be summarized.

In addition, the inclusion or exclusion into each of the defined analysis sets for each participant will be provided in by-participant data listings.

5.3 Protocol Deviations

All major/important protocol deviations (PDs) will be presented by deviation category and subcategory for each vaccination schedule cohort, sorted by treatment arm for Day 1 to Day 57 (Cohort 1, 29) and Day 1 to 85 (Cohort 1, 57) and Day 1 to end of study for the ITT Analysis Set.

Protocol deviations will be presented in a by-participant listing by vaccine schedule cohort and sorted by vaccination schedule cohort and treatment arm and participant number for major/important PDs and all PDs.

Protocol deviations will be reviewed by medical monitors and categorized as noted in the study specific protocol deviation specifications, including assessment of severity (major/important or exclusionary). Study vaccine errors (including overdose, underdose, and administration error) must be documented as protocol deviations. A brief description should be provided for the deviation, including if the participant was symptomatic or asymptomatic, and whether the event was accidental or intentional.

Prior to database lock (or data freeze if first analysis is completed), protocol deviations and analysis sets will be reviewed and confirmed to decide which participants and/or participant data

will be excluded from certain analyses. Decisions regarding exclusion of participants and/or data from analyses will be documented and approved prior to database lock.

5.4 Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the following demographic characteristics for participants in the Safety Analysis Set and Per Protocol Set by vaccination schedule cohort, treatment arm, and overall:

Continuous descriptive analysis:

- Age (years)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)

Categorical descriptive analysis:

- Age Category (18-59 years, 60-80 years)
- Sex
- Race
- Ethnicity

Demographic data will also be presented in the by-participant data listings.

5.5 Medical History

All medical conditions and prior surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Any signs and/or symptoms present in a subject prior to the study vaccination will be recorded as Medical History. The number and percent of participants with each medical condition and prior surgical procedure will be presented by vaccination schedule cohort, treatment arm, and overall, for each SOC and PT for the Safety Analysis Set.

Medical history data will also be presented in the by-participant data listings by vaccine schedule cohort and sorted by treatment arm and participant number.

5.6 Prior and Concomitant Medications

All prior and concomitant medications (including medications, blood products, and vaccines) will be coded using World Health Organization (WHO) drug classifications.

5.6.1 Prior Medications

Prior medications are defined as any medication that ended prior to the first administration of the study vaccine.

The number and percent of participants in the Safety Analysis Set with prior medications will be tabulated by vaccination schedule cohort, treatment arm, and overall by anatomical, therapeutic, and chemical (ATC) class level 2 term and preferred term. Participants who used the same

medication on multiple occasions will only be counted once in the specific category.

Prior medications will be presented in a by-participant listing by vaccine schedule cohort and sorted by treatment arm and participant number.

5.6.2 Concomitant Medications

Concomitant medications include medications and vaccines (other than the study vaccine) taken by the participant after the first administration of the study vaccine. Medications that were stopped on the same date as the first study vaccine administration will be defined as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.

The number and percent of participants in the Safety Analysis Set using concomitant medications will be tabulated by vaccination schedule cohort, treatment arm, and overall by ATC class level 2 term and preferred term. Participants who used the same medication on multiple occasions will only be counted once in the specific category.

Concomitant medications will be presented in a by-participant listing by vaccine schedule cohort and sorted by treatment arm and participant number.

5.7 Surgical and Medical Procedures

All surgical and medical procedures after the first study vaccine administration will be classified by SOC and PT using the MedDRA. Surgical and medical procedure data will be presented in by-participant data listings by vaccine schedule cohort and sorted by treatment arm and participant number.

6. EFFICACY ANALYSIS AND ENDPOINTS

There is no efficacy analysis planned for this study.

7. IMMUNOGENICITY ANALYSIS

The Per Protocol (PPS) Analysis Set will be used for the primary, secondary, and exploratory immunogenicity analyses. If more than 5% participants are excluded from PPS Analysis Set as compared to mITT Analysis Set, the analysis will be repeated for the mITT Analyses Set. The PPS Analysis Set for the second/final analyses may exclude the last timepoint due to missing values or protocol deviations. The exclusionary information for the PPS and mITT sets can be found in the Protocol Deviation Specifications and Other Analysis Exclusionary Criteria document. The immunogenicity assessments for the study may be found in Appendix C.

Descriptive immunogenicity analysis including geometric mean titer (GMT), geometric mean fold rise (GMFR), proportion of participants with antibody titer ≥pre-specified thresholds, and seroconversion rate (SCR) will be produced for each study group (i.e., investigational arms and historical control group) at all available time points. Immunogenicity analyses will not be conducted for the control vaccine group from the study.

Geometric mean (GM) will be calculated as the mean of the antibody results after the data are log-transformed and then antilog the log-mean to present the results on the original scale. Two-

sided 95% CI will be obtained by taking the log transformation of the antibody results and calculated based on t-distribution; then antilog the confidence limit.

GMFR analysis will include participants with antibody results available at both baseline (prior to dose) and post-vaccination. It will be calculated as the mean of the difference after log-transformed results (post-baseline minus baseline) and exponentiating the mean. Two-sided 95% CI will be obtained by taking log transform of the antibody results and calculated the 95% CI based on t-distribution for the mean difference after the data are log-transformed, then antilog the confidence limit.

For GMT and GMFR imputation, refer to section 4.4.

A sensitivity analysis for GMTs and GMFRs may be conducted using an analysis of covariance (ANCOVA) model with the dose level as a factor and baseline antibody level (log scale) as a covariate.

The percentage of participants with seroconversion (SC) will be summarized and the 95% CI by the Clopper-Pearson method will be presented.

Seroconversion is defined as binary variable for participants with non-missing values at pre-vaccination and post-vaccination as:

- = 1 if there is a pre-vaccination titer below the LLOQ for the respective assay and a post-vaccination titer ≥4 x LLOQ
- = 1, if there is a pre-vaccination titer ≥ LLOQ and a ≥4-fold increase in post-vaccination titer
- = 0, otherwise

An alternative definition to the seroconversion rate (SCR) is if there is at least 4-fold increase (post-vaccination) from pre-vaccination titer when titer <LLOQ are imputed as LLOQ/2. An analysis for this alternative definition will be completed as described above.

The LLOQ will be equal to 10 for HAI assays, 10 for MN assays, and 13 for ELLA assays. The ULOQ will be 1280 for HAI assays, 12802 for MN assays, and 137280 for ELLA assays.

Immunogenicity results for each assay will be listed.

7.1 Primary Immunogenicity Endpoints and Analyses

Primary objective 2 is to describe the hemagglutination inhibition (HAI) antibody responses against the HA glycoprotein through 28 days after the second vaccination. This will be done by measuring serum HAI antibody titers against the H5N1 HA glycoprotein on Days 1, 29, 36 and 57 (Cohort D1,29) and on Days 1, 57, 64 and 85 (Cohort D1,57), in:

  - ARCT-2304 recipients (by dose level)
  - Historical control vaccine recipients

Primary objective 3 is to describe the neuraminidase enzyme-linked lectin assay (ELLA) antibody responses against the NA glycoprotein, through 28 days after the second vaccination. This will be measured by serum ELLA antibody titers against the H5N1 NA glycoprotein on

Days 1, 29, 36, and 57 (Cohort D1,29) and on Days 1, 57, 64, and 85 (Cohort D1,57), in:

- ARCT-2304 recipients (by dose level)

For both objectives, descriptive immunogenicity analysis including GMT, GMFR, and SCRs (including analysis utilizing the alternative SCR definition) will be produced by vaccine schedule cohort and treatment arm at all available time points as indicated above, along with the 95% CIs.

The proportion of participants with antibody titer≥1:10, 1:20, 1:40, 1:80, 1:160, 1:320 will be presented for objective 2 and objective 3.

Missing data will not be imputed unless otherwise specified.

7.2 Secondary Immunogenicity Endpoints and Analyses

Secondary objective 2 is to describe the persistence of humoral immune response, following ARCT-2304, as measured by HAI and ELLA assays against the HA and NA glycoproteins throughout the entire study period. This will be done by measuring serum HAI and ELLA antibody titers against the HA and the NA glycoproteins on Days 1, 29, 36, 57, and 240 (Cohort D1,29) and Days 1, 57, 64, 85, and 240 (Cohort D1,57) in:

- ARCT-2304 recipients (by dose level)

Secondary objective 3 is to describe serum neutralizing microneutralization (MN) antibody titer against the HA glycoprotein through 28 days after the second vaccination. This will be measured by serum MN antibody titers against the HA glycoprotein on Days 1, 29, 36, 57, and 240 (Cohort D1,29) and on Days 1, 57, 64, 85, and 240 (Cohort D1,57), in:

- ARCT-2304 recipients (by dose level)
- Historical control vaccine recipients

For both objectives, descriptive immunogenicity analysis including GMT, GMFR, and SCRs (including analysis utilizing the alternative SCR definition) will be produced by vaccine schedule cohorts and treatment arm at all available time points indicated above, along with the 95% CIs.

The proportion of participants with antibody titer ≥1:10, 1:20, 1:40, 1:80, 1:160, and 1:320 will be presented for objective 2 for HAI, with the addition of 1:640 and 1:1280 for ELLA, and antibody titer ≥1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, and 1:1280 for objective 3.

Missing data will not be imputed unless otherwise specified.

7.3 Exploratory Efficacy Endpoints and Analyses

The exploratory objective is to by describe HA and NA-specific CD4+ and CD8+ T-cell responses elicited by the different dose levels of ARCT-2304. This will be measured by expression of activation markers and subset-specific markers by ELISpot following HA and NA peptide pool stimulation on Days 1, 8, 29 and 36 (Cohort D1,29) and on Days 1, 8, 57 and 64 (Cohort D1,57), in:

- ARCT-2304 recipients (by dose level).

Percentages of T-cells responding to HA and NA influenza vaccine antigens by assessing cells

expressing markers such as interferon-gamma (IFN-γ), interleukin 13 (IL-13), interleukin 4 (IL-4), interleukin 2 (IL-2), and TNF-α (tumor necrosis factor alpha) (e.g., RNA sequencing) will be produced by vaccine schedule cohort and treatment arm, as well as overall.

7.4 Prognostic Factors and Subgroup Analyses

Subgroup analyses will be performed for the primary immunogenicity endpoints (primary objective 2 and primary objective 3).

Separate analyses will be performed for each of the following subgroups within each cohort:

- Males
- Females
- Participants 18-59 years old at enrollment
- Participants 60-80 years old at enrollment

8. SAFETY ANALYSIS

All safety summaries will be conducted using the Safety Analysis Set. No formal hypothesis testing will be performed to compare differences between treatment arms.

8.1 Extent of Exposure

All study vaccine administration information on Day 1 and Day 29/Day57, including if study vaccine was administered, if it was administered per protocol, date and time of administration, reason if not administered, and location of injection (left deltoid/right deltoid), will be presented in the by-participant data listings.

Number and percentage of participants who received each vaccine will be summarized by vaccine schedule cohort, treatment arm, and overall for the Safety Analysis Set.

8.2 Adverse Events

An AE is any untoward medical occurrence in a participant or participant administered a medicinal product, whether or not considered related to the study vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

8.2.1 Serious Adverse Events (SAE)

An SAE is defined as any AE that, at any dose:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent disability/incapacity.
- Is a congenital anomaly/birth defect.

- Is a medically important event.

8.2.2 Medically Attended Adverse Events (MAAE)

MAAEs are defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits (including phone/telehealth visits) to or from medical personnel for any reason, but do not fulfill seriousness criteria. Routine study visits will not be considered medically attended visits.

8.2.3 Adverse Events of Special Interest (AESI)

Adverse events of special interest include:

- Myocarditis / pericarditis
- Anaphylaxis
- Thrombocytopenia
- Generalized convulsion
- Acute disseminated encephalomyelitis
- Acute peripheral facial paralysis (Bell's Palsy)
- Guillain Barre Syndrome

Cases of myocarditis and/or pericarditis occurring in temporal association with vaccination will be considered potentially related, unexpected, and serious.

8.2.4 Assessment of Intensity

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

- Mild (Grade 1): transient with no limitation in normal daily activity
- Moderate (Grade 2): some limitation in normal daily activity
- Severe (Grade 3): unable to perform normal daily activity
- Potentially Life-Threatening (Grade 4): an event in which the participant was at immediate risk of death at the time of the event
- Fatal (Grade 5): an event with a fatal outcome

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

8.2.5 Assessment of Causality

The investigator is obligated to assess the relationship between study vaccine and each occurrence of each AE. The AE must be characterized as related or unrelated:

- **Related**: An AE that followed a temporal sequence from administration of a drug

(including the course after withdrawal of the drug), or for which possible involvement of the drug could not be ruled out, although factors other than the drug, such as underlying diseases, concurrent medical conditions, concomitant drugs, and concurrent treatments, were also responsible.

- **Unrelated**: An AE that did not follow a temporal sequence from study administration of a drug and/or that could reasonably be explained by other factors, such as underlying diseases, concurrent medical conditions, concomitant drugs, and concurrent treatments.

8.2.6 Assessment of Outcome of AE

The investigator will assess the outcome of all AEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not yet recovered/not yet resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).
- Unknown.

All SAEs with the outcomes of 'recovering/resolving' and 'not yet recovered/not yet resolved' will be reviewed at visit Day 240 to confirm the outcome of the event.

8.2.7 Solicited Local and Systemic AEs

Solicited events are reactogenic events that are recorded in the electronic diary card (eDiary). Solicited local reactions and systemic AEs will be recorded daily for seven consecutive days after study vaccination. If the participant missed completing a daily eDiary, the participant will contact the site immediately (within 24 hours of the missed day). Site staff will collect missed eDiary data via a paper diary and manually enter it in Rave EDC (electronic data capture).

If the eDiary was not completed, and a paper diary was collected within 24 hours of the missing eDiary timepoint, it will be pooled with the eDiary data for reporting purposes.

If the participant has experienced worsening symptoms of a solicited adverse event, they will enter this information in a Worsening Symptoms eDiary. If the Worsening Symptoms eDiary was not completed, a paper diary can be collected within 24 hours of the missing Worsening Symptoms eDiary timepoint.

Solicited local (injection site) reactions:

- Injection site pain
- Erythema
- Swelling

Solicited systemic AEs:

- Fatigue
- Headache

- Myalgia
- Arthralgia
- Dizziness
- Nausea
- Chills
- Fever (≥100.4 °F [≥38.0 °C]).

Severity grading for solicited AEs are presented in Table 5.

Table 5. Severity Grading for Solicited Local Reactions and Systemic Adverse Events

	Mild	**Moderate**	**Severe**
Pain	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Erythema	25-50 mm	51-100 mm	> 100 mm
Swelling	25-50 mm	51-100 mm	> 100 mm
Fatigue	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Headache	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Myalgia	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Arthralgia	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Nausea	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Dizziness	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Chills	No interference with daily activities	Interferes with daily activities	Prevents daily activity
Fever (°F°C)	100.4 – 101.1 (38.0-38.4)	101.2 – 102.0 (38.5-38.9)	≥102.1 (≥39.0)

Note: Based on Food and Drug Administration (FDA) Guidance Document: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

8.2.8 Unsolicited AEs

An unsolicited AE is an AE that is not listed as 'solicited' as outlined above. Solicited AEs that last for more than 7 days will be considered as unsolicited AEs. All unsolicited AEs including SAEs, MAAEs, and AESIs, will be coded using MedDRA. All unsolicited AEs collected following the first administration will be considered AEs and will be included in the summaries. Any (serious and non-serious) unsolicited AEs will be collected within 28 days after each study vaccination.

8.3 Adverse Event Summaries

8.3.1 Solicited Local and Systemic AEs

The vaccination diary and worsening symptom diary will be compiled, and the last entry will be used in summary tables. If the electronic diary card (eDiary) was not completed by the participant, and a paper diary was collected within 24 hours of the missing eDiary timepoint by site staff, the paper diary data will be included in the solicited adverse events analyses.

All electronic diary and paper diary entries (vaccination diary and worsening symptom diary) will be presented in a listing by vaccine schedule cohort and sorted by treatment arm and participant number.

For solicited AEs, the following will be summarized by vaccine schedule cohort, treatment arm, and overall:

- the number and percentage of participants experiencing at least one solicited AE within 7 days of each vaccination
- the number and percentage of participants experiencing at least one solicited AE by category (local or systemic) and by type (see section 8.2.7) within 7 days of each vaccination
- the number and percentage of participants experiencing a solicited AE overall and within each category and type within 7 days of each vaccination by severity (mild, moderate, severe)
- the number and percentage of participants experiencing a solicited AE overall and within each category and type within 7 days of vaccination by diary day after each vaccination.

An eDiary compliance table will include the following summarized by vaccine schedule cohort, treatment arm, and overall:

- number and percentage of participants who recorded in their eDiary by period, where period include the following for each vaccination: Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 1-3, Day 1-5, Day 1-7.
- percentage of diary data that was completed as eDiary and as paper diary.

Duration and time to onset of events will be summarized by vaccine schedule cohort, treatment arm, and overall using descriptive statistics for the continuous variables.

Injection-site erythema and swelling will be summarized according to categories based on linear measurements, where mild is 25-50 mm, moderate is 51-100 mm, and severe is >100 mm. The frequency and percentage of participants in each group will be generated by vaccine schedule cohort, treatment arm, and overall.

Use of antipyretics and analgesics will be summarized vaccine schedule cohort, treatment arm, and overall, by frequency and percentage of participants reporting use.

Body temperature will be summarized by frequency and percentage of participants for 0.5°C increments from 38.0°C up to ≥40°C. In addition, frequency and percentage of participants by grade (mild, moderate, or severe) will be provided by vaccine schedule cohort, treatment arm, and overall.

Separate summaries will be performed for each of the following subgroups within each cohort for solicited adverse events:

- Males
- Females
- Participants 18-59 years old at enrollment
- Participants 60-80 years old at enrollment

A sensitivity analysis will be performed excluding all paper diary data. The following will be summarized:

- the number and percentage of participants experiencing at least one solicited AE within 7 days of each vaccination
- the number and percentage of participants experiencing at least one solicited AE by category (local or systemic) and by type within 7 days of each vaccination
- the number and percentage of participants experiencing a solicited AE overall and within each category and type within 7 days of vaccination by severity (mild, moderate, severe)

8.3.2 Unsolicited AEs, SAEs, MAAEs, and AESIs

Summary tables will include the number of participants (%) experiencing an event along with the number of events. Participants will be counted only once for each SOC and PT level (categorical descriptive analysis). All AE summaries will be presented by vaccine schedule cohort, treatment arm, SOC and PT.

For unsolicited AEs, the following will be summarized by vaccine schedule cohort, treatment arm, and overall for the Safety Analysis Set:

i. The first final analysis will include an overall summary of AEs from Day 1 to Day 57 (Cohort 1,29) and Day 1 to 85 (Cohort 1,57), as well as separate summaries for younger adults aged 18-59 and older adults aged 60-80, which consists of the following:

   a. the number and percentage of participants experiencing an unsolicited AE within 28 days after vaccination for the first dose, second dose, or either dose
   b. the number and percentage of participants experiencing an unsolicited AE related to study vaccine within 28 days after vaccination for the first dose, second dose, or either dose
   c. the number and percentage of participants experiencing an unsolicited AE by greatest intensity within 28 days after vaccination for the first dose, second dose, or either dose
   d. the number and percentage of participants experiencing an unsolicited AE related to study vaccine by greatest intensity within 28 days after vaccination for the first dose, second dose, or either dose
   e. the number and percentage of participants experiencing an unsolicited AE within 60 minutes after study vaccination for the first dose, second dose, or either dose
   f. the number and percentage of participants experiencing an MAAE
   g. the number and percentage of participants experiencing an MAAE related to study vaccine
   h. the number and percentage of participants experiencing an AESI
   i. the number and percentage of participants experiencing an AESI related to study vaccine

j. the number and percentage of participants experiencing an SAE
k. the number and percentage of participants experiencing an SAE related to study vaccine
l. the number and percentage of participants experiencing an SAE by greatest intensity
m. the number and percentage of participants experiencing an SAE related to study vaccine by greatest intensity
n. the number and percentage of participants experiencing an AE of Grade 3 or higher
o. the number and percentage of participants experiencing an AE leading to study withdrawal
p. the number and percentage of participants experiencing an AE leading to death

ii. The second final analysis will include an overall summary of selected AEs from Day 1 to Day 240, which consists of the following:

a. the number and percentage of participants experiencing an MAAE
b. the number and percentage of participants experiencing an MAAE related to study vaccine
c. the number and percentage of participants experiencing an AESI
d. the number and percentage of participants experiencing an AESI related to study vaccine
e. the number and percentage of participants experiencing an SAE
f. the number and percentage of participants experiencing an SAE related to study vaccine
g. the number and percentage of participants experiencing an SAE by greatest intensity
h. the number and percentage of participants experiencing an SAE related to study vaccine by greatest intensity
i. the number and percentage of participants experiencing an AE of Grade 3 or higher
j. the number and percentage of participants experiencing an AE leading to study withdrawal
k. the number and percentage of participants experiencing an AE leading to death

iii. the number and percentage of participants experiencing an unsolicited AE by SOC and PT within 28 days after vaccination for the first dose, second dose, or either dose

iv. the number and percentage of participants experiencing an unsolicited AE related to study vaccine by SOC and PT within 28 days after vaccination for the first dose, second dose, or either dose

v. the number and percentage of participants experiencing an unsolicited AE by SOC, PT and greatest intensity within 28 days after vaccination for the first dose, second dose, or either dose

vi. the number and percentage of participants experiencing an unsolicited AE related to study vaccine by SOC, PT, and greatest intensity within 28 days after vaccination for the first dose, second dose, or either dose

vii. the number and percentage of participants experiencing an unsolicited AE within 60 minutes after study vaccination administered by SOC and PT

viii. the number and percentage of participants experiencing an MAAE by SOC and PT

ix. the number and percentage of participants experiencing an MAAE related to study vaccine by SOC and PT

x. the number and percentage of participants experiencing an AESI by SOC and PT

xi. the number and percentage of participants experiencing an AESI related to study vaccine by SOC and PT

xii. the number and percentage of participants experiencing an SAE by SOC and PT

xiii. the number and percentage of participants experiencing an SAE related to study vaccine by SOC and PT

xiv. the number and percentage of participants experiencing an AE Grade 3 or higher by SOC and PT

xv. the number and percentage of participants experiencing an AE leading to study withdrawal by SOC and PT

xvi. the number and percentage of participants experiencing an AE leading to death by SOC and PT

In the overall summary of unsolicited AEs tables (i and ii), besides tabulating the number and percentage of participants, the total number of unsolicited AE episodes will also be provided. If a participant has repeated episodes of a particular unsolicited AE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of unsolicited AEs will be calculated by dividing the number of participants who have experienced the event by the total number of participants in the Safety Analysis Set. Thus, the incidence of unsolicited AEs is shown in terms of the total number of participants and not in terms of the total number of episodes. If a participant has repeated episodes of a particular unsolicited AE, only the most severe episode, or the episode with the strongest causal relationship to study vaccine, will be counted in the summary tables.

A participant with more than one type of unsolicited AE in a particular SOC will be counted only once in the total of participants experiencing unsolicited AEs in that particular SOC. Since a participant could have more than one type of unsolicited AE within a particular SOC, the sum of participants experiencing different unsolicited AE within the SOC could appear larger than the total number of participants experiencing unsolicited AEs in that SOC. Similarly, a participant who has experienced an unsolicited AE in more than one SOC will be counted only once in the total number of participants experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each participant, grouped by vaccine schedule cohort and treatment arm. The listing will contain the following information: vaccine schedule cohort, treatment arm, verbatim term, SOC, PT, intensity, action taken with study vaccine (if applicable), relationship to study vaccine, relationship to study procedure (other than vaccine), date and day of onset, date and day of resolution, treatment given to treat the adverse event (if applicable), the outcome, whether the event was an SAE and corresponding criteria, AESI, or MAAE, and whether it led to withdrawal. Listings will be presented by vaccine schedule cohort sorted by treatment arm, participant identification number, onset date, SOC, and PT.

Missing data will not be imputed.

8.4 Clinical Laboratory Assessments

Table 6 shows the laboratory assessments for ARCT-2304-01 study. Safety laboratory tests will be performed by the central laboratory at screening, Days 1, 8, 29, 36 (D1,29 cohort) and at screening, Days 1, 8, 57, 64 (D1,57 cohort).

Table 6. Laboratory Assessments

Screening only	Hematology	Blood Chemistry	Coagulation
Hepatitis B virus surface antigen, Hepatitis C virus antibody, Human immunodeficiency virus type 1 and 2 antibodies; Follicle-stimulating hormone (may be measured to confirm menopausal status at the discretion of the investigator) β-human chorionic gonadotropin for women of childbearing potential (WOCBP)	Complete blood count: Red blood cells (RBC) Hemoglobin Hematocrit White blood cells (WBC) total and differential Platelet count	Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) Creatinine Random glucose Total bilirubin Total protein	Partial thromboplastin time Prothrombin time*

*Summary Tables for Prothrombin Time will also be generated excluding samples out of normal range from site 1442 before 03 March 2025 due to known issues with laboratory equipment.

Should safety laboratory testing at 7 days post vaccination result in a Grade 2 or greater toxicity score, then repeat testing must be performed within the next 10 days and this may include an unscheduled visit. Should the participant's laboratory test value not return to baseline, then periodic testing may be required until the abnormality is deemed to be associated with a new stable AE or determined to be not clinically significant (NCS) by the investigator. If a participant does have a laboratory Grade 2 or greater toxicity score following the administration of the first dose that has not returned to baseline, the Sponsor or Sponsor designee must be contacted to agree on continued dosing (see protocol).

Those values that fall within the normal range of the laboratory will automatically be classified as normal. All values that have a toxicity score of Grade 1 or greater will be evaluated by the

investigator and classified as 'abnormal clinically significant CS' or 'abnormal not clinically significant NCS' as follows:

- Abnormal clinically significant (CS) – laboratory abnormality cannot be explained or is judged by the investigator to be potentially clinically significant.
- Abnormal not clinically significant (NCS) – laboratory abnormality can be explained by a condition that is not related to vaccination and does not increase the risk for an adverse outcome of vaccination

Toxicity grades will be defined based on normal ranges and according to Guidance for Industry – Toxicity Grading Scale for Healthy adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trails: Table for Laboratory abnormalities (CBER 2007). A list of laboratory – specific normal ranges and associated toxicity grades will be provided in the laboratory manual.

All laboratory test values with toxicity score of Grade 3 or greater will be recorded as AE as well Grade 1 or greater abnormal clinically significant test values.

For laboratory assessments, the following will be summarized:

- Continuous clinical laboratory values will be summarized by presenting descriptive statistics of raw data and change from baseline values at each time point by vaccine schedule cohort and treatment arm.
- The percentage of participants who have hematology, chemistry, and coagulation results below or above the laboratory normal ranges will be tabulated by vaccine schedule cohort, treatment arm, and overall by timepoint.
- The number and percentage of participants who have treatment-emergent ≥ Grade 3 abnormal clinically significant laboratory values by vaccine schedule cohort, treatment arm, and overall by timepoint.
- The maximum grading from pre-vaccination up to 7 days post-vaccination will be tabulated by vaccine schedule cohort, treatment arm, and overall.
- All laboratory data from all (scheduled or unscheduled) visits will be listed.

8.5 Vital Signs

Descriptive summaries of the vital signs (both raw and change from baseline values) including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature will be prepared for each vaccine schedule cohort and treatment arm. The number and percentage of patients with abnormal clinical significance will also be provided for each vaccine schedule cohort, treatment arm, and overall.

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected at scheduled visits will be included in the summary tables.

8.6 ECG/Cardiac Enzymes Test

12-Lead Electrocardiography (ECG) and cardiac enzyme testing results will be presented in by-participant data listings.

8.7 Physical Examination

By-participant data listing will contain abnormal physical examination findings by visit.

8.8 Pregnancy Test Results

All information related to pregnancy testing (urine and serum based) will be presented in the by-participant data listings.

9. DSMB AND CENTRAL CARDIAC ADJUDICATION COMMITTEE

The study will include the use of an independent unblinded DSMB and a Central Cardiac Adjudication Committee.

9.1 DSMB

An independent, external DSMB will be established to evaluate participant safety throughout the entire study period. The DSMB will perform:

i. planned reviews of all available safety data

ii. reviews of all available safety and reactogenicity data if a pause rule is met and study vaccination is paused or if any safety concern is raised by principal investigator (PI) or sponsor.

The DSMB will make recommendations regarding study continuation, study design modification, and/or study termination. The responsibilities, roles, and procedures of the DSMB are described in the DSMB Charter.

Four DSMB meetings will be scheduled following the study design in Section 3.1.

1) Data Safety Monitoring Board (DSMB) review will be performed as soon as 7-day safety and reactogenicity data are available after the first vaccination for the first group of participants (Lead-in Cohort 1). The favorable outcome of reactogenicity and safety assessment by the DSMB will permit the expansion of recruitment of study participants in age group 18-59 years of age.
2) The second planned DSMB review will be performed as soon as 7-days safety and reactogenicity data are available after the second vaccination for the first group of participants (Lead-in Cohort 1). The safety review will include the totality of safety data (including all available safety of participants in the expansion age group 18-59 years. The favorable outcome of reactogenicity and safety assessment by the DSMB will permit the initiation of second vaccination in the expansion age group 18-59 years and recruitment of lead-in participants in the 60-80 years age group.
3) DSMB will review all available data for the Lead-in Cohort 2 as soon as 7-day safety and reactogenicity data after the first vaccination is available. A favorable outcome from the DSMB will permit the expansion of recruitment in age group 60-80 years
4) Following post-dose 2 assessment of Lead-in Cohort 2, DSMB will make a decision regarding administration of the second dose in the expansion age group 60-80 years.

Besides the four scheduled DSMB reviews as indicated above, the DSMB will perform periodic reviews of safety and reactogenicity data as soon as 7-day post-dose data are available (e.g., the first 80 and 120 recruited participants).

9.2 CENTRAL CARDIAC ADJUDICATION COMMITTEE

The study will include the use of an independent Central Cardiac Adjudication Committee.

A central cardiac adjudication committee evaluates any potential myocarditis/pericarditis cases (refer to Protocol for additional information). Further details are provided in the cardiac adjudication committee charter.

10. ANALYSIS TIMING

The results of this study may be released sequentially in two separate final analyses.

10.1 Interim Analysis

No interim analysis is planned for the study.

10.2 First Analysis

An analysis including all available safety, reactogenicity, and immunogenicity data associated with primary endpoints will be conducted on cleaned data through Day 57 (Cohort D1,29) and Day 85 (Cohort D1,57). Additionally, study participant information will be summarized. The results will be reported on a study group level only in a blinded fashion. Unblinded results may be generated by the unblinded team for unblinded staff. Refer to the Unblinding Plan for additional information. Neither blinded nor unblinded individual listings will be generated for this first analysis.

10.3 Second Analysis

A final analysis of safety and immunogenicity data associated with primary, secondary, and available exploratory endpoints will be performed as soon as the data are cleaned and locked. The results of this analysis will be presented in a final clinical study report. Data summaries and individual data listings with information on treatment allocation on the participant level will be generated and presented.

11. SAMPLE SIZE AND POWER CALCULATIONS

The sample size is not based on formal power calculations, it is based on clinical considerations to provide sufficient safety information to analyze the primary safety objective. With a sample size of n=150 participants who receive ARCT-2304, the probability of observing at least one adverse event is 98% and 78% if the true event rate is 2.5% and 1.0%, respectively. With a

sample size of n=50 per dose level, the probability of observing at least one adverse event is 92% and 72%, if the true event rate is 5.0% and 2.5%, respectively.

A sample size of up to 200 participants will provide evaluable and sufficient pre- and post-vaccination information to analyze the primary and secondary immunogenicity objectives.

12. REFERENCES

CBER 2007

Food and Drug Administration Guidance Document: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Document issued on September 2007. Available at https://www.fda.gov/media/73679/download (Accessed 15 Aug 2024).

13. APPENDICES

13.1 Appendix A: Schedule of Assessments for Days 1, 29 Cohort

Study Period	**Screening[a] (Day -28 – Day 1)**	**Treatment Period (Day 1 – Day 29)**			**Follow-up Period (Day 30 – Day 240)**					
Visit Type	**Screening Visit[a]**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Unscheduled Visit**
Visit Number	-	**V1**	**V2**	**V3**	**V4**	**V5**	-	-	**V6**	-
Study Day	**Day -28 to Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 36**	**Day 57**	**Day 120**	**Day 180**	**Day 240**	**NA**
Visit Window (Days)	**-28**	-	**+2**	**-1 /+2**	**-1 /+3**	**-3/+3**	**-7/+14**	**-7/+14**	**-7/+28**	**NA**
Study Event										
Informed Consent	X									
Demographics Data	X									
Medical History (including prior medication/ vaccinations)	X									
Physical Examination[b]	X	X*	X	X*	X	X			X	X
Vital Sign Measurement[c]	X	X*	X	X*	X	X			X	X
Electrocardiography (ECG)	X[d]									(X)
Blood for Screening Testing[e]	X									
Blood Sample for Safety Laboratory Tests[f]	X	X*	X	X*	X					(X)
Pregnancy Testing[g]	X	X*		X*						(X)

Study Period	**Screening[a] (Day -28 – Day 1)**	**Treatment Period (Day 1 – Day 29)**			**Follow-up Period (Day 30 – Day 240)**					
Visit Type	**Screening Visit[a]**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Unscheduled Visit**
Visit Number	-	**V1**	**V2**	**V3**	**V4**	**V5**	-	-	**V6**	-
Study Day	**Day -28 to Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 36**	**Day 57**	**Day 120**	**Day 180**	**Day 240**	**NA**
Visit Window (Days)	-28	-	+2	-1 /+2	-1 /+3	-3/+3	-7/+14	-7/+14	-7/+28	**NA**
Study Event										
Inclusion/Exclusion	X	X								
Randomization		X*								
Blood Sample for Antibody-mediated Immunogenicity[h]		X*		X*	X	X			X	
Blood Sample for Cell-mediated Immunogenicity[i]		X*	X	X*	X					
Study Vaccination[j]		X		X						
Post-Vaccination Safety Assessment		X		X						
Distribution of eDiary and Training		X								
Diary compliance check		D2 (±1) and D5 (±1)[m]		D30 (±1) and D33 (±1)[m]						
eDiary Review			X		X					
Follow-up Safety Call[k]							X	X		

Study Period	**Screening[a] (Day -28 – Day 1)**	**Treatment Period (Day 1 – Day 29)**			**Follow-up Period (Day 30 – Day 240)**					
Visit Type	**Screening Visit[a]**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Unscheduled Visit**
Visit Number	-	**V1**	**V2**	**V3**	**V4**	**V5**	-	-	**V6**	-
Study Day	**Day -28 to Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 36**	**Day 57**	**Day 120**	**Day 180**	**Day 240**	**NA**
Visit Window (Days)	**-28**	-	**+2**	**-1 /+2**	**-1 /+3**	**-3/+3**	**-7/+14**	**-7/+14**	**-7/+28**	**NA**
Study Event										
Assessment of Unsolicited AEs[l]		X	X	X	X	X				
Review of Safety Laboratory Results[m]		X	X	X	X					
Assessment of AEs with Medically Attended Visits[n]		← During the entire study period →								
Assessment of SAEs[n]		← During the entire study period →								
Assessment of AESIs[n]		← During the entire study period →								
Recording of Concomitant Medications and Vaccinations		← During the entire study period →								
Study Completion									X	
Early Termination		If participant terminates the study early, the Study Completion Procedures (except sample for antibody-mediated immunogenicity) should be completed								

13.2 Appendix B: Schedule of Assessments for Days 1, 57 Cohort

Study Period	**Screening[a] (Day -28 – Day 1)**	**Treatment Period (Day 1 – Day 57)**				**Follow-up Period (Day 58 – Day 240)**					
Visit Type	**Screening Visit[a]**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Unscheduled Visit**
Visit Number	-	V1	V2	-	V3	V4	V5	-	-	V6	-
Study Day	**Day -28 to Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 64**	**Day 85**	**Day 120**	**Day 180**	**Day 240**	**NA**
Visit Window (Days)	-28	-	+2	-1 /+2	-1 /+2	-1 /+3	-3 /+3	-7/ +14	-7 /+14	-7/+28	**NA**
Study Event											
Informed Consent	X										
Demographics Data	X										
Medical History (including prior medication/ vaccinations)	X										
Physical Examination[b]	X	X*	X		X*	X	X			X	X
Vital Sign Measurement[c]	X	X*	X		X*	X	X			X	X
Electrocardiography (ECG)	X[d]										(X)
Blood for Screening Testing[e]	X										
Blood Sample for Safety Laboratory Tests[f]	X	X*	X		X*	X					(X)
Pregnancy Testing[g]	X	X*			X*						(X)
Inclusion/Exclusion[a]	X	X									

Study Period	**Screening[a] (Day -28 – Day 1)**	**Treatment Period (Day 1 – Day 57)**				**Follow-up Period (Day 58 – Day 240)**					
Visit Type	**Screening Visit[a]**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Unscheduled Visit**
Visit Number	-	V1	V2	-	V3	V4	V5	-	-	V6	-
Study Day	**Day -28 to Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 64**	**Day 85**	**Day 120**	**Day 180**	**Day 240**	**NA**
Visit Window (Days)	-28	-	+2	-1 /+2	-1 /+2	-1 /+3	-3 /+3	-7/ +14	-7 /+14	-7/+28	**NA**
Study Event											
Randomization		X*									
Blood Sample for Antibody-mediated Immunogenicity[h]		X*			X*	X	X			X	
Blood Sample for Cell-mediated Immunogenicity[i]		X*	X		X*	X					
Study Vaccination[j]		X			X						
Post-vaccination Safety Assessment		X			X						
Distribution of eDiary and Training		X									
Diary compliance check		D2 (±1) and D5 (±1)[o]			D58 (±1) and D61 (±1)[o]						
eDiary Review			X			X					
Follow-up Safety Call[k]				X				X	X		

Study Period	**Screening[a] (Day -28 – Day 1)**	**Treatment Period (Day 1 – Day 57)**				**Follow-up Period (Day 58 – Day 240)**					
Visit Type	**Screening Visit[a]**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone Call**	**Phone Call**	**Clinic Visit**	**Unscheduled Visit**
Visit Number	-	**V1**	**V2**	-	**V3**	**V4**	**V5**	-	-	**V6**	-
Study Day	**Day -28 to Day 1**	**Day 1**	**Day 8**	**Day 29**	**Day 57**	**Day 64**	**Day 85**	**Day 120**	**Day 180**	**Day 240**	**NA**
Visit Window (Days)	-28	-	+2	-1 /+2	-1 /+2	-1 /+3	-3 /+3	-7/ +14	-7 /+14	-7/+28	**NA**
Study Event											
Assessment of Unsolicited AEs[l]		X	X	X	X	X	X				
Review of Safety Laboratory Results[m]		X	X		X	X					
Assessment of AEs with Medically Attended Visits[n]			← During the entire study period →								
Assessment of SAEs[n]			← During the entire study period →								
Assessment of AESIs[n]			← During the entire study period →								
Recording of Concomitant Medications and Vaccinations			← During the entire study period →								
Study Completion										X	
Early Termination			If participant terminates the study early, the Study Completion Procedures (except sample for antibody-mediated immunogenicity) should be completed								

* Procedures that should be completed before study vaccination.

a The following procedures will be conducted at the screening visit: informed consent process; collection of demographic data; medical history and concomitant medications; full physical examination including vital signs, ECG, pregnancy test (if applicable); collection of blood samples for screening and safety laboratory tests; and assessment of inclusion/exclusion criteria (this can be done either at screening visit or on Day 1).

b Physical examination: a full physical examination, including height and weight, will be performed at Screening; symptom-directed physical examinations will be performed at all other scheduled time points. Interim physical examinations will be performed at the discretion of the Investigator.

c Vital sign measurements: systolic and diastolic blood pressures, heart rate, respiratory rate, body temperature (by any method), and heart rate. Vital signs will be collected once, before dose administration and at least 60 minutes after administration of each dose (before participants are discharged from the clinic). Vital signs should be measured in a seated position after the participant has rested comfortably for at least 5 minutes.

d ECG will be performed at screening visit in all participants to identify potential asymptomatic myocarditis and pericarditis cases. In participants with signs or cardiac symptoms suggestive of myocarditis and/or pericarditis, diagnostic evaluation should be performed according to applicable guidelines on Myocarditis and Pericarditis after mRNA vaccines, including laboratory safety measurements (troponin-I, Troponin-T, creatine kinase myocardial band (CK-MB)) with ECG.

e Screening laboratory testing will include the following:
Serology: hepatitis B virus surface antigen, hepatitis C virus antibody, human immunodeficiency virus type 1 and 2 antibodies
Follicle-stimulating hormone level may be measured to confirm menopausal status at the discretion of the Investigator, β-human chorionic gonadotropin (WOCBP).

f Safety Laboratory tests should be included prior to the study vaccination (when applicable) and include:
Hematology: Complete blood count: red blood cells (RBC), hemoglobin, hematocrit, total and differential white blood cells (WBC) and platelet count
Blood Chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen (BUN), creatinine, random glucose, total bilirubin and total protein. Coagulation: partial thromboplastin time and prothrombin time. Blood samples for cardiac enzymes will be collected on Day 1 prior to vaccination (baseline) for all participants. The testing of baseline and post-vaccination samples for cardiac enzymes (Troponin-I, Troponin-T, CK-MB) might be performed based on the investigator's or Sponsor's discretion.

g A pregnancy test (β-human chorionic gonadotropin) will be performed on all female participants of childbearing potential at Screening (serum test); urine test can be used before the study vaccination (urine or serum pregnancy test at the discretion of the Investigator).

h For all participants, blood samples will be collected for the analysis of antibody-mediated immunogenicity.

i For a subset of participants in the D1,29 cohort and D1,57, blood samples will be collected for the analysis of cell-mediated immunogenicity. Testing for CD4+ and CD8+ T-cell response in D1,57 cohort samples might be performed as future research evaluation.

j Participants will receive intramuscular ARCT-2304 or a licensed seasonal influenza vaccine and placebo according to randomization. All participants will remain at the study site for at least 60 minutes after administration of each dose, for safety monitoring.

k Trained healthcare providers will call all participants to collect information relating to any medically attended AEs, AEs leading to study withdrawal, SAEs, AESIs, and information on concomitant medications associated with those events. For the Lead-in participants, four additional safety phone calls will be performed (on Day 2 and Day 4 after each vaccination). This call will follow a script and will be made by trained healthcare personnel.

l Unsolicited AEs will be collected from study vaccination (Day 1) to Day 57 (Days 1, 29 cohort) or to Day 85 (Days 1, 57 cohort).

m	Laboratory abnormalities should be assessed as soon as the laboratory reports are available. Additional tests might be conducted in case of any Grade ≥3 or clinically significant laboratory abnormalities.
n	Medically attended AEs, SAEs, AESIs, and AEs leading to withdrawal from the study will be collected from Day 1 to the study end.
o	Compliance checks for eDiary completion will be performed by site staff on Day 2 (±1), Day 5 (±1), Day 30 (±1) and Day 33 (±1) (D1, D29 Cohort) and on Day 2 (±1), Day 5 (±1), Day 58 (±1) and Day 61 (±1) (D1, D57 Cohort) after vaccination. The site will perform a check to verify that the participant has completed the eDiary. Participants will be contacted by telephone if the eDiary is incomplete. Compliance checks will be documented in the source but not included in the CRF.

13.3 Appendix C: Immunogenicity Assessments for ARCT-2304-01

Assay	Purpose	Sample	Days	Comment
HAI	Primary/Secondary endpoint	Serum	Days 1, 29, 36, 57, 240 (D1,29 cohort) and on Days 1, 57, 64, 85, 240 (D1,57 cohort)	Quantification of antibody response against the HA glycoprotein All ARCT-2304 vaccinated participants and historical control vaccine recipients
ELLA	Primary/Secondary endpoint	Serum	Days 1, 29, 36, 57, 240 (D1,29 cohort) and on Days 1, 57, 64, 85, 240 (D1,57 cohort)	Quantification of antibody response against the NA glycoprotein All ARCT-2304 vaccinated participants
Neutralization (MN)	Secondary endpoint	Serum	Days 1, 29, 36, 57, 240 (D1,29 cohort) and on Days 1, 57, 64, 85, 240 (D1,57 cohort)	Functional assessment of antibody response against the HA glycoprotein All ARCT-2304 vaccinated participants and historical control vaccine recipients
ELISpot (CMI)*	Exploratory endpoint	Whole blood (PBMCs)	Days 1, 8, 29, 36 (D1,29 cohort only)	Analysis HA and NA-specific CD4+ and CD8+ T-cell responses (Subset)

Abbreviations: CMI, Cell-mediated immunogenicity; HAI, hemagglutination inhibition; ELLA, enzyme-linked lectin assay; HA, hemagglutination; NA, neuraminidase; MN, Microneutralization; PBMC, peripheral blood mononuclear cell;
*CMI samples will be collected from a subset of approximately 10 participants per dose level in the D1,29 cohort only.

Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: Complete with Docusign: Arcturus ARCT-2304-01 SAP v2.0 22JAN2025.docx
Source Envelope:
Document Pages: 47
Signatures: 4
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Envelope Originator:
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
1/22/2026 12:01:52 PM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 1/22/2026 12:36:20 PM Viewed: 1/22/2026 12:36:28 PM Signed: 1/22/2026 12:37:01 PM
Electronic Record and Signature Disclosure: Not Offered via Docusign		
[redacted] Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 1/22/2026 12:36:20 PM Viewed: 1/22/2026 3:14:11 PM Signed: 1/22/2026 3:15:14 PM
Electronic Record and Signature Disclosure: Accepted: 1/22/2026 3:14:11 PM ID: [redacted]		

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 1/22/2026 12:36:20 PM Viewed: 1/22/2026 12:36:51 PM Signed: 1/22/2026 12:39:33 PM
Electronic Record and Signature Disclosure: Not Offered via Docusign		
[redacted] Security Level: Email, Account Authentication (Required), Login with SSO	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] Signed using mobile With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 1/22/2026 12:36:21 PM Viewed: 1/22/2026 12:37:53 PM Signed: 1/22/2026 12:38:57 PM
Electronic Record and Signature Disclosure: Accepted: 1/22/2026 12:37:53 PM ID: [redacted]		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	1/22/2026 12:36:21 PM
Certified Delivered	Security Checked	1/22/2026 12:37:53 PM
Signing Complete	Security Checked	1/22/2026 12:38:57 PM
Completed	Security Checked	1/22/2026 3:15:14 PM

Payment Events	Status	Timestamps

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