CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 22-0020 Stage 2
Study Title:
A Phase 2 Randomized, Open-Label, Multisite Trial to Inform Public Health Strategies Involving the Use of MVA-BN Vaccine for Mpox
NCT05512949

Version 2.0

DATE: 05 August 2024

RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 22-0020 Stage 2**
Development Phase:	Phase II
Products:	JYNNEOS Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN)
Form/Route:	Subcutaneous (SC)
Indication Studied:	Mpox
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	September 7, 2022
Clinical Trial Completion Date:	October 2024 (projected)
Date of the Analysis Plan:	August 5, 2024
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
C	Celsius
CEF	Chicken Embryo Fibroblast
CFR	Code of Federal Regulations
CI	Confidence Interval
CM	Centimeter
CRF	Case Report Form
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
DV	Protocol Deviation
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
EUA	Emergency Use Authorization
FA	Functional Scale Assessment
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMFR	Geometric Mean Fold Rise
GMTR	Geometric Mean Titer Ratio
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Intradermal
IRB	Institutional Review Board
LAR	Legal Authorized Representative
LLOD	Lower Limit of Detection

List of Abbreviations *(continued)*

MA	Memory Aid
MAAE	Medically Attended Adverse Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MH	Medical History
mITT	Modified Intention to Treat
mL	Milliliter
mM	Millimolar
mmHg	Millimeters of Mercury
MOP	Manual of Procedures
MPXV	Monkeypox virus
MS	Measurement
MVA-BN	JYNNEOS Modified Vaccinia Ankara-Bavarian Nordic
N	Number (typically refers to participants)
NAAT	Nucleic Acid Amplification Test
NI	Non-inferiority
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
No.	Number
N/A	Not Applicable
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PHEIC	Public Health Emergency of International Concern
PI	Principal Investigator
PMID	PubMed reference number
PP	Per Protocol
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Term
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event

List of Abbreviations *(continued)*

SAP	Statistical Analysis Plan
SC	Subcutaneous
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
$TCID_{50}$	Median Tissue Culture Infectious Dose
TFF	Tangential Flow Filtration
UC	University of California
µL	Microliter
UP	Unanticipated Problems
U.S.	United States
VV-WR	Vaccinia Virus, Western Reserve Strain
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase 2 Randomized, Open-Label, Multisite Trial to Inform Public Health Strategies Involving the Use of MVA-BN Vaccine for Mpox" (DMID Protocol 22-0020) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses for Stage 2 and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for immunogenicity and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

On July 23, 2022, the WHO Director-General declared that the multi-country outbreak of mpox constitutes a Public Health Emergency of International Concern (PHEIC). Since the first case of mpox was detected in the United Kingdom in a returning traveler from Nigeria on May 6, 2022, the outbreak has rapidly spread to 110 countries or locations worldwide, including 103 that are non-endemic, marking the first time mpox has spread widely outside Central and West Africa. In August of 2022, the number of confirmed mpox cases in the U.S. surpassed that of any other country [1,2]. To mitigate the consequences of this outbreak in the U.S., JYNNEOS vaccine is being offered to individuals considered to be at high risk for acquiring the disease. In Stage 1 of this platform study, we evaluated dose sparing strategies in adults because JYNNEOS, the only licensed vaccine for mpox, was in short supply. In Stage 2 of this study, we will evaluate vaccine safety and immunogenicity among adolescents ages 12 to 17 years to extend eligibility to the adolescent population, a population that may be at risk if the outbreak persists.

Mpox is a reemerging infectious disease caused by Monkeypox virus (MPXV), a large double-stranded DNA virus belonging to the *Orthopoxvirus* [3]. MPXV is a zoonotic orthopoxvirus, primarily transmitted to humans via contact with infected animals, and causing disease similar to smallpox, although with substantially lower mortality [3,4,5]. MPXV is endemic to West and Central Africa, where the incidence of human mpox cases has increased as much as 20-fold since the end of the smallpox vaccination campaign in 1980 [6,7]. Outbreaks in non-endemic countries have been related to the exotic pet trade [8] and international travel [10,11,12]. Prior to the current global mpox outbreak, secondary human-to-human transmission in non-endemic countries was rare, and documented only twice since 2018, with both cases involving travelers returning from Nigeria. Mpox reemerged in Nigeria in 2017 after more than 40 years with no reported cases [13,14]. On May 18, 2022, the first U.S. case of mpox was detected as part of the larger global outbreak [15]. The U.S. was the fourth non-endemic country to detect a case in a returning traveler. On August 4, 2022, the U.S. Department of Health and Human Services declared the U.S. mpox outbreak to be a public health emergency [16]. As of January 11, 2023, there have been 84,648 confirmed mpox cases worldwide including 29,980 confirmed cases and 21 deaths in the United States [1]. Vaccination is being used as a mitigation strategy in the current mpox outbreak for those exposed to and those deemed to be at higher risk of being exposed to mpox. There is one FDA-approved vaccine for mpox: JYNNEOS Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN); however, it is only approved for individuals ages 18 and older. On August 9, 2022, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the emergency use of the licensed SC dose for individuals less than 18 years of age determined to be at high risk for mpox.

While JYNNEOS is available under EUA for individuals younger than 18 years of age, an FDA approved mpox vaccine for adolescents is lacking and remains a public health need. Most reported cases in the global 2022 mpox outbreak have involved men who have sex with men, with a median age of 34 years. Among global cases with age data available, 1.2% are individuals ages 0-17 years [17]; in the United States, from May 17 through September 24, 2022, MPXV infections in persons under 18 years of age accounted for 0.3% of reported cases [18]. Among 55 adolescents ages 13-17 years, 89% were male, and the most common route of exposure was through male-to-male sexual contact (66%). Prior to the global 2022 outbreak, mpox occurred primarily in children and adolescents in endemic countries [19,20]. Increased MPXV transmission within adolescent populations could occur if the outbreak continues, or in future outbreaks, given the mode of transmission through skin and mucosal contact during sexual activity or other activities involving close contact with an infected individual.

2.1. Purpose of the Analyses

These analyses will assess the immunogenicity and safety of two doses of $1x10^8$ $TCID_{50}$ MVA-BN given subcutaneously 4 weeks apart among adolescents ages 12 to 17 years in comparison with adults ages 18 to 50 years and will be included in the clinical study report.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
Primary	
To determine if peak (Day 43) humoral immune responses in adolescents ages 12 to 17 years are non-inferior to adults after receipt of a 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN.	Vaccinia virus specific PRNT GMT at Day 43
To describe safety of a 2-dose 1 x 10^8 $TCID_{50}$ MVA-BN regimen administered SC in adolescents ages 12 to 17 years.	Frequency and severity of solicited systemic and local AE for 7 days after each vaccination. Frequency severity, and relatedness of unsolicited AEs for 28 days after each vaccination. Frequency and description of protocol specified AESIs from Day 1 through 210. Frequency and description of related MAAEs from Day 1 through 210. Frequency and relatedness of SAEs for duration of the study. Frequency and description of withdrawals and discontinuations of vaccination.
Secondary	
To evaluate humoral immune responses at baseline, prior to the second vaccination, and following receipt of the 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN in adolescents compared to adults on each study day.	Vaccinia virus specific PRNT GMT at Study Day 1, 29, 43, 210, and 394
To evaluate the kinetics of the humoral immune responses to the 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN in adolescents and adults through Day 394 after the second dose is administered.	Vaccinia virus specific PRNT half-life (t ½)
To compare relative safety and reactogenicity between adolescent and adult study arms.	Frequency and severity of solicited systemic and local AE for 7 days after each vaccination. Frequency severity, and relatedness of unsolicited AEs for 28 days after each vaccination. Frequency and description of protocol specified AESIs from Day 1 through 210. Frequency and description of related MAAEs from Day 1 through 210. Frequency and relatedness of SAEs for duration of the study. Frequency of withdrawals or discontinuation of vaccination in each study arm.

OBJECTIVES	ENDPOINTS (OUTCOME MEASURES)
To evaluate seroconversion between adolescent and adult study arms.	Vaccinia virus specific PRNT GMT at Study Day 29, 43, 210, and 394
Exploratory	
To evaluate other measures of the humoral immune responses for each regimen	Results from additional immunologic assays for vaccinia and other related viruses.
To evaluate humoral immune responses of the 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN to monkeypox virus in adolescents compared to adults.	Monkeypox virus specific PRNT GMT at Day 1 and 43.

3.2. Study Definitions and Derived Variables

Participants between ages 12 to 17 years at enrollment, inclusive, were analyzed as Adolescents. Participants at least 18 years old at enrollment were analyzed as Adults. These age group definitions were used for all clinical sites, including Ponce Medical School Foundation, Inc., CAIMED Center (Puerto Rico) where the legal age for an adult is 20 years old.

Baseline value will be defined as the last value obtained prior to the first vaccination/dose of study product.

Seroconversion for the Vaccinia virus specific plaque reduction neutralization test (PRNT) will be defined as any positive result if negative at baseline or a 2-fold increase in antibody titers above baseline if positive at baseline. A positive result is defined as antibody titers ≥ lower limit of detection (LLOD), i.e., a detectable result, and a negative result is defined as antibody titers <LLOD.

Immunogenicity results <LLOD will be imputed as ½ LLOD. If there are technical replicates, analyses will be performed on the geometric mean after imputations.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This study is a Phase 2 open-label, non-placebo controlled, multi-site clinical trial that will evaluate the safety and immunogenicity of two doses of $1x10^8$ $TCID_{50}$ MVA-BN given subcutaneously 4 weeks apart among adolescents ages 12 to 17 years compared to adults. Approximately 315 adolescents aged 12 to 17 will be enrolled, and at least 25% of adolescent participants will be aged 12 to 14 in order to ensure adequate enrollment numbers for younger adolescents. Approximately 135 adults ages 18 to 50 will be enrolled. The adults enrolled for Stage 2 will be combined with Stage 1 Arm 3 adults, which received the same subcutaneous standard dose as Stage 2 participants, to create the comparator group ("Pooled Adults") for the primary analysis.

Participants will not be stratified by clinical trial site, demographic characteristics, or Human Immunodeficiency Virus (HIV) infection status; however, these data will be collected during screening and enrollment. Each participant may be screened either in a separate visit in the 7 days prior to Day 1 or on Day 1. Participants will be followed as outlined in the Schedule of Activities. The last follow-up visit will be at about 1 year after the second vaccination. The study design for Stage 2 is presented in Table 1.

4.2. Discussion of Study Design, Including the Choice of Control Groups

This study is non-placebo controlled. Adolescents will be compared to adults dosed with the same regimen. Adults will be pooled from Stage 1 Arm 3 and Stage 2 Arm 4 as "Pooled Adults" for the primary immunogenicity analysis only.

4.3. Selection of Study Population

Stage 2 will enroll healthy, non-pregnant, non-breastfeeding, vaccinia-naïve adolescents ages 12 to 17 years, inclusive and a comparator arm of healthy, non-pregnant, non-breastfeeding, vaccinia-naïve adults ages 18 to 50 years, inclusive. Participants with stable medical conditions and well-controlled HIV infection can participate. Stage 2 will aim to enroll a population that is representative of the U.S. population based on the 2020 U.S. Census data to ensure broad applicability of the study findings given the aim of obtaining full licensure of JYNNEOS in adolescents. In addition, the goal is to enroll at least 25% adolescent participants ages 12 to14 years.

Participant Eligibility Criteria must be confirmed by an investigator named on the delegation log. If there is any uncertainty, the Principal Investigator (PI) should make the decision on whether a potential participant is eligible for study enrollment. They may also contact DMID Medical Officers to discuss. No exemptions are granted on Inclusion/Exclusion Criteria.

Inclusion Criteria

To be eligible to participate in Stage 2, an individual must meet the following inclusion criteria:

1. Adult ages 18 to 50 years inclusive at the time of consent; OR Adolescent ages 12 to 17 years inclusive at the time of consent.
2. Adult participant is able to read the written informed consent, states willingness to comply with all study procedures and is anticipated to be available for all study visits; OR Parent(s)/Legal Authorized Representative (LAR)(s) of the participating adolescent is able to read and provides written informed permission and participating adolescent provides assent as appropriate for age or development and

approved by IRB. Adolescent states willingness to comply with all study procedures and is anticipated to be available for all study visits.

3. Adult participant is able to understand and agrees to adhere to Lifestyle Considerations during the study; OR Parent(s)/LAR(s) of the participating adolescent is able to understand and states willingness to comply with Lifestyle Considerations. *Note: During this study, participants are asked to:*
   - *Follow public health guidance on preventing mpox infection and notify the clinical site if exposed to an individual with mpox.*
   - *Contact the clinical site immediately if they develop signs and symptoms consistent with mpox and a positive MPXV diagnostic test to schedule a study sick visit.*
   - *Contact the clinical site if they develop COVID-19 illness (with positive test for SARS-CoV-2 including those performed at home by the participant) during the study.*
   - *Refrain from receiving a live vaccine or COVID-19 vaccine in the 4 weeks before or after each study vaccination…*
   - *Refrain from receiving any other vaccine in the one week before or after each study vaccination.*
   - *Decline participation in another study evaluating investigational vaccines through Day 210 in Stage 2.*
   - *Decline participation in another study evaluating an investigational mpox vaccine, smallpox vaccine, or MVA-based vaccine through end of trial.*

   Of note, participants may enroll in non-interventional, observational studies (e.g., natural history study of mpox). However, concurrent participation in this trial and observational studies can only occur if the recommended blood collection volumes as specified by site Institutional Review Board guidance are not exceeded.
4. Females of reproductive potential who have sexual intercourse with male partners must be using highly effective contraception for at least 1 month prior to signing ICF and agrees to use acceptable method of contraception through Day 57.
5. In good general health as evidenced by medical history, physical examination, and clinical judgement of the investigator to be in stable state of health. *Note: Participants with pre-existing stable chronic medical conditions defined as conditions not requiring significant change in therapy or hospitalization for worsening disease in the 4 weeks prior to enrollment can be included at the discretion of the investigator. This includes stable, well-controlled HIV positive individuals.*
6. Individuals with HIV must be on suppressive ART for at least 6 months, report a CD4 count of greater than 350 cells/µL and no AIDS-defining illness in the last year.

Exclusion Criteria

For Stage 2 of the study, an individual who meets any of the following criteria will be excluded from participation in this study.

1. Ever received a licensed or an investigational smallpox or mpox vaccine. *Note: this includes Dryvax, Acam2000, LC 16 m8, MVA-based vaccine candidate or licensed vaccines, and Jynneos, Imvamune or Imvanex).*
2. Any history of mpox, cowpox, or vaccinia infection.

3. Close contact of anyone known to have mpox in the 3 weeks prior to signing ICF.
4. Immunocompromised as determined by the investigator.
5. Recent or current use of any immunosuppressing medications in the 4 weeks prior to signing ICF. *Note: topical, ophthalmic, inhaled, intranasal and intraarticular corticosteroids are acceptable, but receipt of ≥20 mg/day of prednisone or equivalent for ≥14 consecutive days in the 4 weeks prior to signing ICF is exclusionary.*
6. Pregnant or breast feeding.
7. Received or plans to receive a live vaccine or any COVID-19 vaccine in the 4 weeks before or after each study vaccination.
8. Received or plans to receive any other vaccine in the one week before or after each study vaccination.
9. Received experimental therapeutic agent or vaccine in the 3 months prior to signing ICF.
10. Has known allergy or history of anaphylaxis or other serious adverse reaction to a vaccine or vaccine products. *Note: this includes individuals with history of severe allergic reaction to gentamicin, ciprofloxacin, chicken or egg protein.*
11. Has tattoos, scars, or other marks which would, in the opinion of the investigator, interfere with assessment of the vaccination site.
12. Has any medical disease or condition that, in the opinion of the participating site PI or appropriate sub-investigator, precludes study participation. *Note: this includes acute, subacute, intermittent, or chronic medical disease or condition that would place the participant at an unacceptable risk of injury, render the participant unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the participant's successful completion of this trial.*
13. Adolescent or adult participant has a history of myocarditis/pericarditis or a history of structural congenital heart defect/cardiac dysrhythmia that, in the opinion of the investigator, poses increased risk to the participant.
14. Adolescent or adult participant has a history of COVID-19 (with positive test for SARS-CoV-2) in the 4 weeks prior to receipt of the first study vaccination. *Note: This includes positive rapid antigen test, polymerase chain reaction (PCR) assay, or other nucleic acid amplification (NAAT) test including those performed by the participant at home.*

4.4. Study Products

4.4.1. Vaccinations Administered

Participants will receive 0.5 mL subcutaneous MVA-BN 1 x 10^8 $TCID_{50}$, administered on Day 1 and Day 29.

4.4.2. Identity of Investigational Product(s)

Product: JYNNEOS is FDA-approved and licensed as a smallpox and monkeypox vaccine in the United States. The vaccine, when thawed, is a milky, light yellow to pale white colored suspension that is licensed for subcutaneous injection. JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus. MVA-BN is grown in primary Chicken Embryo Fibroblast (CEF) cells suspended in a serum-free medium containing no material of direct animal origin, harvested from the CEF cells, purified, and concentrated by several Tangential Flow Filtration (TFF) steps including benzonase digestion.

Each 0.5 milliliter (mL) dose is formulated to contain 0.5 x 10^8 to 3.95 x 10^8 infectious units of MVA-BN live virus in 10 millimolar (mM) Tris (tromethamine), 140 mM sodium chloride at pH 7.7. Each 0.5 mL dose may contain residual amounts of host-cell DNA (≤ 20 microgram (mcg)), protein (≤ 500 mcg), benzonase (≤ 0.0025 mcg), gentamicin (≤ 0.163 mcg), and ciprofloxacin (≤ 0.005 mcg).

4.4.3. Method of Assigning Participants to Vaccination Groups (Randomization)

Stage 2 is not randomized. All participants will receive two 0.5 mL doses of 1x10^8 $TCID_{50}$ MVA-BN given subcutaneously. For Stage 2, the aim is to enroll at least 25% of adolescents ages 12 to 14 years.

4.4.4. Selection of Doses in the Study

The dose licensed for adults, 0.5 mL MVA-BN 1 x 10^8 $TCID_{50}$, administered subcutaneously, will be used.

4.4.5. Selection and Timing of Dose for Each Participant

Doses will be given 4 weeks apart, which is the schedule licensed for adults.

4.4.6. Blinding

Stage 2 will not utilize blinding or masking procedures as it is not randomized. Research laboratories will be blinded to participant age group for the purposes of immunogenicity/efficacy evaluations.

4.4.7. Prior and Concomitant Therapy

At screening (i.e., the screening visit or Day 1 visit if the screening visit is not conducted separately), participants will be asked about receipt of immunosuppressive therapy, experimental therapeutic agents and vaccines, other medications, and vaccines. At each subsequent study visit through Day 57, new concomitant medication(s) and changes to existing medications will be recorded as well as receipt of a vaccine. For this study, concomitant medications to be reported in the Case Report Form (CRF) are prescription drugs, over-the-counter medications, and supplements. Concomitant medications taken and vaccines received in the 4 weeks prior to providing informed consent will be recorded in the CRF. Any drug taken or vaccine received by the participant during the trial should be recorded on the appropriate CRF through Day 57. In Stage 2, after Day 57, concomitant medication associated with a protocol specified AESI or related MAAE occurring through Day 210 and clinically relevant to report will be recorded in the CRF. After Day 57, any concomitant medication(s) associated with a related SAE occurring through the end of study and clinically relevant to report will be recorded in the CRF. Clinically relevant is defined as a medication that is prescribed or dose of an existing medication changed because of a SAE, AESI or MAAE. Medications taken that are unrelated to the adverse event do not need to be recorded (e.g., topical medication for acne). An exception to this schedule for recording concomitant therapy is during sick visits for those who have laboratory-confirmed mpox (illness). During sick visits, concomitant medications and treatment will be collected. Sick visits will be reported in Listing 13.

Medications that might interfere with the evaluation of the immune response to MVA-BN should not be used by the participant during the study-reporting period unless clinically indicated as part of the participant's health care for a condition diagnosed after enrollment. This would include any systemic immunosuppressant medication that may impact the immunogenicity endpoints. In the event medical conditions dictate the use of these medications, participants are encouraged to obtain adequate care, comply with the course of therapy as prescribed by their physician and inform the study Investigator as soon as practical.

4.4.8. Vaccination Compliance

All participants will receive two doses of study product administered in the clinic. Participants will be directly observed at the time of dosing by a member of the clinical research team who is licensed/credentialed to administer vaccines.

4.5. Immunogenicity and Safety Variables

See Table 2 for the Stage 2 schedule of study procedures.

Multiple observations within a specific visit period are accepted. In the case of multiple observations within a specific window, the assessment value that is closest to the scheduled visit window will be used in the analyses for the post-baseline records. For screening and baseline visits, the last assessment value prior to the administration of study product will be used. If observations have the same distance to the scheduled assessment, the latest one will be used.

Safety Variables

Adverse Events (AE): Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not the event is considered intervention-related (21 CFR 312.32 (a)). An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time the participant is screened and prior to the first dose will be considered as baseline and not reported as an AE. However, if the severity (i.e., grade) of any pre-existing medical condition increases, it should be recorded as an AE.

Adverse events can be further divided into solicited adverse events and unsolicited adverse events. Solicited adverse events are those for which the study team will specifically query the participant whether they occurred. Unsolicited adverse events are those events that the participant report occurring without being queried about the specific event.

Solicited Adverse Events: This study will collect the following solicited adverse events based on prior studies: local (pain at the site of the injection, erythema/redness, induration/swelling, pruritis) and systemic reactogenicity (fever, chills, nausea, headache, fatigue, change in appetite, myalgia [exclusive of the injection site], and arthralgia). Solicited adverse events will be collected on a memory aid by participants and reviewed by site staff and investigators. In addition, there is an expectation that some participants will develop skin discoloration and nodules which will be reported as AEs and not collected on the memory aid and followed through to resolution. For this study, the following toxicity grading scale is used: *"FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"* as a reference.

Of note, pruritis/itching, arthralgia, chills, and change in appetite are not included in the FDA toxicity table and will be graded according to Table 5. Additional clarification of induration grading is provided in Table 6.

Systemic and local solicited adverse events will be collected from Day 1 through Day 8, and Day 29 through Day 36. However, participants with ongoing systemic and/or local reactogenicity at Day 8 or Day 36 visit, will be asked to measure erythema/redness and/or induration/swelling until it has resolved, if applicable, and record end date of all other signs and symptoms.

Unsolicited Events: Unsolicited events are all AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

Unsolicited adverse events will be collected from Day 1 through Day 57. All AEs will be followed through resolution or until the site investigator deems the event to be chronic or the participant is stable.

Serious Adverse Events: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes (21 CFR 312.32 (a)):

- death
- a life-threatening adverse event*
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in inpatient hospitalization, etc.

* An adverse event is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include grade 4 severity unless the adverse event might have caused death.

For Stage 2, all SAEs will be collected from Day 1 through Day 394 (i.e., the end of study). All SAEs will be followed through resolution or until the site investigator deems the event to be chronic or the participant is stable.

Medically Attended Adverse Events (MAAE): A medically attended adverse event (MAAE) is defined as AEs with medically attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. Adverse events (e.g., abnormal vitals) identified at a routine study visit will not be considered MAAEs. In Stage 2, MAAEs that are deemed related to the vaccine or vaccination procedure will be collected from Day 1 through 210 and all SAEs will be collected from Day 1 through the end of the study. All related MAAEs will be followed through resolution or until the site investigator deems the event to be chronic or the participant is stable.

Suspected Unexpected Serious Adverse Reactions (SUSAR): A SUSAR is a SAE that is considered related to study product and unexpected. Unexpectedness to study product will be determined by what is listed in the JYNNEOS package insert.

Adverse Event of Special Interest (AESI): In Stage 2, protocol specified Adverse Events of Special Interest (AESIs) will be collected. AESIs are any adverse events for which additional data (in addition to standard AE data) are desired. The Sponsor (DMID), regulatory agency, or industry partner may request AESI reporting; the decision to collect AESI may be driven by a regulatory requirement or a known/potential risk from the study product or class. Non-structured data similar to SAEs will be collected for AESIs. AESIs encompass the following terms:

Protocol Specified AESIs: For Stage 2 of this trial, a protocol specified AESI is defined as a case of myocarditis or pericarditis. All participants with signs and symptoms of myocarditis/pericarditis (e.g., chest pain, shortness of breath, palpitations, etc.) in whom myocarditis/pericarditis is excluded, or for whom an alternative diagnosis is made, will not be considered a suspect case and as such, not reported as an AESI. All other suspected cases of myocarditis or pericarditis should be reported as an AESI and the case adjudicated using the Brighton Collaboration case definitions for myocarditis and pericarditis. The Brighton Collaboration

case definitions will be used to classify into possible, probable, or definite myocarditis or pericarditis cases [23]. In Stage 2, protocol specified AESIs will be collected from Day 1 through 210. All protocol specified AESIs will be followed through resolution or until the site investigator deems the event to be chronic or the participant is stable.

Severity: All AEs or SAEs will be assessed for severity, according to the toxicity grading scale, FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. For adverse events (AEs) not included in the protocol-defined grading scale, the following guidelines will be used to describe severity.

Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the participant's usual activities of daily living.

Moderate (Grade 2): Events that are 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 (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Life-threatening (Grade 4): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or care provided.

Relationship to Study Intervention: For each reported adverse event or reaction, the Principal Investigator or designee must assess the relationship of the event to the study product using the following guideline:

Related: The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

Not Related: There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Pregnancies: Pregnancy is not an AE. However, any pregnancy that occurs during study participation (through Day 394 for Stage 2) should be reported to the sponsor on the appropriate DCF. Pregnancy should be followed for safety and outcome. This follow-up will include pregnancy outcome (termination, pre-term birth, term birth) and newborn outcome (live birth, fetal demise, stillbirth; presence of any congenital anomalies). No in-person visits will be required for pregnancy outcome determination.

Unanticipated Problems (UP): The Department of Health and Human Services Office for Human Research Protections (OHRP) considers unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent, parental permission and assent documents; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents arising from noncompliance with study procedures will be reported as protocol deviations. An incident that qualifies as both a UP and a protocol deviation will be reported as both.

Immunogenicity Variables

The Bavarian Nordic (BN) Vaccinia virus Western Reserve strain (VV-WR) PRNT assay will be used as the primary assay to determine immunogenicity. Five time points (Days 1, 29, 43, 210, and 394) will be tested.

This study will also measure a monkeypox Virus Specific PRNT and will test a minimum of 2 time points (Days 1 and 43). Additional time points (Days 29, 210, and/or 394) may be evaluated as able (given lab throughput and cost).

Additional exploratory assessments of humoral immunity including Enzyme-linked Immunosorbent Assays (ELISAs) may be performed on samples from this trial.

5. SAMPLE SIZE CONSIDERATIONS

As a primary endpoint in Stage 2, 500 participants (130 adults in Arm 4; 70 adults in Arm 3 (Stage 1); 300 adolescents in Arm 5) will provide approximately 92% power for a test of non-inferiority (NI margin = 0.67) of geometric mean titers (GMT) using unequal variances and two-sided, type I error of 0.05 (Table 3). This assumes that the adult arm will have a standard deviation of 0.6 and adolescent arm will have a standard deviation of 0.5. The standard deviation on Day 42 in prior large studies using the SC route was 0.41 [21] and 0.59 [22], so the estimates used in calculations are justifiable. Stage 2 will enroll approximately 450 participants (135 adults in Arm 4; 315 adolescents in Arm 5) assuming a 5% drop-out rate. Participant enrollment into the adolescent cohort will be stratified into two 3-year age groups, at least 78 adolescents ages 12 to 14 years, and a maximum of 237 adolescents ages 15 to 17 years, in order to ensure that adequate numbers of younger adolescents are enrolled (i.e., about 25% of all adolescents enrolled). Arms 3 and 4 will be combined as a comparator group in the primary analysis only. It is not anticipated that there will be significant differences in immunogenicity outcomes between these two groups, however, a sensitivity analysis excluding Arm 3 participants will be performed.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, age group, and participant, and when appropriate by visit number within participant. All summary tables will be structured with a column for each age group in the order Adolescents, Adults, and will be annotated with the total population size relevant to that table/age group, including any missing observations.

6.2. Timing of Analyses

For Stage 2, the interim analysis will be performed after all participants have been followed through Study Day 43 (i.e., 14 days after the second dose for the last participant). The following tables and figures will be included in the interim analysis:

- Table 7 (rows 1-5 only): Participant Disposition by Age Group
- Table 8 (safety and mITT populations only): Analysis Populations by Age Group
- Table 13: Summary of Categorical Demographic and Baseline Characteristics by Age Group, All Enrolled Participants
- Table 14: Summary of Continuous Demographic and Baseline Characteristics by Age Group, All Enrolled Participants
- Table 16: Vaccinia Virus Specific PRNT Summary and Primary Hypothesis Testing, mITT Population
- Table 18 (Day 1, Day 29, and peak day time points only): Vaccinia Virus Specific PRNT Summary and Secondary Hypothesis Testing, mITT Population
- Table 21: Monkeypox Virus Specific PRNT Summary and Hypothesis Testing, mITT Population
- Figure 6 and Figure 8 (Day 1, Day 29, and Day 43 time points only): GMT of Vaccinia/Monkeypox Virus Specific PRNT by Time Point and Age Group, mITT Population
- Table 29 and Table 31: Vaccinia/Monkeypox Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion Results by Time Point and Age Group, mITT Population
- Table 39: Overall Summary of Adverse Events
- Table 43: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Age Group
- Table 58 and Table 59: Related Unsolicited Adverse Events Within 28 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Dose

An interim Clinical Study Report (CSR) will be performed on partially locked data. The interim CSR will include the final analysis of immunogenicity data through Day 43 and safety data through Day 210.

The final analysis of the remaining data will be performed after final database lock.

6.3. Analysis Populations

Summaries and analysis of safety data will be presented for the Safety Population. Summaries and analysis of immunogenicity data will be presented for the Modified Intent-To-Treat (mITT) Population and, if there are protocol deviations which may affect analysis, the Per Protocol (PP) Population. The PP Population will serve as a qualitative comparison to results in the mITT Population. The composition of analysis populations, including reasons for participant exclusion, by age group, will be presented in Table 8. A listing of all participants, visits, and observations excluded from the analysis populations will be provided in the CSR (Listing 5).

6.3.1. Modified Intent-to-Treat (mITT) Population

The mITT population will include all enrolled participants who received at least one dose of vaccine and contributed both pre- and at least one post-vaccination venous blood sample for immunogenicity testing for which valid results were reported.

6.3.2. Per Protocol (PP) Population

The PP population will be defined as all participants in the mITT subset with the following exclusions:

- Data from all available visits for participants found to have been ineligible at baseline.
- Data from all visits after the protocol deviations that are considered to affect the science (as determined by the sponsor at an ad hoc meeting). Major protocol deviations include but are not limited to the following
    - Did not receive second study vaccination
    - Did not receive full dose or received incorrect dose
    - Received any non-study vaccination within 7 days of study vaccination
- Data from any visit that occurs substantially out of window. Substantially out of window will be defined as a visit, including dosing visit, occurring more than three days before or more than seven days after the visit window. Visit windows for visits post dose 2 will be adjusted to reflect the actual date of receipt of Dose 2 not based on days post Dose 1.

6.3.3. Safety Population

The safety analysis population will include all enrolled participants who receive at least one dose of study vaccine.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses.

As part of an exploratory analysis, select analyses will present the Adolescent subgroups separately – 12 to 14 years old and 15 to 17 years old, inclusive.

6.5. Missing Data and Outliers

All attempts will be made to collect all data per protocol. No imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine

the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

6.6. Interim Analyses and Data Monitoring

Safety Review

Safety oversight will be conducted by a Data Safety Monitoring Board (DSMB) that is an independent group of experts that monitors participant safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information and solicited and unsolicited AE/SAEs. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor will be responsible for reviewing SAEs in real time.

For Stage 2 of the study, the DSMB will conduct the following reviews:

- Approximately 115 to 130 days after the study start. Given the planned 8 to 10-week enrollment period, and second dose of vaccine given on day 29, the window for review in Stage 2 was extended. As such, the review will focus on AEs utilizing real time reports where able.
- Ad hoc meeting:
    - When trial-level halting criteria are met
    - At the request of DMID to review a potential safety concern identified in the trial.
- Interim and final data will be shared with the DSMB, but the DSMB does not need to meet to review the final data.

The DSMB will review applicable data to include, but not limited to, study progress and participant, clinical, safety and safety related data. Additional data may be requested by the DSMB. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this trial.

DMID or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of this trial. The DMID Medical Monitor is empowered to stop enrollment and study product administration if AEs that meet the halting criteria are reported. The DMID Medical Monitor will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during this trial.

Immunogenicity Interim Analysis

After all participants have completed Day 43, analysis of the primary outcome and select secondary and exploratory outcomes (see Section 6.2) will proceed. The risk of introducing bias prior to data freeze is considered small and outweighed by the benefits of informing public health decisions during this global public health crisis. The study team may disseminate this data to public health officials and partners as needed and include it in publications and presentations to inform the global scientific community prior to the conclusion of the study.

6.7. Multicenter Studies

Data will be pooled across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for vaccination and assessment of solicited and unsolicited adverse events, and the study relies on central laboratories for the assessment of immunogenicity endpoints.

6.8. Multiple Comparisons/Multiplicity

There is only one primary endpoint and one secondary endpoint involving hypothesis testing. No adjustments for multiple testing are planned.

7. STUDY PARTICIPANTS

7.1. Disposition of Participants

Table 10 will present a summary of the reasons that participants were screened but not enrolled.

The composition of analysis populations, including reasons for participant exclusion, by age group, will be presented in Table 8.

The disposition of participants in the study will be tabulated by age group (Table 7). The table shows the total number of participants screened, enrolled, receiving at least 1 dose, receiving all 2 doses, discontinued dosing or terminated from study follow-up and the number completing the study.

A flowchart showing the disposition of study participants, adapted from the CONSORT Statement [23] will be included (Figure 1). This figure will present the number of participants screened, enrolled, lost to follow-up, and analyzed, by age group.

A listing of participants who discontinued dosing or terminated from study follow-up and the reason will be included in Listing 2.

7.2. Protocol Deviations

A summary of participant-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and age group for all participants (Table 4). Deviations will be reviewed by the Sponsor for possible participant exclusion from the per protocol population and will be classified as either major or minor. All participant-specific protocol deviations and non-participant specific protocol deviations will be included in Appendix 3 as data listings (Listing 3 and Listing 4, respectively).

7.3. Demographic and Other Baseline Characteristics

Summaries of age, sex at birth, ethnicity, race, and HIV Status will be presented by age group, overall and by site (Table 11, Table 12, Table 13, and Table 14). Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, participants may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option.

Individual participant listings (Appendix 3) will be presented for all demographics (Listing 6); pre-existing medical conditions (Listing 7); vital signs and oral temperature (Listing 14); and concomitant medications (Listing 16).

7.3.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 25.1 or higher.

Summaries of participants' pre-existing medical conditions will be presented by age group (Table 15).

Individual participant listings will be presented for all medical conditions (Listing 7).

7.3.2. Prior and Concomitant Medications

Summaries of medications started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Anatomical Therapeutic Chemical (ATC) Level 1 and Level 2 and age group (Table 69).

Individual participant listings will be presented for all concomitant medications (Listing 16).

8. IMMUNOGENICITY EVALUATION

All immunogenicity variables will be listed by age group, participant, and visit (Listing 8). Immunogenicity data summaries and analysis will be presented for the mITT population and, if there are protocol deviations which may affect the analysis, the PP population. Although it is not anticipated that the inclusion/exclusion of Arm 3 adults will affect the results, immunogenicity summaries and analyses will be presented for both Adults (Arm 3 and Arm 4) and Adults – Arm 4 only. Any differences in hypothesis test conclusions will be noted.

8.1. Primary Immunogenicity Analysis

The primary objectives of this protocol are (1) to determine if the peak (Day 43) humoral immune responses in adolescents ages 12 to 17 years are non-inferior to adults ages 18 to 50 years after receipt of a 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN and (2) to describe the safety of a 2-dose 1 x 10^8 $TCID_{50}$ MVA-BN regimen administered SC in adolescents ages 12 to 17 years.

Primary Hypothesis

- At Day 43 the humoral immune response of the 1 x 10^8 $TCID_{50}$ MVA-BN SC (standard dose regimen) in adolescents will be non-inferior to the standard 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adults, as assessed by PRNT GMT.

The results of this test, GMTs, and GMT Ratios for Day 43 will be presented in Table 16 (mITT population) and Table 17 (PP population). GMTs will be presented with its corresponding 95% confidence intervals (CIs) (using Student's t-distribution). A non-inferiority test will be performed with an unequal variance and two-sample t-test statistic to obtain GMT Ratio (defined as the ratio of Adolescents to Adults) and its corresponding 95% CIs and p-values. The humoral immune response will be considered non-inferior in adolescents if the 95% confidence interval of the GMT Ratio is entirely above 0.67 (NI=-0.174 log10 scale). No stepwise testing will be done in Stage 2.

Geometric Mean Fold Rises (GMFRs) from baseline and corresponding 95% CIs (using Student's t-distribution) and percent of participants with seroconversion with corresponding 95% CIs (Clopper-Pearson methodology) will be reported by age group at Day 29, 43, 210, and 394 in Table 29 (mITT population) and Table 30 (PP population).

8.2. Secondary Immunogenicity Analyses

The secondary immunogenicity objectives of this protocol are (1) to evaluate humoral immune responses at baseline, prior to the second vaccination, and following receipt of the 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN in adolescents compared to adults on each study day; (2) to evaluate the kinetics of the humoral responses to the 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN in adolescents compared to adults through Day 365 after the second dose is administered; and (3) to evaluate seroconversion between adolescent and adult study arms.

Secondary Hypotheses

- At Day 394 the humoral immune response of the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adolescents will be non-inferior to the standard 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adults, as assessed by PRNT GMT.

- The humoral immune response of the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adolescents, as assessed by PRNT GMT, will be similar to the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adults at all study days.
- The humoral immune response of the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adolescents as assessed by vaccinia specific PRNT half-life, will be similar to the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adults.

Non-inferior test results for Day 394 and peak day (any day post-dose 1, including Day 43) and GMTs and GMT Ratios for Days 1, 29, 210, 394, and peak day will be calculated as described in the above Section 8.1 for Vaccinia virus specific PRNT. The results of these tests will be presented in Table 18 (mITT population) and Table 19 (PP population).

Half-life, defined as the time from expected peak response (Day 43) to 50% maximal response (see Section 3.2), will be estimated using the first participant visit with titer results less than or equal to half the titer results at Day 43. The number of participants with results at Day 43, median, minimum, maximum, mean and its corresponding 95% CIs (Student's t-distribution) will be presented by age group. P-value will be calculated from a Mann Whitney U test to compare the rate of decay in responses of adolescents to adults. The results of these tests will be presented in Table 20 (mITT population) for Vaccinia virus specific PRNT.

Immune response will be presented graphically using reverse cumulative distribution (RCD) curves (Figure 2, Figure 3, Figure 4, and Figure 5), and longitudinal presentation of GMTs (Figure 6, Figure 7, Figure 8, and Figure 9).

8.3. Exploratory Immunogenicity Analyses

The exploratory objectives of this study are (1) to evaluate other measures of the humoral immune responses for each regimen and (2) to evaluate humoral immune responses of the 2-dose SC regimen of 1 x 10^8 $TCID_{50}$ MVA-BN to monkeypox virus in adolescents compared to adults.

Exploratory Hypothesis

- The humoral immune response of the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adolescents, as assessed by monkeypox specific PRNT GMT, will be similar to the 1 x 10^8 $TCID_{50}$ MVA-BN SC regimen in adults at Day 1 and 43.

Monkeypox Virus Specific PRNT

Non-inferior test results for Day 43 and GMTs and GMT Ratios for Days 1 and 43 will be calculated as described in above Section 8.1 and Section 8.2 for Monkeypox virus specific PRNT. The results will be presented in Table 21 (mITT population) and Table 22 (PP population).

GMFRs from baseline and corresponding 95% CIs will be reported by age group at Day 43 in Table 31 (mITT population) and Table 32 (PP population).

Days 29, 210, and/or 394 may also be reported in all the above tables if possible given lab throughput and cost.

The ratio of Monkeypox Virus Specific PRNT to Vaccinia Virus Specific PRNT will also be presented in Table 33 (GMT, mITT population), Table 34 (GMT, PP population), Table 35 (GMFR, mITT population), and Table 36 (GMFR, PP population).

Other Assays

Additional assessments of humoral immunity including ELISAs, if performed, will be presented in the same formats shown in Table 23 and Table 24; beginning with Figure 2 and ending with Figure 9; and included in Listing 8. Note, these tables may be included separately from the Primary CSR.

Other Exploratory Analyses

Adolescents will be stratified by age subgroup – age 12 to 14 years and age 15 to 17 years. GMT and GMT Ratios (defined as the ratio of Adolescent subgroups to Adults) for Vaccinia virus specific PRNT and monkeypox specific PRNT assays will be presented in Table 25 (mITT Population) and Table 26 (PP Population), and GMFR and proportion of seroconversions will be presented in Table 27 (mITT Population) and Table 28 (PP Population), respectively.

9. SAFETY EVALUATION

Safety data will be assessed for the Safety Population by age group: Adolescents and Adults (Arm 4 only).

9.1. Measurements of Study Product Compliance

The number of doses of study product administered to participants will be presented by age group as part of the participant disposition table (Table 7). Table 9 presents the number of participants who received their first dose within a specified time frame, by site and age group.

9.2. Adverse Events

When calculating the frequency of adverse events (i.e., on a per participant basis), each participant will only be counted once and any repetitions of adverse events within a participant will be ignored; the denominator will be the total population size. All adverse events reported will be included in the summaries and analyses.

The incidence of the secondary safety outcomes is presented by age group in Table 37 and by adolescent subgroup in Table 38; each summarized by maximum severity and relatedness. A summary of all safety events is presented in Table 39 and Table 40 (Adolescent subgroup).

9.2.1. Solicited Events and Symptoms

Systemic solicited adverse events were collected pre-vaccination, and systemic and local solicited adverse events were collected 30 minutes post-vaccination and then daily for 7 days after each vaccination and graded on a scale of 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (life-threatening).

Systemic events include: fever, chills, nausea, headache, fatigue, change in appetite, myalgia, and arthralgia. Local events include: pain at the injection site, erythema/redness, induration/swelling, and pruritis at the injection site. The proportion of participants reporting at least one solicited adverse event will be summarized for each solicited adverse event, any systemic symptom, any local symptom, and any symptoms (Table 43). A similar table will be generated to assess adolescents stratified by age subgroup (Table 44). The 95% CI calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option) will be presented and a Fisher's exact test will be performed to test for the difference in the proportion of participants reporting a solicited adverse event (Table 45).

For each systemic and local event, any systemic event, any local event, and any solicited event, the maximum severity over 7 days after each vaccination will be summarized for the Safety population. The number and percentage of participants reporting each event will be summarized by the maximum severity and age group, separately for each vaccination and over all vaccinations. For each event the denominator is the number of participants with non-missing data for the specific event (Table 46).

The number of participants reporting a solicited adverse event will be summarized for each day post vaccination for each vaccination and for all vaccinations combined both in summary tables (Table 47, Table 48, Table 49, Table 50, Table 51, and Table 52) and graphically in bar charts (Figure 10, Figure 11, Figure 12, Figure 13, Figure 14, and Figure 15). A comparison of the event rate for each age group between vaccination 1 and vaccination 2 will be presented (Table 53).

Solicited adverse events by participant will be presented in Listing 9 and Listing 10.

9.2.2. Unsolicited Adverse Events

The proportion of participants reporting at least one unsolicited adverse event will be summarized by MedDRA system organ class and preferred term for each vaccination and over all vaccinations. Denominators for percentages are the number of participants who received the vaccination being summarized.

Adverse events by participant will be presented in Listing 11. Injection site skin discoloration and nodule measurements and their associated adverse event will be presented in Listing 12.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, vaccination and age group:

- Summary of adverse events occurring in 5% or more of participants (Table 41 and Table 42)
- Participant incidence and total frequency of adverse events over time by dose with 95% CI (Days 1-8, Days 9-29 (pre-vaccination), Days 29 (post-vaccination)-36, and Days 37-57) (Table 54 and Table 55);
- Summary of severity and relationship to study product (Table 56 and Table 57);
- Participant incidence and total frequency of related adverse events over time (Within 28 Days Post Dose) (Table 58 and Table 59);
- Participant listing of non-serious adverse events of moderate or greater severity (Table 61);
- Bar chart of non-serious related adverse events by severity and MedDRA system organ class (Figure 16);
- Bar chart of non-serious related adverse events by severity (Figure 17).

Duration of injection site AEs will be presented by vaccination and age group in Table 63.

9.3. Deaths, Serious Adverse Events and other Significant Adverse Events

The following listings will be presented including Participant ID, Age (years) Adverse Event Description, Adverse Event Onset Date/End Date, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Study Product, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events (including SUSARs) (Table 60);
- Medically Attended Adverse Events (MAAEs), Unanticipated Problems (Ups), and Adverse Events of Special Interest (AESIs) (Table 62).

9.4. Pregnancies

For any participants in the Safety population who become pregnant during the study, every attempt will be made to follow these participants to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A table summarizing the total pregnancies, number of live births, and number of spontaneous abortions, elective abortions or still births by age group will be presented. In addition, a listing of pregnancies and outcomes will be presented (Listing 17, Listing 18, Listing 19, Listing 20, and Listing 21).

9.5. Clinical Laboratory Evaluations

Not applicable.

9.6. Vital Signs and Physical Evaluations

Vital sign measurements include systolic blood pressure, diastolic blood pressure, pulse, and oral temperature. Vital signs will be assessed at Day 1 and Day 29 prior to vaccination and as needed at other study visits if an interim change in medical status is reported by the participant. Vital signs will be tabulated by visit and age group (Table 64, Table 65, Table 66, Table 67, and Table 68). Vitals will be listed in Listing 14.

Physical Examinations will be performed at Day 1, Day 15, Day 29, and Day 43 and as needed at other study visits if an interim change in medical status is reported by the participant. The following body system will be assessed: Skin. Other body systems may be assessed if indicated. All abnormal findings will be listed in Listing 15. Additional injection site measurements will be listed as described in Section 9.2.2.

9.7. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-participant listing of concomitant medication use will be presented (Listing 16). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and age group for the Safety population (Table 69).

9.8. Other Safety Measures

Not applicable.

10. PHARMACOKINETICS

Not applicable.

11. IMMUNOGENICITY

See Section 8.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001." The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01." For seroconversions, percentages will be reported to the nearest tenth; values greater than zero but < 0.1% will be presented as "<0.1;" values greater than 99.9% but less than 100% will be reported as ">99.9." For other variables, percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1;" values greater than 99% but less than 100% will be reported as ">99."

14. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all tables, figures and listings.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Changes from Protocol v6.0

- Secondary objective for kinetics of humoral immune responses will be evaluated through Day 394 (Section 3.1) instead of Day 365 (Protocol v6.0 Section 2) to align with study visits outlined in Table 2.
- Monkeypox-related hypothesis testing has been updated from a secondary hypothesis (Protocol v6.0 Section 8.1) to an exploratory hypothesis (Section 8.3) to match the exploratory endpoint outlined in the study objectives and endpoints (Section 3.1).

Changes from SAP v1.0

- Description of interim CSR was added to Section 6.2.
- Updated analysis plan for half-life to be consistent with what was done in Stage 1 (Section 8.2).
- Updated per protocol population to not be inclusive of 3 days before or 7 days after visit window (Section 6.3.2).
- Added subsection for serious and minor protocol deviations to Table 4.
- Added a column for major and minor participant-specific and non-participant-specific protocol deviations (Listing 3 and Listing 4, respectively).
- Added a listing for injection site skin discoloration and nodule measurements (Listing 12).
- Arm 3 from Stage 1 will no longer be considered in safety analyses per protocol.

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendix 1, Appendix 2, and Appendix 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Stage 2 Study Design

Arm	Dose of JYNNEOS (MVA- BN)	Route of Administration[a]	Vaccination Day	
			Day 1	Day 29
3 (Adult – Stage 1)[a]	1 x 10^8 $TCID_{50}$ (0.5 mL)	Subcutaneous	X	X
4 (Adult)	1 x 10^8 $TCID_{50}$ (0.5 mL)	Subcutaneous	X	X
5 (Adolescent)	1 x 10^8 $TCID_{50}$ (0.5 mL)	Subcutaneous	X	X

Notes: Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group, "Pooled Adults", for the primary endpoint (Day 43).

[a] Subcutaneous is administered in the fatty subcutaneous tissue of the upper arm.

9.5.1 Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Stage 2 (Arms 4 and 5) Schedule of Study Procedures

Procedures	Optional Screening Visit Day -7 to -1	Visit 1 Enroll Baseline Day 1	Visit 2 Day 8 +/- 1 day	Visit 3 Day 29 +/- 3 days	Visit 4 Day 36 +/-1 day	Visit 5 Day 43 +/- 3 days	Visit 6 Day 57 +/- 3 days [6]	Visit 7 Day 90 +/- 5 days [6]	Visit 8 Day 210 +/- 7 days	Visit 9 Day 394 +/- 14 days	Sick or Unscheduled Visit [7]
Days post second vaccination					7 +/-1 days	14 +/-3 days	28 +/-3 days	61 +/-5 days	181 +/- 7 days	365 +/- 14 days	
Informed consent and assent where appropriate	X	X[1]									
Demographics	X	X[1]									
Medical history	X	X[1]	X	X	X	X	X	X	X	X	X
Vaccine administration		X		X							
Targeted physical exam	X	X[1]	X[2]	X[2]	X[2]	X[2]	X[2]	X[6]	X[2]	X[2]	X[2]
Vital signs	X	X[1]	X[2]	X[2]	X[2]	X[2]	X[2]	X[6]	X[2]	X[2]	X[2]
Concomitant medicine review [3]	X	X	X	X	X	X	X	X	X	X	X
SAE[4]		All SAE, Day 1 through 394									X[4]
Protocol specified AESI and related MAAE [4]		Protocol specified AESI and related MAAEs, Day 1 through 210									X[4]
Unsolicited AEs[4]		Unsolicited AEs, Day 1 through Day 57									X[4]
Solicited (Local and Systemic) AEs		Day 1 through Day 8		Day 29 through Day 36							X
Pregnancy test [5]	X	X[1]		X							
Maximum blood volume per visit (ml) [8]		15		15		15			15	15	
Maximum blood volume total (ml) [8]		15		30		45			60	75	
Blood collection visits [8]		X		X		X			X	X	

[1] If there is no screening visit, these activities should be conducted at the Day 1 visit prior to enrollment.

[2] A targeted (symptom-driven) physical exam will be done at screening (i.e., screening visit or Day 1), on Days 8, 29, 36, and 43 (at least assessment of vaccination site and presence of skin reactogenicity will be done), and as needed in all other visits if interim change in medical status reported by participant. Vital signs (temperature, blood pressure and heart rate) will be done on Day 1 and 29 prior to vaccination. However, if there was a separate screening visit and vital signs (temperature, BP, and HR) were done at that visit, only a temperature is needed on Day 1. Vital signs can be done at other visits on an as needed basis.

[3] For Stage 2, after Day 57, only concomitant medications that are associated with a protocol specified AESI or related MAAE through Day 210, and all SAE through Day 394 and clinically relevant to report, will be recorded in the CRF. In addition, during sick visits concomitant medications will be collected.

[4] If SAE/MAAE/AESI or unsolicited AE are reported during a sick visit or unscheduled visit and within the reporting window, it will be reported. See more information about collection of AEs in the safety section of the protocol. See SAP section 4.5 for additional details on AESIs.

[5] A pregnancy test will be done at the screening visit (if conducted) and on Day 1 prior to enrollment. If there is no screening visit, then pregnancy test done will be done on Day 1 only. Females of reproductive potential must have negative serum or urine pregnancy test in the 24 hours prior to Day 1 and 29 study vaccinations and results confirmed prior to enrollment. Pregnancy testing is required only for adolescents who have reached menarche based on medical history.

[6] The Day 57 visit may occur via phone call visit if the participant has no skin changes at either injection site documented at the Day 43 visit. All Day 90 visits in Stage 2 will occur via phone call by a delegated study staff member. For both Day 57 and Day 90 visits, the site may opt to have the participant come in for an in-person visit if deemed necessary. In addition, those who qualify for a phone visit at Day 57 and all Day 90 visits may be conducted virtually via video teleconference (e.g., Zoom, FaceTime) if deemed necessary. If an in-person visit is deemed necessary, site may do vital signs and a physical examination on an as needed basis.

[7] Participants reporting mpox-like illness who have a positive diagnostic test result will be seen at a sick visit. An unscheduled visit may also occur for reasons including, but not limited to AE follow up, blood draw, or early termination final visit.

[8] Stage 2 participants will have blood drawn on Days 1, 29, 43, 210 and 394. For Stage 2, a minimally acceptable blood volume on Day 1 and on Day 43 is set at 5-mL of whole blood (SST for serum), regardless of age. Should the site not be able to collect that blood before the first vaccination, the participant will not be permitted to continue. Maximum blood draw at the pre-specified visits in Stage 2 is 15 mL.

9.7.1 Sample Size

Table 3: Sample Size/Probability Estimates

NI Margin	Sample Size Arm 5 (Standard Deviation 0.5)	Sample Size Arm 3+4 (Standard Deviation 0.6)	Total sample size for NI test	Power
0.67 $Log_{10}(0.67) = -0.174$	300	200	500	0.92

10.2 Protocol Deviations

Table 4: Distribution of Protocol Deviations by Category, Type, and Age Group

[Implementation Note: Deviation types with zero counts will be excluded from the table. Categories with only one deviation type present will exclude the 'Any type' row. Categories with no deviation type present will only present 'Any type' row.]

Category	Deviation Type	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)	
		Number of Participants	Number of Deviations	Number of Participants	Number of Deviations	Number of Participants	Number of Deviations
Major Deviations							
Eligibility/enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Vaccination administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Missed treatment administration						
	Delayed treatment administration						
	Other						
Follow-up visit schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Other						
Protocol procedure/assessment	Any type						
	Incorrect version of ICF signed						
	Blood not collected						

Category	Deviation Type	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)	
		Number of Participants	Number of Deviations	Number of Participants	Number of Deviations	Number of Participants	Number of Deviations
	Urine not collected						
	Stool not collected						
	Other specimen not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Specimen temperature excursion						
	Other						
Vaccination administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						
[Repeat for Minor Deviations]							
[Repeat for All Deviations]							
Notes: N = Number of participants enrolled.							

12.2.2 Displays of Adverse Events

Table 5: Solicited Adverse Event Grading Scale

Mild:	No interference with activity
Moderate:	Some interference with activity
Severe:	Prevents daily activity
Potentially Life Threatening:	ER visit or hospitalization
Note: If not otherwise specified in "*FDA Guidance for Industry, Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*"	

Table 6: Induration Grading Scale

Rule Type	Functional scale assessment (FA)	Measurement (MS)	Rule to Apply for Final Grading	Final Grade
Standard tox table	0 or 1	<2.5cm	**Rule 1:** FA = 0 or 1 AND MS < 2.5cm	None
	1	2.5-5cm	**Rule 2:** FA =1 AND MS 2.5-5cm	1
	2	5.1-10cm	**Rule 3:** FA = 2 OR MS 5.1-10cm	2
	3	>10cm	**Rule 4:** FA = 3 OR MS >10cm	3
	4	Any	**Rule 5:** FA = 4 OR Necrosis associated with induration or both induration and erythema	4
Graded MS, FA None	0	2.5-5cm	Rule 1	None
One assessment missing	0	Missing	N/A	None
	1	Missing	N/A	1
	Missing	2.5-5.0 cm	N/A	1
	2/3/4	Missing	Rules 3,4,5	2/3/4
	Missing	<2.5cm	N/A	None
	Missing	5.1-10cm/>10cm	Rules 3,4	2/3
One assessment marked “not done”	0	Not Done	N/A	None
	1	Not Done		1
	2/3/4	Not Done	Rules 3,4,5	2/3/4
	Not Done	<2.5cm	N/A	None
	Not Done	2.5-5cm	N/A	1
	Not Done	5.1-10cm/>10cm	Rules 3,4	2/3
Two Assessments Missing/ Not Done	Missing	Missing	N/A	Missing
	Not Done	Not Done	N/A	Not Done

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Not applicable.

14.1 Description of Study Subjects

14.1.1 Disposition of Participants

Table 7: Participant Disposition by Age Group

[Implementation Note: Only rows 1-5 ('Screened' to 'Completed Primary Endpoint') will be included in the interim report. Listing 2 and Listing 5 will not be included in the interim report, and thus the footnote references will be excluded from the report.

Only rows 1-6 ('Screened' to 'Completed Study Day 210') will be included in the interim CSR. The remaining rows 7-9 ('Completed Final Blood Draw' to 'Completed Study Day 394 Per Protocol') will only be included in the CSR addendum after all participants have either been terminated or completed the protocol.

Participant Disposition	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		Adults (Arm 3)[d] (N=X)		All Stage 2 Participants[e] (N=X)		All Participants (N=X)	
	n	%	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	x	--	--	--
Enrolled	x	100	x	100	x	100	x	100	x	100
Received Dose 1	x	xx	x	xx	x	xx	x	xx	x	xx
Received Dose 2[a]										
Completed Primary Endpoint (Study Day 43)										
Completed Study Day 210[b]					N/A	N/A			N/A	N/A
Completed Final Blood Draw (Study Day 394)					N/A	N/A			N/A	N/A
Completed Follow-up (Study Day 394)					N/A	N/A			N/A	N/A
Completed Study Day 394 Per Protocol[c]					N/A	N/A			N/A	N/A

Notes: N = Number of participants enrolled.

n = Number of participants meeting the row criteria.

[a] Refer to Listing 2: Early Terminations or Discontinued Participants for reasons participants discontinued or terminated early.

[b] Safety data cut-off for the interim CSR.

[c] Refer to Listing 5: Participants Excluded from Analysis Populations for reasons participants are excluded from the Analysis populations.

[d] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.

[e] Stage 2 participants consist of Arm 4 (Adults) and Arm 5 (Adolescents).

Table 8: Analysis Population Exclusions by Age Group

[Implementation Note: 'Any Reason' will only be included if at least 2 reasons for exclusion for a given analysis population are present or if there are no reasons for exclusion. Only reasons with at least 1 count will be included in the table. 'Major protocol deviation X' will be replaced with events considered a major protocol deviation as discussed with the study team, e.g., 'Received non-study vaccination within 7 days of study vaccination.' Per Protocol Population will not be included in the interim report.

Per Protocol Population will only be assessed for the days listed.

Analysis Populations	Reason Participants Excluded	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		Adults (Arm 3)[a] (N=X)	
		n	%	n	%	n	%
Safety Population	Did not receive study product	x	xx	x	xx	N/A	N/A
mITT Population	Any Reason					x	xx
	Did not receive study product						
	No pre-vaccination sample with immunogenicity results						
	No post-vaccination sample with immunogenicity results						
Per Protocol Population, All Study Days	Any Reason					x	xx
	Did not receive study product						
	No pre-vaccination sample with immunogenicity results						
	No post-vaccination sample with immunogenicity results						
	Found to have been ineligible at baseline						
Per Protocol Population, Study Day 29	[Major protocol deviation 1]					N/A	N/A
	[Major protocol deviation 2]					N/A	N/A
	Visit substantially out of window					N/A	N/A
Per Protocol Population, Study Day 43	[Major protocol deviation 1]						
	Visit substantially out of window						
Per Protocol Population, Study Day 210	[Major protocol deviation 1]					N/A	N/A
	Visit substantially out of window					N/A	N/A
Per Protocol Population, Study Day 394	[Major protocol deviation 1]					N/A	N/A
	Visit substantially out of window					N/A	N/A

Analysis Populations	Reason Participants Excluded	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		Adults (Arm 3)[a] (N=X)	
		n	%	n	%	n	%

Notes: N = Number of participants enrolled.

n = Number of participants meeting row criteria.
Participants may be excluded from an analysis population for multiple reasons.
[a] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.

Table 9: Dates of First Study Vaccination by Site

Age Group	Site	Total (Entire period of enrollment)	22MAR2023-21APR2023	22APR2023-21MAY2023	22MAY2023-21JUN2023	22JUN2023-20JUN2023
Adolescents (Arm 5)	Saint Louis University	x	x	x	x	x
	Cincinnati Children's Hospital					
	University of Rochester					
	University of Maryland Baltimore					
	Emory Children's Center					
	Kaiser Permanente					
	Baylor College of Medicine					
	Vanderbilt University					
	Duke University					
	George Washington University					
	University of Texas Medical Branch					
	Washington University					
	University of Alabama at Birmingham					
	Ponce Medical School Foundation, Inc., CAIMED Center					
	Children's Hospital of Philadelphia					
	University of Pittsburgh					
	All Sites					
Adults (Arm 4)	Saint Louis University					
	Kaiser Permanente					
	Baylor College of Medicine					
	Vanderbilt University					
	Duke University					
	George Washington University					
	University of Alabama at Birmingham					

Age Group	Site	Total (Entire period of enrollment)	22MAR2023-21APR2023	22APR2023-21MAY2023	22MAY2023-21JUN2023	22JUN2023-20JUN2023
	Ponce Medical School Foundation, Inc., CAIMED Center					
	Brigham and Women's Hospital					
	University of Pittsburgh					
	All Sites					
All Participants	Saint Louis University					
	Cincinnati Children's Hospital					
	University of Rochester					
	University of Maryland Baltimore					
	Emory Children's Center					
	Kaiser Permanente					
	Baylor College of Medicine					
	Vanderbilt University					
	Duke University					
	George Washington University					
	University of Texas Medical Branch					
	Washington University					
	University of Alabama at Birmingham					
	Ponce Medical School Foundation, Inc., CAIMED Center					
	Children's Hospital of Philadelphia					
	University of Pittsburgh					
	All Sites					

Notes: N = Number of participants enrolled.

n = Number of participants meeting row criteria.

Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis. Arm 3 dosing commenced on [DDMMYYY]. All Arm 3 participants completed their first dose by [DDMMYYY].

Table 10: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Any Screen Failure	N/A	x	100
Inclusion and Exclusion	Number of participants failing any eligibility criterion	x	xx
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible But Not Enrolled	N/A	x	N/A

[a] More than one criterion may be marked per participant.
[b] Denominator for percentages is the total number of screen failures.

14.1.2 Demographic Data by Study Group

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Site

		Sex		Ethnicity				Race						
Age Group	**Site**	**Male n (%)**	**Female n (%)**	**Not Hispanic or Latino n (%)**	**Hispanic or Latino n (%)**	**Not Reported n (%)**	**Unknown n (%)**	**American Indian or Alaska Native n (%)**	**Asian n (%)**	**Native Hawaiian or Other Pacific Islander n (%)**	**Black or African American n (%)**	**White n (%)**	**Multi-Racial n (%)**	**Unknown n (%)**
Adolescents (Arm 5)	Saint Louis University (N=X)	x (xx)												
	Cincinnati Children's Hospital (N=X)													
	University of Rochester (N=X)													
	University of Maryland Baltimore (N=X)													
	Emory Children's Center (N=X)													
	Kaiser Permanente (N=X)													
	Baylor College of Medicine (N=X)													
	Vanderbilt University (N=X)													
	Duke University (N=X)													
	George Washington University (N=X)													
	University of Texas Medical Branch (N=X)													

		Sex		Ethnicity				Race						
Age Group	**Site**	**Male n (%)**	**Female n (%)**	**Not Hispanic or Latino n (%)**	**Hispanic or Latino n (%)**	**Not Reported n (%)**	**Unknown n (%)**	**American Indian or Alaska Native n (%)**	**Asian n (%)**	**Native Hawaiian or Other Pacific Islander n (%)**	**Black or African American n (%)**	**White n (%)**	**Multi-Racial n (%)**	**Unknown n (%)**
	Washington University (N=X)													
	University of Alabama at Birmingham (N=X)													
	Ponce Medical School Foundation, Inc., CAIMED Center (N=X)													
	Children's Hospital of Philadelphia (N=X)													
	University of Pittsburgh (N=X)													
	All Participants (N=X)													
Adults (Arm 4)	Saint Louis University (N=X)													
	Kaiser Permanente (N=X)													
	Baylor College of Medicine (N=X)													
	Vanderbilt University (N=X)													
	Duke University (N=X)													
	George Washington University (N=X)													

		Sex		Ethnicity				Race						
Age Group	**Site**	**Male n (%)**	**Female n (%)**	**Not Hispanic or Latino n (%)**	**Hispanic or Latino n (%)**	**Not Reported n (%)**	**Unknown n (%)**	**American Indian or Alaska Native n (%)**	**Asian n (%)**	**Native Hawaiian or Other Pacific Islander n (%)**	**Black or African American n (%)**	**White n (%)**	**Multi-Racial n (%)**	**Unknown n (%)**
	University of Alabama at Birmingham (N=X)													
	Ponce Medical School Foundation, Inc., CAIMED Center (N=X)													
	Brigham and Women's Hospital (N=X)													
	University of Pittsburgh (N=X)													
	All Participants (N=X)													
Adults (Arm 3)[a]	Saint Louis University (N=X)													
	Hope Clinic of the Emory Vaccine Center (N=X)													
	Baylor College of Medicine (N=X)													
	Vanderbilt University (N=X)													
	UC San Diego (N=X)													
	George Washington University (N=X)													
	NIH Clinical Research Center (N=X)													

		Sex		Ethnicity				Race						
Age Group	**Site**	**Male n (%)**	**Female n (%)**	**Not Hispanic or Latino n (%)**	**Hispanic or Latino n (%)**	**Not Reported n (%)**	**Unknown n (%)**	**American Indian or Alaska Native n (%)**	**Asian n (%)**	**Native Hawaiian or Other Pacific Islander n (%)**	**Black or African American n (%)**	**White n (%)**	**Multi-Racial n (%)**	**Unknown n (%)**
	Brigham and Women's Hospital (N=X)													
	All Participants (N=X)													

Notes: N = Number of participants enrolled in each age group at the specified site.

[a] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Site

Age Group	Variable	Age (years)				
	Statistic	Mean	Standard Deviation	Median	Minimum	Maximum
Adolescents (Arm 5)	Saint Louis University (N=X)	xx.x	xx.x	xx.x	x	x
	Cincinnati Children's Hospital (N=X)					
	University of Rochester (N=X)					
	University of Maryland Baltimore (N=X)					
	Emory Children's Center (N=X)					
	Kaiser Permanente (N=X)					
	Baylor College of Medicine (N=X)					
	Vanderbilt University (N=X)					
	Duke University (N=X)					
	George Washington University (N=X)					
	University of Texas Medical Branch (N=X)					
	Washington University (N=X)					
	University of Alabama at Birmingham (N=X)					
	Ponce Medical School Foundation, Inc., CAIMED Center (N=X)					
	Children's Hospital of Philadelphia (N=X)					
	University of Pittsburgh (N=X)					
	All Participants (N=X)					
Adults (Arm 4)	Saint Louis University (N=X)					
	Kaiser Permanente (N=X)					
	Baylor College of Medicine (N=X)					
	Vanderbilt University (N=X)					

Age Group	Variable	Age (years)				
	Duke University (N=X)					
	George Washington University (N=X)					
	University of Alabama at Birmingham (N=X)					
	Ponce Medical School Foundation, Inc., CAIMED Center (N=X)					
	Brigham and Women's Hospital (N=X)					
	University of Pittsburgh (N=X)					
	All Participants (N=X)					
Adults (Arm 3)[a]	Saint Louis University (N=X)					
	Hope Clinic of the Emory Vaccine Center (N=X)					
	Baylor College of Medicine (N=X)					
	Vanderbilt University (N=X)					
	UC San Diego (N=X)					
	George Washington University (N=X)					
	NIH Clinical Research Center (N=X)					
	Brigham and Women's Hospital (N=X)					
	All Participants (N=X)					

Notes: N = Number of participants enrolled in each age group at the specified site.

[a] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.

Table 13: Summary of Categorical Demographic and Baseline Characteristics by Age Group, All Enrolled Participants

[Implementation Note: 'Unknown' and 'Not Reported' rows will only be included if populated.]

Variable	Characteristic	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		Adults (Arm 3)[a] (N=X)	
		n	%	n	%	n	%
Sex at Birth	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						
Age Group	12-14 years old			N/A	N/A	N/A	N/A
	15-17 years old			N/A	N/A	N/A	N/A
	≥18 years old	N/A	N/A				
HIV Status	Negative	x	xx	x	xx	x	xx
	Positive						

Notes: N = Number of participants enrolled.
n = Number of participants meeting the row criteria.
N/A = Not applicable.
[a] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.

Table 14: Summary of Continuous Demographic and Baseline Characteristics by Age Group, All Enrolled Participants

Variable	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)	Adults (Arm 3)[a] (N=X)
Age (years)	Mean	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Minimum	x	x	x
	Maximum	x	x	x

Note: N = Number of participants enrolled.

[a] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.

14.1.3 Prior and Concurrent Medical Conditions

Table 15: Summary of Participants with Pre-Existing Medical Conditions by MedDRA System Organ Class and Age Group

[Implementation Note: 'Any PT' rows will only be included if there are more than one type of PT.]

MedDRA System Organ Class	MedDRA Preferred Terms	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)	
		n	%	n	%	n	%
Any SOC	Any PT	x	xx	x	xx	x	xx
[SOC 1]	Any PT						
	[PT 1]						
	[PT 2]						
[SOC 2]	Any PT						
	[PT 1]						
…	…						

Notes: N = Number of participants in the Safety Population.
n = Number of participants reporting medical history within the specified SOC. A participant is only counted once per SOC.

14.2 Immunogenicity Data

Table 16: Vaccinia Virus Specific PRNT Summary and Primary Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)	Pooled Adults (Arm 3 + Arm 4)[c] (N=X)
At Day 43 the humoral immune response in adolescents non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	x	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.xx (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
	p-value[a]	N/A	x.xxx	x.xxx
	Non-inferiority result[b]	N/A	Yes or No	Yes or No

Notes: N = Number of participants in the mITT Population.

n = Number of participants with data at time point.

GMT = Geometric mean titer.

GMTR = Geometric mean titer ratio of adolescents to adults.

CI = Confidence Interval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR.

[a] Two-sample t-test with unequal variance, noninferiority (NI) margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be non-inferior to adults.

[b] If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=-0.174 log10 scale) prior to rounding, the result is "Yes".

[c] Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis. Arm 3 participants were excluded for a sensitivity analysis (Adults [Arm 4]).

Table with similar format:

Table 17: Vaccinia Virus Specific PRNT Summary and Primary Hypothesis Testing, Per Protocol Population

Pseudocode for Table 16 and Table 17

```
proc ttest data= DSNIN alpha= 0.05 h0= -0.174
            test= diff plots= none;
 by AVISITN;
 class ACTARMN;
 var LOG_AVAL;
 ods output ConfLimits= DSNOUT_CI        (where= (method='Satterthwaite')) /*GMTR (95% CI)*/
                        Ttests=  DSNOUT_PVAL(where= (method='Satterthwaite')) /*P-Value*/
                        ;

run;

/*Alternatively use PROC TTEST options h0= 0.67 test= ratio and var AVAL*/
```

Table 18: Vaccinia Virus Specific PRNT Summary and Secondary Hypothesis Testing, mITT Population

[Implementation Note: Peak humoral immune response will consider any visit day, including Day 43. "Peak" may include a measurement from any study visit.]

Hypothesis	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
At Day 1 humoral immune response in adolescent non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
At Day 29 humoral immune response in adolescents non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
At Day 210 humoral immune response in adolescents non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
At Day 394 humoral immune response in adolescents non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
	p-value[a]	N/A	x.xxx
	Non-inferiority result[b]	N/A	Yes or No

Hypothesis	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
At peak (any day post-dose 1) humoral immune response in adolescents non-inferior to adults, as assessed by Vaccinia specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
	p-value[a]	N/A	x.xxx
	Non-inferiority result[b]	N/A	Yes or No

Notes: Peak humoral response is the maximum titer response for each participant across all study visits, including supplemental visits.

N = Number of participants in the mITT Population.

n = Number of participants with data at time point.

GMT = Geometric mean titer.

GMTR = Geometric mean titer ratio of adolescents to adults.

CI = Confidence Interval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t -test for GMTR.

[a] Two-sample t-test with unequal variance, noninferiority (NI) margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be non-inferior to adults.

[b] If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=-0.174 log10 scale) prior to rounding, the result is "Yes".

Table with similar format:

Table 19: Vaccinia Virus Specific PRNT Summary and Secondary Hypothesis Testing, Per Protocol Population

Table 20: Vaccinia Virus Specific PRNT Half-Life Secondary Hypothesis Testing, mITT Population

Hypothesis	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
Humoral immune responses in adolescents as assessed by Vaccinia specific PRNT half-life similar to adults	n	x	x
	Median (Minimum, Maximum)	xx.x	xx.x
	Mean (95% CI)	xx	xx
	p-value[a]	x.xxx	x.xxx

Notes: N = Number of participants in the mITT Population.
N = Number of participants with data at Day 43 and post-Day 43.
CI = Confidence Interval, calculated using Student's t-distribution.
[a] Wilcoxon Mann Whitney test.

Table 21: Monkeypox Virus Specific PRNT Summary and Hypothesis Testing , mITT Population

Hypothesis	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
At Day 1 humoral immune response in adolescents non-inferior to adults, as assessed by Monkeypox specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
At Day 43 humoral immune response in adolescents non-inferior to adults, as assessed by Monkeypox specific PRNT GMT	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
	p-value[a]	N/A	x.xxx
	Non-inferiority result[b]	N/A	Yes or No

Notes: N = Number of participants in the mITT Population.

N = Number of participants with data at time point.

GMT = Geometric mean titer.

GMTR = Geometric mean titer ratio of adolescents to adults.

CI = Confidence Interval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR.

[a] Two-sample t-test with unequal variance, noninferiority (NI) margin of 0.67 and two-sided type I error rate of 0.05 to test the null hypothesis that humoral immune response in adolescents will be non-inferior to adults.

[b] If the lower bound of the GMTR 95% CI is greater than or equal to 0.67 (NI=-0.174 log10 scale) prior to rounding, the result is "Yes".

Table with similar format:

Table 22: Monkeypox Virus Specific PRNT Summary and Hypothesis Testing, Per Protocol Population

Table 23: Anti-MVA Binding Antibody Geometric Mean Titer (GMT) Results and Geometric Mean Titer Ratio (GMTR) to Adolescents Results with 95% Confidence Intervals by Age Group, mITT Population

[Implementation Note: For other assays, replace "Anti-MVA Binding Antibody" with assay name. This table for other exploratory assays may be presented separate from the Interim CSR.

"Peak Anytime Post Dose 1" may include a measurement from any study visit.]

Time Point	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
Study Day 1, Pre-Dose 1	n	x	x
	GMT (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	GMTR (95% CI)	N/A	x.xx (x.xx, x.xx)
Study Day 29, Pre-Dose 2	n		
	GMT (95% CI)		
	GMTR (95% CI)		
Study Day 43, Post Dose 2	n		
	GMT (95% CI)		
	GMTR (95% CI)		
Study Day 210, Post Dose 2	n		
	GMT (95% CI)		
	GMTR (95% CI)		
Study Day 394, Post Dose 2	n		
	GMT (95% CI)		
	GMTR (95% CI)		
Peak Anytime Post Dose 1	n		
	GMT (95% CI)		
	GMTR (95% CI)		

Time Point	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
Notes: Peak humoral response is the maximum titer response for each participant across all study visits, including supplemental visits. N = Number of participants in the mITT Population. N = Number of participants with data at time point. GMT = Geometric Mean Titer. GMTR = Geometric mean titer ratio of adolescents to adults. CI = Confidence Interval, calculated using Student's t-distribution for GMT and Welch-Satterthwaite t-test for GMTR.			

Tables with similar format:

Table 24: Anti-MVA Binding Antibody Geometric Mean Titer (GMT) Results and Geometric Mean Titer Ratio (GMTR) to Adolescents Results with 95% Confidence Intervals by Age Group, Per Protocol Population

Table 25: Vaccinia Virus Specific PRNT Geometric Mean Titer (GMT) Results and Geometric Mean Titer Ratio (GMTR) to Adolescents Results with 95% Confidence Intervals by Adolescent Age Subgroup, mITT Population

[Implementation Note: The subgroups will be "12-14 years (N=X)", "15-17 years (N=X)", and "All Adolescents (N=X)".]

Table 26: Vaccinia Virus Specific PRNT Geometric Mean Titer (GMT) Results and Geometric Mean Titer Ratio (GMTR) to Adolescents Results with 95% Confidence Intervals by Age Subgroup, Per Protocol Population

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years (N=X)", "Adolescents (Arm 5) 15-17 years (N=X)", and "Adults (Arm 4) 18+ years (N=X)".]

Table 27: Monkepox Virus Specific PRNT Geometric Mean Titer (GMT) Results and Geometric Mean Titer Ratio (GMTR) to Adolescents Results with 95% Confidence Intervals by Age Subgroup, mITT Population

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years (N=X)", "Adolescents (Arm 5) 15-17 years (N=X)", and "Adults (Arm 4) 18+ years (N=X)".]

Table 28: Monkepox Virus Specific PRNT Geometric Mean Titer (GMT) Results and Geometric Mean Titer Ratio (GMTR) to Adolescents Results with 95% Confidence Intervals by Age Subgroup, Per Protocol Population

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years (N=X)", "Adolescents (Arm 5) 15-17 years (N=X)", and "Adults (Arm 4) 18+ years (N=X)".]

Table 29: Vaccinia Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion Results by Time Point and Age Group, mITT Population

[Implementation Note: "Peak Anytime Post Dose 1" may include a measurement from any study visit.]

Time Point	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
Study Day 29 (Pre-Dose 2)	n	x	x
	GMFR[a] (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
	% with Seroconversion[b] (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Study Day 43 (Post Dose 2)	n		
	GMFR[a] (95% CI)		
	% with Seroconversion[b] (95% CI)		
Study Day 210 (Post Dose 2)	n		
	GMFR[a] (95% CI)		
	% with Seroconversion[b] (95% CI)		
Study Day 394 (Post Dose 2)	n		
	GMFR[a] (95% CI)		
	% with Seroconversion[b] (95% CI)		
Peak Anytime Post Dose 1	n		
	GMFR[a] (95% CI)		
	% with Seroconversion[b] (95% CI)		

Notes: Peak humoral response is the maximum titer response for each participant across all study visits, including supplemental visits.

N = Number of participants in the mITT Population.

N = Number of participants with data at time point.

CI = Confidence Interval, calculated using Student's t-distribution for GMFR and Clopper-Pearson methodology for seroconversion.

[a] GMFR represents the geometric mean fold rise in antibody for the corresponding time point compared to pre-dose 1.

[b] Seroconversion represents the percentage of participants with at least a 2-fold rise in antibody titer compared to pre-dose 1 if any detectable result at pre-dose 1, or any detectable result if result < lower limit of detection (LLOD) at pre-dose 1.

Tables with similar format:

Table 30: Vaccinia Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion Results by Time Point and Age Group, Per Protocol Population

Table 31: Monkeypox Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion Results by Time Point and Age Group, mITT Population

[Implementation Note: Peak Anytime Post Dose 1 will not be included. Only Day 43 will be presented.]

Table 32: Monkeypox Virus Specific PRNT Geometric Mean Fold Rise (GMFR) and Seroconversion Results by Time Point and Age Group, Per Protocol Population

[Implementation Note: Peak Anytime Post Dose 1 will not be included. Only Day 43 will be presented.]

Table 33: Ratio of Monkeypox Virus Specific PRNT Geometric Mean Titer (GMT) to Vaccinia Virus Specific PRNT GMT Results with 95% Confidence Intervals by Time Point and Age Group, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
Study Day 1, Pre-Dose 1	n	x	x
	GMT Ratio(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Study Day 43, Post Dose 2	n		
	GMT Ratio (95% CI)		

Notes: N = Number of participants in the mITT Population.
N = Number of participants with data at time point.
GMT Ratio = Monkeypox virus specific PRNT Geometric Mean Titer/Vaccinia virus specific PRNT Geometric Mean Titer.
CI = Confidence Interval, calculated using Welch-Satterthwaite t-test.

Table with similar format:

Table 34: Ratio of Monkeypox Virus Specific PRNT Geometric Mean Titer (GMT) to Vaccinia Virus Specific PRNT Geometric Mean Titer (GMT) Results with 95% Confidence Intervals by Time Point and Age Group, Per Protocol Population

Table 35: Ratio of Monkeypox Virus Specific PRNT Geometric Meant Fold Rise (GMFR) to Vaccinia Virus Specific PRNT GMFR by Time Point and Age Group, mITT Population

Time Point	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)
Study Day 43, Post Dose 2	n	x	x
	GMFR Ratio[a] (95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)

Note: N = Number of participants in the mITT Population.

N = Number of participants with data at time point.

CI = Confidence Interval, calculated using Welch-Satterthwaite t-test.

[a] GMFR Ratio represents the geometric mean fold rise in Monkeypox virus specific antibody compared to pre-dose 1 divided by the geometric mean fold rise in Vaccinia virus specific antibody compared to pre-dose 1.

Table with similar format:

Table 36: Ratio of Monkeypox Virus Specific PRNT Geometric Meant Fold Rise (GMFR) to Vaccinia Virus Specific PRNT Geometric Mean Fold Rise (GMFR) by Time Point and Age Group, Per Protocol Population

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 37: Summary of Secondary Safety Outcome by Age Group

[Implementation Note: Life-threatening (Grade 4) severity row will only be added if an event occurred.]

			Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)		
Participants[a] with	**Relatedness**	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**Adolescents vs. Adults p-value[c]**
At least one solicited systemic or local AE	Any Relatedness	Mild (Grade 1)	x	xx	x	xx	x	xx	x.xxx
		Moderate (Grade 2)							
		Severe (Grade 3)							
At least one unsolicited AE	Related	Mild (Grade 1)							
		Moderate (Grade 2)							
		Severe (Grade 3)							
	Not Related	Mild (Grade 1)							
		Moderate (Grade 2)							
		Severe (Grade 3)							
At least one unsolicited SAE[b]	Related	Any Severity							
	Not Related	Any Severity							
At least one AESI	Any Relatedness	Any Severity							
At least one MAAE	Related	Any Severity							
Withdrawal of Study	N/A	N/A							
Discontinuation of Vaccination	N/A	N/A							
Notes: N = Number of participants in the Safety Population.									

	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)	All Participants (N=X)	
n = Number of participants meeting the row criteria. [a] Participants are counted once for each category regardless of the total number of events. [b] Refer to the Listing of Serious Adverse Events for more details. [c] Fisher's exact test.				

Table with similar format:

Table 38: Summary of Secondary Safety Outcome by Age Subgroup

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years (N=X)", "Adolescents (Arm 5) 15-17 years (N=X)", and "Adults (Arm 4) 18+ years".]

Table 39: Overall Summary of Adverse Events

[Implementation Note: Table 60 will not be in the interim report; thus footnote b can be removed for the report. Life-threatening (Grade 4) severity row will only be added if an event occurred.]

		Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)	
Event Category[a]	**Subcategory**	**n**	**%**	**n**	**%**	**n**	**%**
At least one local solicited adverse event	Any Severity	xx	xx	xx	xx	xx	xx
At least one systemic solicited adverse event	Any Severity						
At least one unsolicited adverse event	Any Severity						
At least one related unsolicited adverse event	Any Severity						
	Mild (Grade 1)						
	Moderate (Grade 2)						
	Severe (Grade 3)						
At least one severe (Grade 3) or higher unsolicited adverse event	Any Relatedness						
	Related						
	Not Related						
At least one serious adverse event[b]	Any Severity						
At least one related, serious adverse event	Any Severity						
At least one adverse event leading to study withdrawal[c]	Any Severity						
At least one adverse event leading to discontinuation of study product[c]	Any Severity						
At least one medically attended adverse event (MAAE)	Any Severity						
At least one unanticipated problem (UP)	Any Severity						
At least one suspected unexpected serious adverse reaction (SUSAR)	Any Severity						

		Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)	
Event Category[a]	**Subcategory**	**n**	**%**	**n**	**%**	**n**	**%**
Notes: N = Number of participants in the Safety Population. n = Number of participants meeting the row criteria. [a] Participants are counted once for each category regardless of the number of events. [b] A listing of Serious Adverse Events is included in Listing of Serious Adverse Events. [c] As reported on the Adverse Event eCRF.							

Table with similar format:

Table 40: Overall Summary of Adverse Events by Age Subgroup

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years" and "Adolescents (Arm 5) 15-17 years."]

Table 41: Adverse Events Occurring in 5% of Participants in Any Age Group by MedDRA System Organ Class and Preferred Term, and Age Group, Safety Population

[Implementation Note: AEs will only be included if at least 5% of participants in any age group experienced the event, and then split into serious and non-serious. This table will consider events that occurred during any point of the study. A solicited event will only be counted once per associated dose.]

MedDRA Preferred Term	MedDRA System Organ Class	Adolescents (Arm 5) (N=X)			Adults (Arm 4) (N=X)			All Participants (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
Any PT	Any SOC	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.									
Other (Non-serious) Adverse Events										
Any PT	Any SOC	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc									

N = Number of participants in the Safety Population (number of participants at risk).
n = Number of participants reporting event.
Events = Total frequency of events reported.

Table with similar format:

Table 42: Adverse Events Occurring in 5% of Participants in Any Age Group by MedDRA System Organ Class and Preferred Term, and Adolescent Age Subgroup, Safety Population

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years" and "Adolescents (Arm 5) 15-17 years."]

14.3.1.1 Solicited Adverse Events

Table 43: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Age Group

Symptom	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx
Solicited Symptoms																		
Any Systemic Symptom																		
Fever																		
Chills																		
Nausea																		
Headache																		
Fatigue																		
Change in appetite																		
Myalgia																		
Arthralgia																		
Local Symptoms																		
Any Local Symptom																		
Pain at injection site																		
Erythema/redness																		
Induration/swelling[a]																		
Pruritis at injection site																		

Symptom	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI

Notes: Only events that occurred within the reactogenicity period (7 days post dose) were considered.
N = Number of participants in the Safety Population who received the specified dose.
n = Number of participants meeting the row criteria.
CI = Confidence interval, calculated using Clopper-Pearson methodology.
[a] Graded according to the Induration Grading Scale.

Table with similar format:

Table 44: Number and Percentage of Participants Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Adolescent Age Subgroup

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years" and "Adolescents (Arm 5) 15-17 years."]

Table 45: Comparison of the Proportion of Participants Experiencing Solicited Events by Age Group- Post Either Dose

Symptom	Statistic	Adolescents (Arm 5) (N=X)	Adults (Arm 4) (N=X)	Difference in Adolescents from Adults
Any Symptom	Proportion (95% CI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Systemic Symptoms				
Any Systemic Symptom	Proportion (95% CI)			
Fever	Proportion (95% CI)			
Chills	Proportion (95% CI)			
Nausea	Proportion (95% CI)			
Headache	Proportion (95% CI)			
Fatigue	Proportion (95% CI)			
Change in appetite	Proportion (95% CI)			
Myalgia	Proportion (95% CI)			
Arthralgia	Proportion (95% CI)			
Local Symptoms				
Any Local Symptom	Proportion (95% CI)			
Pain at injection site	Proportion (95% CI)			
Erythema/redness	Proportion (95% CI)			
Induration/swelling[a]	Proportion (95% CI)			
Pruritis at injection site	Proportion (95% CI)			

Notes: Only events that occurred within the reactogenicity period (7 days post dose) were considered.
N = Number of participants in the Safety Population who received at least one dose.
n = Number of participants meeting the row criteria.
Proportion = n divided by N.
CI = Confidence Interval, calculated using Clopper-Pearson methodology.
[a] Graded according to the Induration Grading Scale.

Table 46: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Age Group

[Implementation Note: Keep life-threatening row for relevant symptoms only. If no life-threatening events occurred, remove the associated rows and add the footnote 'No life-threatening (Grade 4) events were observed.']

Symptom	Severity	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	None	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx
	Mild																		
	Moderate																		
	Severe																		
Systemic Symptoms																			
Any Systemic Symptom	None	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Fever	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Chills	None																		

Symptom	Severity	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Nausea	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Headache	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Fatigue	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		

Symptom	Severity	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Change in Appetite	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Myalgia	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Arthralgia	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Local Symptoms																			
Any Local Symptom	None	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx
	Mild																		
	Moderate																		

Symptom	Severity	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Severe																		
	Life-Threatening																		
Pain at injection site	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Erythema/redness	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Induration/swelling[a]	None																		
	Mild																		
	Moderate																		
	Severe																		
	Life-Threatening																		
Pruritis at injection site	None																		
	Mild																		

Symptom	Severity	Post Dose 1 Adolescents (Arm 5) (N=X)			Post Dose 1 Adults (Arm 4) (N=X)			Post Dose 2 Adolescents (Arm 5) (N=X)			Post Dose 2 Adults (Arm 4) (N=X)			Post Either Dose Adolescents (Arm 5) (N=X)			Post Either Dose Adults (Arm 4) (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Moderate																		
	Severe																		
	Life-Threatening																		

Notes: Severity is the maximum severity reported during the reactogenicity period (7 days post dose) for each participant.
N = Number of participants in the Safety Population who received the specified dose.
n = Number of participants meeting the row criteria.
CI = Confidence interval, calculated using Clopper-Pearson methodology.
[a] Graded according to the Induration Grading Scale.

Table 47: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Age Group – Adolescents (Arm 5), Post Dose 1 (N=X)

[Implementation Note: Keep 'Life-Threatening' and 'Not Reported' rows for relevant symptoms only. If no life-threatening events occurred, remove the associated rows and add the footnote 'No life-threatening (Grade 4) events were observed.']

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Systemic Symptoms																							
Any Systemic Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Fever	None																						
	Mild																						

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Chills	None																						
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Nausea	None																						
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Headache	None																						
	Mild																						
	Moderate																						

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																						
	Life-Threatening																						
	Not Reported																						
Fatigue	None																						
	Mild																						
	Moderate																						
	Severe																	-					
	Life-Threatening																						
	Not Reported																						
Change in appetite	None																						
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Myalgia	None																						
	Mild																						
	Moderate																						
	Severe																						

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Life-Threatening																						
	Not Reported																						
Arthralgia	None																						
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Local Symptoms																							
Any Local Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Pain at injection site	None																						
	Mild																						
	Moderate																						
	Severe																						

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Life-Threatening																						
	Not Reported																						
Erythema/redness	None																						
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Induration/swelling[a]	None																						
	Mild																						
	Moderate																						
	Severe																						
	Life-Threatening																						
	Not Reported																						
Pruritis at injection site	None																						
	Mild																						
	Moderate																						
	Severe																						

Symptom	Severity	Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9+	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Life-Threatening																						
	Not Reported																						

Notes: Severity is the maximum severity reported for each participant for each day. Day 9+ represents symptoms that persisted past the reactogenicity period (7 days post dose).
N = Number of participants in the Safety Population who received the specified dose.
n = Number of participants meeting the row criteria. A participant may be counted in more than one of these categories.
[a] Graded according to the Induration Grading Scale.

Tables with similar format:

Table 48: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Age Group – Adolescents (Arm 5), Post Dose 2 (N=X)

Table 49: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Age Group – Adolescents (Arm 5), Post Either Dose (N=X)

Table 50: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Age Group – Adults (Arm 4), Post Dose 1 (N=X)

Table 51: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Age Group – Adults (Arm 4), Post Dose 2 (N=X)

Table 52: Number and Percentage of Participants Experiencing Solicited Events by Symptom, Severity, Dose, Day Post Dosing, and Age Group – Adults (Arm 4), Post Either Dose (N=X)

Table 53: Number and Percentage of Participants Experiencing Solicited Events for Dose 1 Compared with Dose 2 by Age Group

Age Group		Dose 2 – Participants with No Symptoms	Dose 2 – Participants with Mild or Greater Symptoms
Adolescents (Arm 5)	Dose 1 Participant with No Symptoms	n/N (%)	n/N (%)
	Dose 1 Participants with Mild or Greater Symptoms	n/N (%)	n/N (%)
Adults (Arm 4)	Dose 1 Participant with No Symptoms		
	Dose 1 Participants with Mild or Greater Symptoms		
Adolescents (Arm 5)	Dose 1 Participant with No Symptoms	n/N (%)	n/N (%)
	Dose 1 Participants with Mild or Greater Symptoms	n/N (%)	n/N (%)
Adults (Arm 4)	Dose 1 Participant with No Symptoms		
	Dose 1 Participants with Mild or Greater Symptoms		
Adolescents (Arm 5)	Dose 1 Participants with No Symptoms	n/N (%)	n/N (%)
	Dose 1 Participants with Mild or Greater Symptoms	n/N (%)	n/N (%)
Adults (Arm 4)	Dose 1 Participants with No Symptoms		
	Dose 1 Participants with Mild or Greater Symptoms		

Notes: Denominators for percentages are the number of participants in the Safety Population who received the first and second dose (N=X). [x] participants did not get the second dose and are not included in this table.

Only events that occurred within the reactogenicity period (7 days post dose) were considered.

14.3.1.2 Unsolicited Adverse Events

Table 54: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Dose – Adolescents (Arm 5)

MedDRA System Organ Class	MedDRA Preferred Term	Within 7 Days Post Dose 1 (N=X)				8-28 Days Post Dose 1 (N=X)				Within 7 Days Post Dose 2 (N=X)				8-28 Days Post Dose 2 (N=X)				Any Time Post Either Dose (N=X)			
		n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events
Any SOC	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any PT																				
	[PT 1]																				
	[PT 2]																				
[SOC 2]	Any PT																				
	[PT 1]																				
	[PT 2]																				

Notes: A participant is only counted once per PT/time period. Events that span multiple time points will be summarized during the time period in which they began.

N = Number of participants in the Safety Population who received the specified dose.

n = Number of participants experiencing a given PT within the specified time frame regardless of associated dose.

CI = Confidence interval, calculated using Clopper-Pearson methodology.

X events with PT of Y [add "and" and repeat "X events with a PT of Z" if more than 1 PT] associated with Dose 1 injection site were not observed until Post Dose 2 and are counted in 'Within 7 Days Post Dose 2' column.

X events with PT of Y [add "and" and repeat "X events with a PT of Z" if more than 1 PT] associated with Dose 1 injection site were not observed until Post Dose 2 and are counted in '8-28 Days Post Dose 2' column.

Table with similar format:

Table 55: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, and Dose – Adults (Arm 4)

Table 56: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Age Group

[Implementation Note: If no life-threatening events occurred, remove the associated rows and add the footnote 'No Grade 4 events were observed.']

MedDRA System Organ Class	MedDRA Preferred Term	Severity	Adolescents (Arm 5) (N = X)				Adults (Arm 4) (N = X)				All Participants (N = X)			
			Related		Not Related		Related		Not Related		Related		Not Related	
			n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Life-Threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Life-Threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Life-Threatening	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Notes: Maximum severity is taken for each relationship status. A participant may be counted in 'Related' and 'Not Related' for the same PT.
N = Number of participants in the Safety Population.
n = Number of participants meeting the row criteria.

Table with similar format:

Table 57: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Adolescent Age Subgroup

[Implementation Note: The subgroups will be "Adolescents (Arm 5) 12-14 years (N=X)" and "Adolescents (Arm 5)15-17 years (N=X)."]

Table 58: Related Unsolicited Adverse Events Within 28 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Dose – Adolescents (Arm 5)

[Implementation Note: Replace *X* with the number of events and *Y* with the specific PT in the footnotes.]

		Within 28 Days Post Dose 1 (N=X)			Within 28 Days Post Dose 2 (N=X)			Within 28 Days Post Either Dose (N=X)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT									
	[PT 1]									
	[PT 2]									

Notes: N = Number of participants in the Safety Population who received the specified dose.

n = Number of participants who began to experience the given PT within 28 days of a given dose regardless of associated dose.

For each time point, a participant is only counted once per PT.

X events with PT of Y [add "and" and repeat "X events with a PT of Z" if more than 1 PT] associated with Dose 1 injection site were not observed until Post Dose 2 and are counted in 'Within 28 Days Post Dose 2' column.

Participants who did not receive Dose 2 but experienced an unsolicited AE within the specified time frame after when Dose 2 would have occurred are counted toward the 'Within 28 Days Post Dose 2' column. Participant X did not receive Dose 2 but experienced a PT of Z1 and Z2 during the Post Dose 2 time frame.

Table with similar format:

Table 59: Related Unsolicited Adverse Events Within 28 Days Post Dosing by MedDRA System Organ Class and Preferred Term, and Dose – Adults (Arm 4) (N=X)

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 60: Listing of Serious Adverse Events

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	SUSAR/UP/ AESI?	Severity	Relation-ship to Study Vaccination	If Not Related, Alternative Etiology	Action Taken with Study Vaccination	Participant Dis-continued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Age Group: , Participant ID: , AE Number:													
Comments:													
Age Group: , Participant ID: , AE Number:													
Comments:													
Note: SUSAR = Suspected Unexpected Serious Adverse Reaction; UP = Unanticipated Problem; AESI = Adverse Event of Special Interest.													

Table 61: Listing of Non-Serious, Unsolicited, Moderate or Greater Severe Adverse Events

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Vaccination	If Not Related, Alternative Etiology	AESI?	Action Taken with Study Vaccination	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Age Group: , Participant ID: , AE Number:											
Comments:											
Age Group: , Participant ID: , AE Number:											
Comments:											
Note: AESI = Adverse Event of Special Interest.											

Table 62: Listing of Medically Attended Adverse Events (MAAEs), Unanticipated Problems (UPs), and Adverse Events of Special Interest (AESIs)

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and AE Number.]

Adverse Event	Number of Doses Received at Time of Event	No. of Days Post Associated Dose	Duration of Event	Severity	MedDRA System Organ Class	MAAE?	UP?	AESI?	Relationship	Outcome
Age Group: , Participant ID: , AE Number:										
Comments:										
Age Group: , Participant ID: , AE Number:										
Comments:										
Notes: MAAE = Medically Attended Adverse Event; UP = Unanticipated Problem; AESI = Adverse Event of Special Interest.										

Table 63: Duration of Injection Site AEs

[Implementation Note: If no life-threatening events occurred, remove the associated rows and add the footnote 'No Grade 4 events were observed.' This table will consider injection site reactions over the entire study period.]

	Injection Site Bruising	Injection Site Discoloration	Injection Site Erythema	Injection Site Exfoliation	Injection Site Infection	Injection Site Induration	Injection Site Nodule	Injection Site Pain
Adolescents (Arm 5) Post-Dose 1 (N=X)								
Any Severity (n)	x	x	x	x	x	x	x	x
Median Onset Day Post-Dose [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Median Days Duration [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Mild (n)	x	x	x	x	x	x	x	x
Median Onset Day Post-Dose [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Median Days Duration [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Moderate (n)	x	x	x	x	x	x	x	x
Median Onset Day Post-Dose [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Median Days Duration [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Severe (n)	x	x	x	x	x	x	x	x
Median Onset Day Post-Dose [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Median Days Duration [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Life-Threatening (n)	x	x	x	x	x	x	x	x
Median Onset Day Post-Dose [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)
Median Days Duration [Minimum, Maximum]	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)	x (x, x)

	Injection Site Bruising	Injection Site Discoloration	Injection Site Erythema	Injection Site Exfoliation	Injection Site Infection	Injection Site Induration	Injection Site Nodule	Injection Site Pain
Adolescents (Arm 5) Post-Dose 2 (N=X)								
Any Severity (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Mild (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Moderate (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Severe (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Life-Threatening (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Adults (Arm 4) Post-Dose 1 (N=X)								
Any Severity (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								

	Injection Site Bruising	Injection Site Discoloration	Injection Site Erythema	Injection Site Exfoliation	Injection Site Infection	Injection Site Induration	Injection Site Nodule	Injection Site Pain
Mild (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Moderate (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Severe (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Threatening-Life (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Adults (Arm 4) Post-Dose 2 (N=X)								
Any Severity (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Mild (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Moderate (n)								

	Injection Site Bruising	Injection Site Discoloration	Injection Site Erythema	Injection Site Exfoliation	Injection Site Infection	Injection Site Induration	Injection Site Nodule	Injection Site Pain
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Severe (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								
Life-Threatening (n)								
Median Onset Day Post-Dose [Minimum, Maximum]								
Median Days Duration [Minimum, Maximum]								

Notes: Duration is calculated as the total days from first non-zero grade to last non-zero grade. For participants with ongoing events at study completion or early termination, duration is censored at the date of study completion or early termination. Severity is categorized by maximum grade at any day post dose.

N = number of participants in the Safety Population who received the specified dose.

n = number of participants experiencing a given PT.

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.3.4 Abnormal Laboratory Value Listings (by Participant)

Not applicable.

14.3.5 Displays of Laboratory Results

Not applicable.

14.3.6 Displays of Vital Signs

Table 64: Vital Signs by Assessment, Maximum Severity, Time Point, and Age Group – Any Assessment

[Implementation Note: If no life-threatening events occurred, remove the column and add the footnote 'No life-threatening (Grade 4) events were observed.' If there are no missing vitals, then remove 'Missing' column.]

Time Point	Age Group	N	None		Mild		Moderate		Severe		Life-Threatening		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Adolescents (Arm 5)	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Adults (Arm 4)													
Day 29	Adolescents (Arm 5)													
	Adults (Arm 4)													
Max Severity Post Baseline	Adolescents (Arm 5)													
	Adults (Arm 4)													

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.
N = Number of participants in the Safety Population with non-missing data at time point.
n = Number of participants experiencing the given severity.

Table 65: Vital Signs by Assessment, Maximum Severity, Time Point, and Age Group – Oral Temperature (°F)

[Implementation Note: If no life-threatening events occurred, remove the column and add the footnote 'No Grade 4 events were observed.' If there are no missing vitals, then remove 'Missing' column.]

Time Point	Age Group	N	None		Mild		Moderate		Severe		Life-Threatening		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Adolescents (Arm 5)	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Adults (Arm 4)													
Day 29	Adolescents (Arm 5)													
	Adults (Arm 4)													
Max Severity Post Baseline	Adolescents (Arm 5)													
	Adults (Arm 4)													

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.
N = Number of participants in the Safety Population with non-missing data at time point.
n = Number of participants experiencing the given severity.

Table 66: Vital Signs by Assessment, Maximum Severity, Time Point, and Age Group – Diastolic Blood Pressure

[Implementation Note: If no life-threatening events occurred, remove the column and add the footnote 'No life-threatening (Grade 4) events were observed.' If there are no missing vitals, then remove 'Missing' column.]

Time Point	Age Group	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Life-Threatening (Low)		Life-Threatening (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Adolescents (Arm 5)	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Adults (Arm 4)																					
Day 29	Adolescents (Arm 5)																					
	Adults (Arm 4)																					
Max Severity Post Baseline	Adolescents (Arm 5)																					
	Adults (Arm 4)																					

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each participant at any time point post baseline, including unscheduled assessments.
N = Number of participants in the Safety Population with non-missing data at time point.
n = Number of participants experiencing the given severity.

Tables with similar format:

Table 67: Vital Signs by Assessment, Maximum Severity, Time Point, and Age Group – Systolic Blood Pressure

Table 68: Vital Signs by Assessment, Maximum Severity, Time Point, and Age Group – Pulse

14.4 Summary of Concomitant Medications

Table 69: Number and Percentage of Participants with Prior and Concurrent Medications by WHO Drug Classification and Age Group

[Implementation Note: 'Any [ATC #]' row will only be included if there are more than two Level 2 subgroups within the Level 1 group.]

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Adolescents (Arm 5) (N=X)		Adults (Arm 4) (N=X)		All Participants (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	Any [ATC 2]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

Notes: N = Number of participants in the Safety Population.
n = Number of participants reporting taking at least one medication in the specific WHO Drug Class.

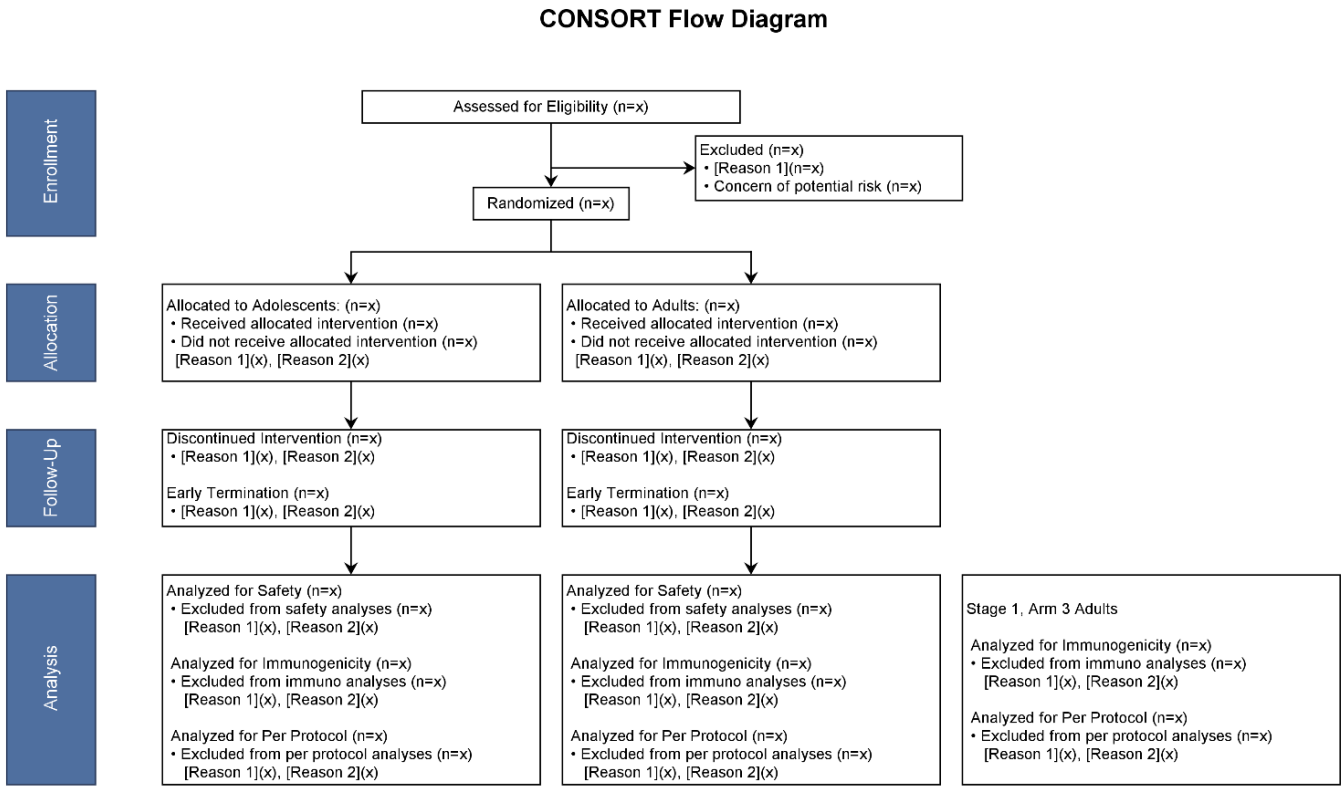
APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram

[Implementation Note: The below figure is just an example and will be updated accordingly for this study.]

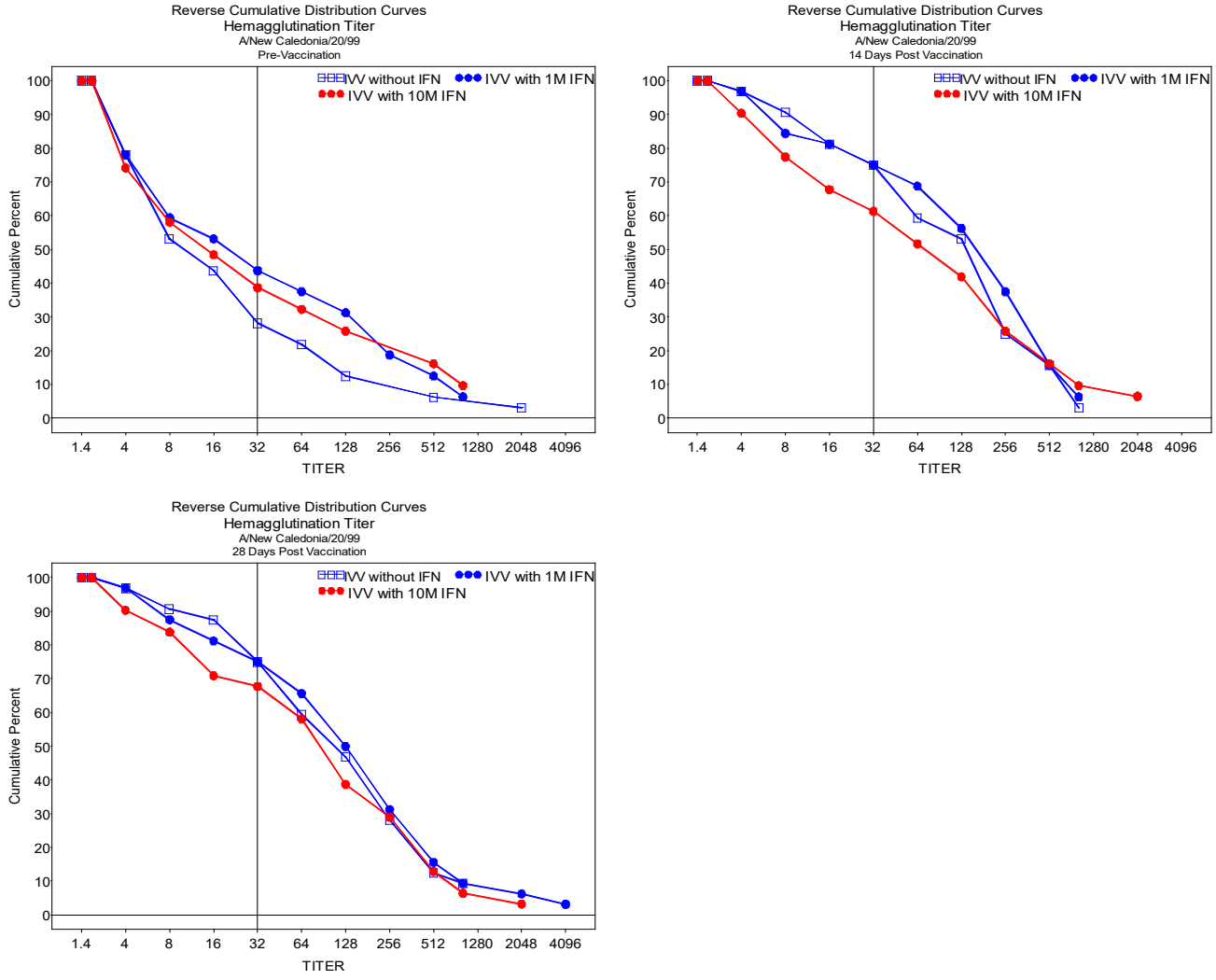


14.2 Immunogenicity Data

14.2.2 Immunogenicity Response Figures by Measure, Age Group, and Time Point

Figure 2: Reverse Cumulative Distribution of Vaccinia Virus Specific PRNT by Time Point and Age Group, mITT Population

[Implementation Note: The figure below is an example only. Groups presented will be Adolescents (Arm 5) and Adults (Arm 4). The figure will include 5 panels for Study Day 1, 29, 43, 210, and 394.]



Figures with similar format:

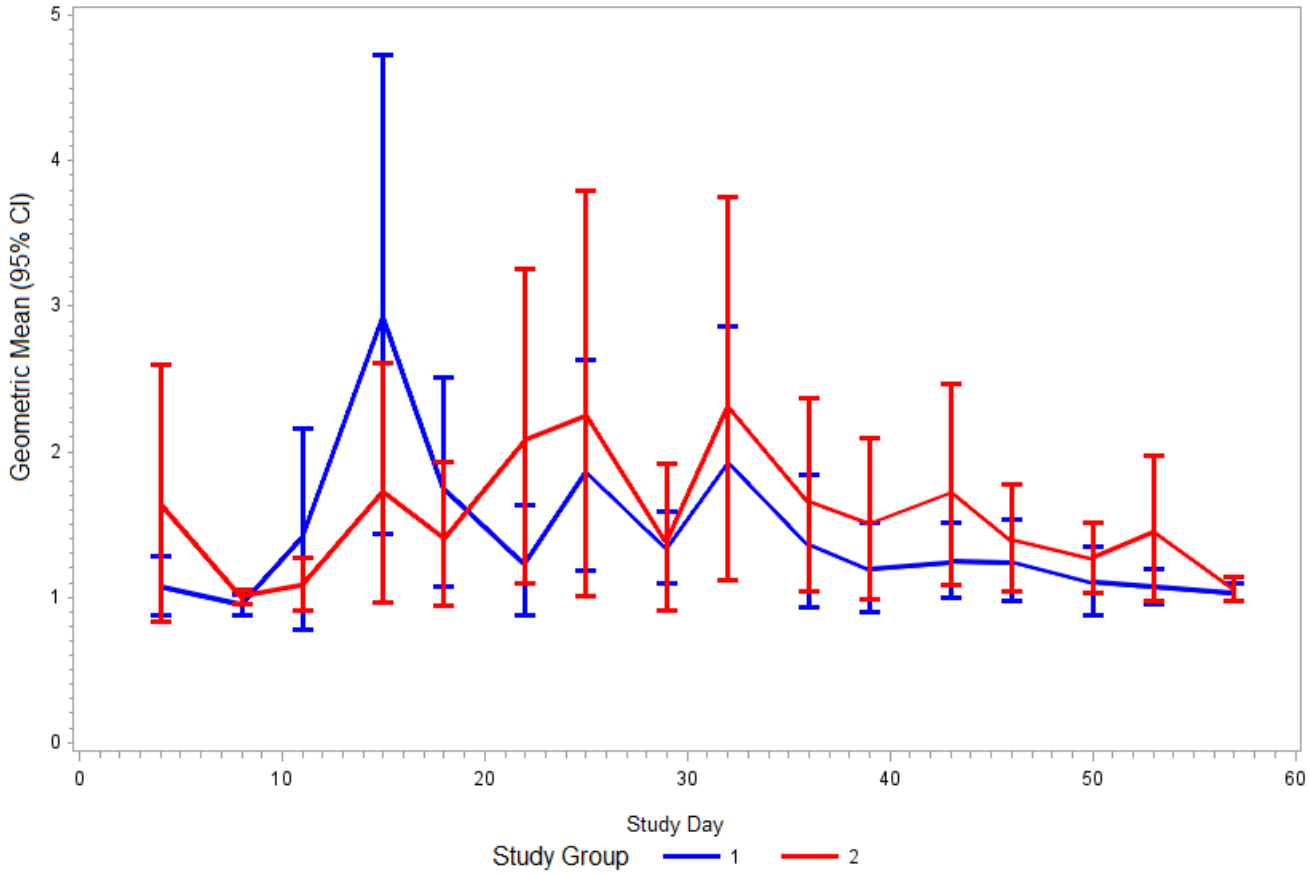
Figure 3: Reverse Cumulative Distribution of Vaccinia Virus Specific PRNT by Time Point and Age Group, Per Protocol Population

Figure 4: Reverse Cumulative Distribution of Monkeypox Virus Specific PRNT by Time Point and Age Group, mITT Population

Figure 5: Reverse Cumulative Distribution of Monkeypox Virus Specific PRNT by Time Point and Age Group, Per Protocol Population

Figure 6: GMT of Vaccinia Virus Specific PRNT by Time Point and Age Group, mITT Population

[Implementation Note: The figure below is an example only. Groups presented will be Adolescents (Arm 5) and Adults (Arm 4). Time Points presented will be Study Day 1, 29, 43, 210, and 394. A dashed line will e added to represent LLOD. Add footnote "Dashed line represents the lower limit of detection (LLOD) of assay."]



Figures with similar format:

Figure 7: GMT of Vaccinia Virus Specific PRNT by Time Point and Age Group, Per Protocol Population

Figure 8: GMT of Monkeypox Virus Specific PRNT by Time Point and Age Group, mITT Population

Figure 9: GMT of Monkeypox Virus Specific PRNT by Time Point and Age Group, Per Protocol Population

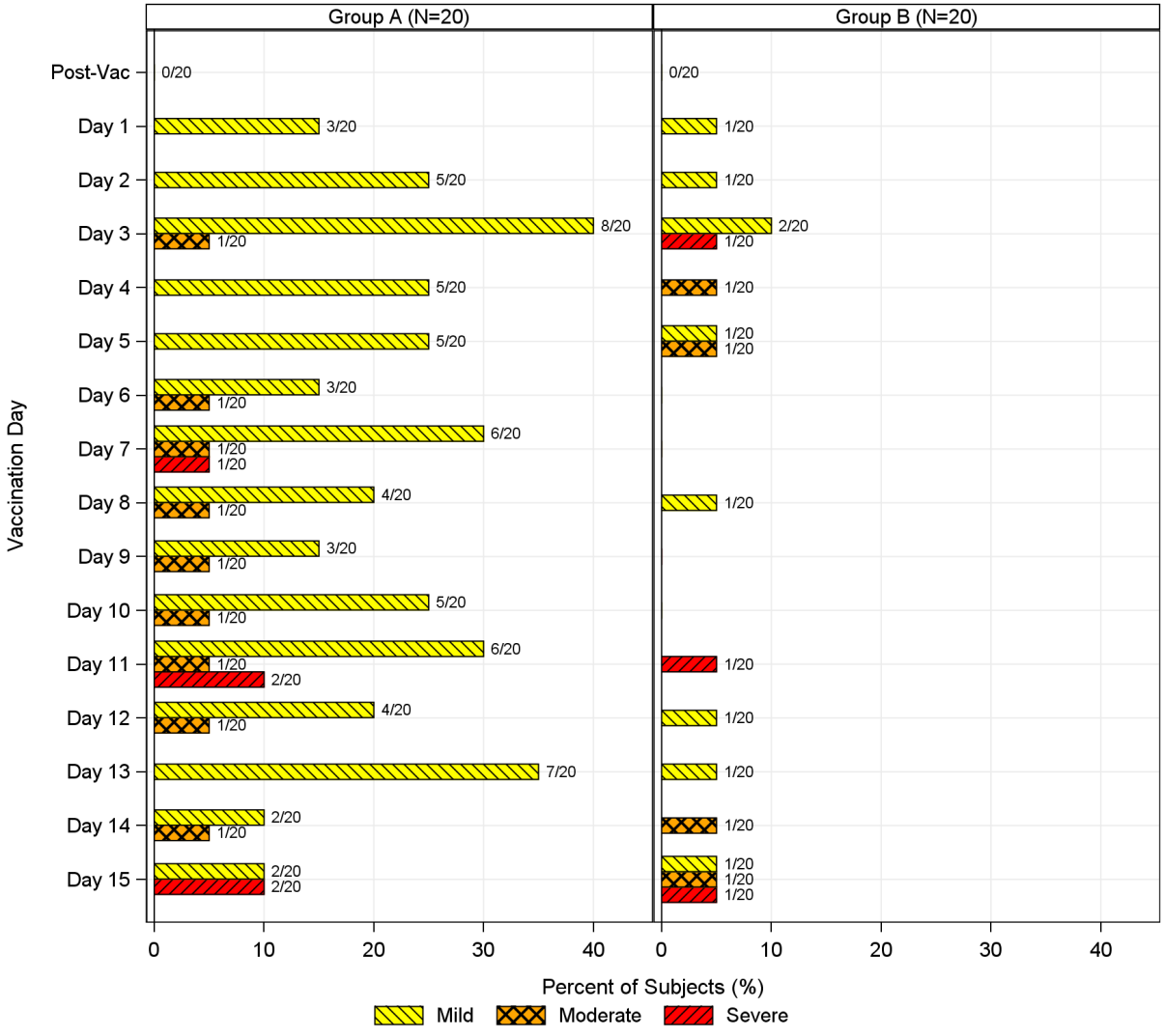
14.3 Safety Data

14.3. Adverse Events

14.3.1.1 Solicited Adverse Events

Figure 10: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Vaccination – Post Dose 1

[Implementation Note: The figure below is an example only. Groups presented will be Adolescents (Arm 5) and Adults (Arm 4). Severities presented will be mild (yellow with black left-diagonal strip pattern), moderate (orange with black lattice pattern), severe(red with black right-diagonal strip pattern), and life-threatening (solid black). The y-axis will have tick marks for Post-Vac, Day 1 through Day 8, and Day 9+. Add the footnote: "Day 9+ represents symptoms that persisted past the reactogenicity period (7 days post dose)."]



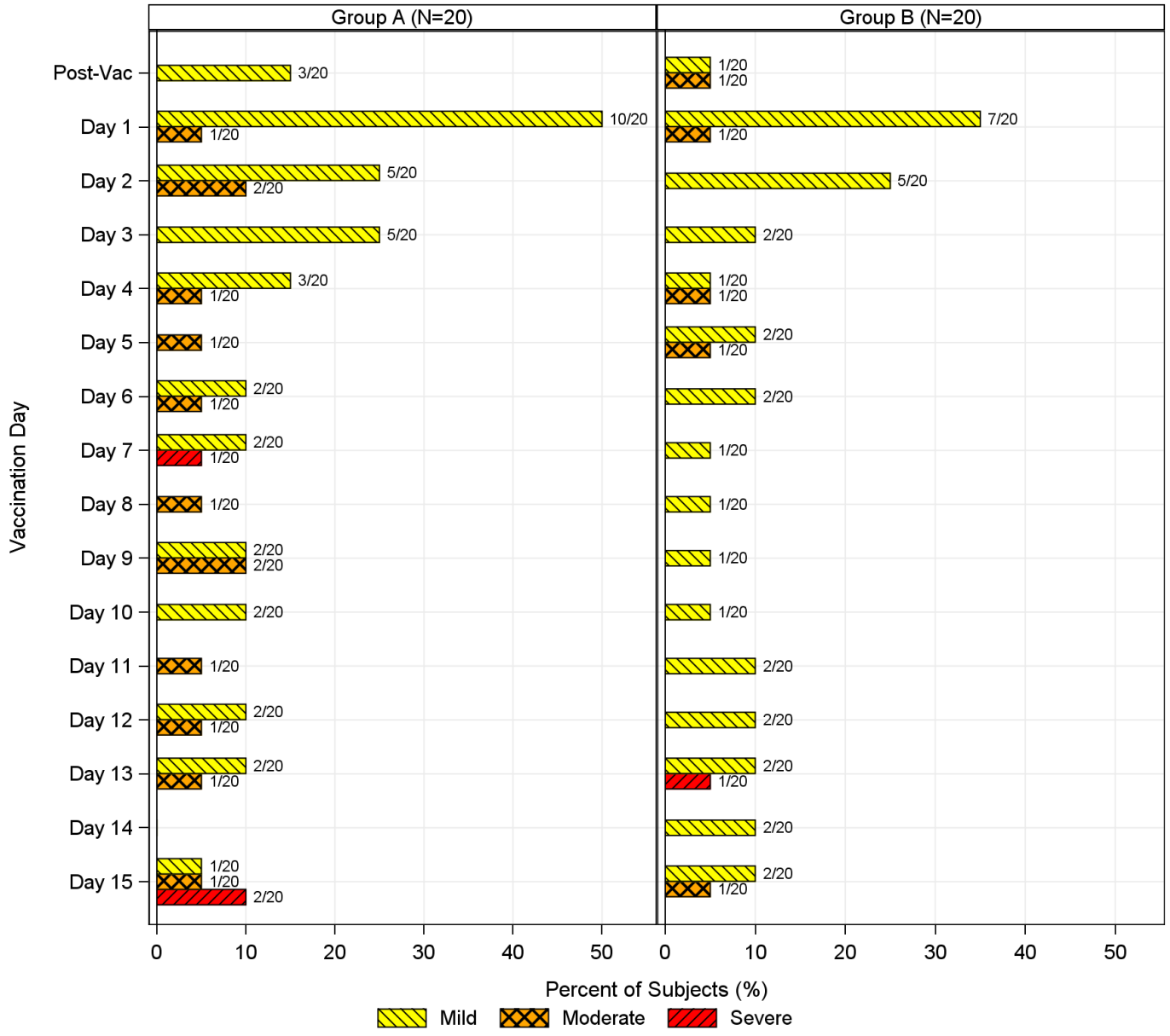
Figures with similar format:

Figure 11: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Vaccination – Post Dose 2

Figure 12: Maximum Severity of Solicited Systemic Symptoms per Participant by Day Post Vaccination – Post Either Dose

Figure 13: Maximum Severity of Solicited Local Symptoms per Participant by Day Post Dose 1

[Implementation Note: The figure below is an example only. Groups presented will be Adolescents (Arm 5) and Adults (Arm 4). Severities presented will be mild (yellow with black left-diagonal strip pattern), moderate (orange with black lattice pattern), severe (red with black right-diagonal strip pattern), and life-threatening (solid black). The y-axis will have tick marks for Post-Vac, Day 1 through Day 8, and Day 9+. Add the footnote: "Day 9+ represents symptoms that persisted past the reactogenicity period (7 days post dose)."]



Figures with similar format:

Figure 14: Maximum Severity of Solicited Local Symptoms per Participant by Day Post Dose 2

Figure 15: Maximum Severity of Solicited Local Symptoms per Participant by Day Post Either Dose

14.3.1.2 Unsolicited Adverse Events

Figure 16: Frequency of Related Adverse Events by MedDRA System Organ Class and Severity

[Implementation Note: The figure below is an example only. Groups presented will be Adolescents (Arm 5) and Adults (Arm 4). Severities presented will be mild (yellow with black left-diagonal strip pattern), moderate (orange with black lattice pattern), severe (red with black right-diagonal strip pattern), and life-threatening (solid black).]

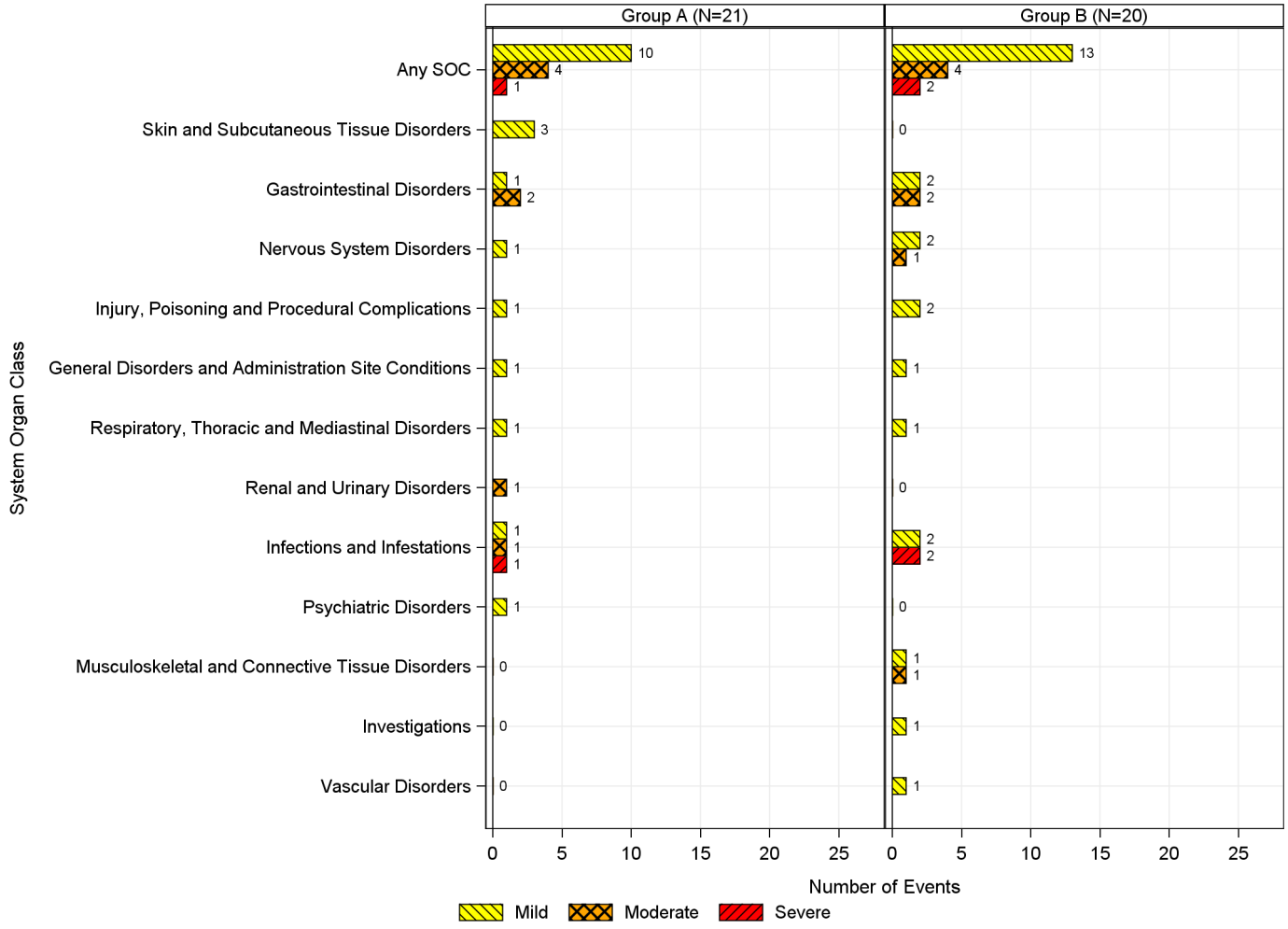
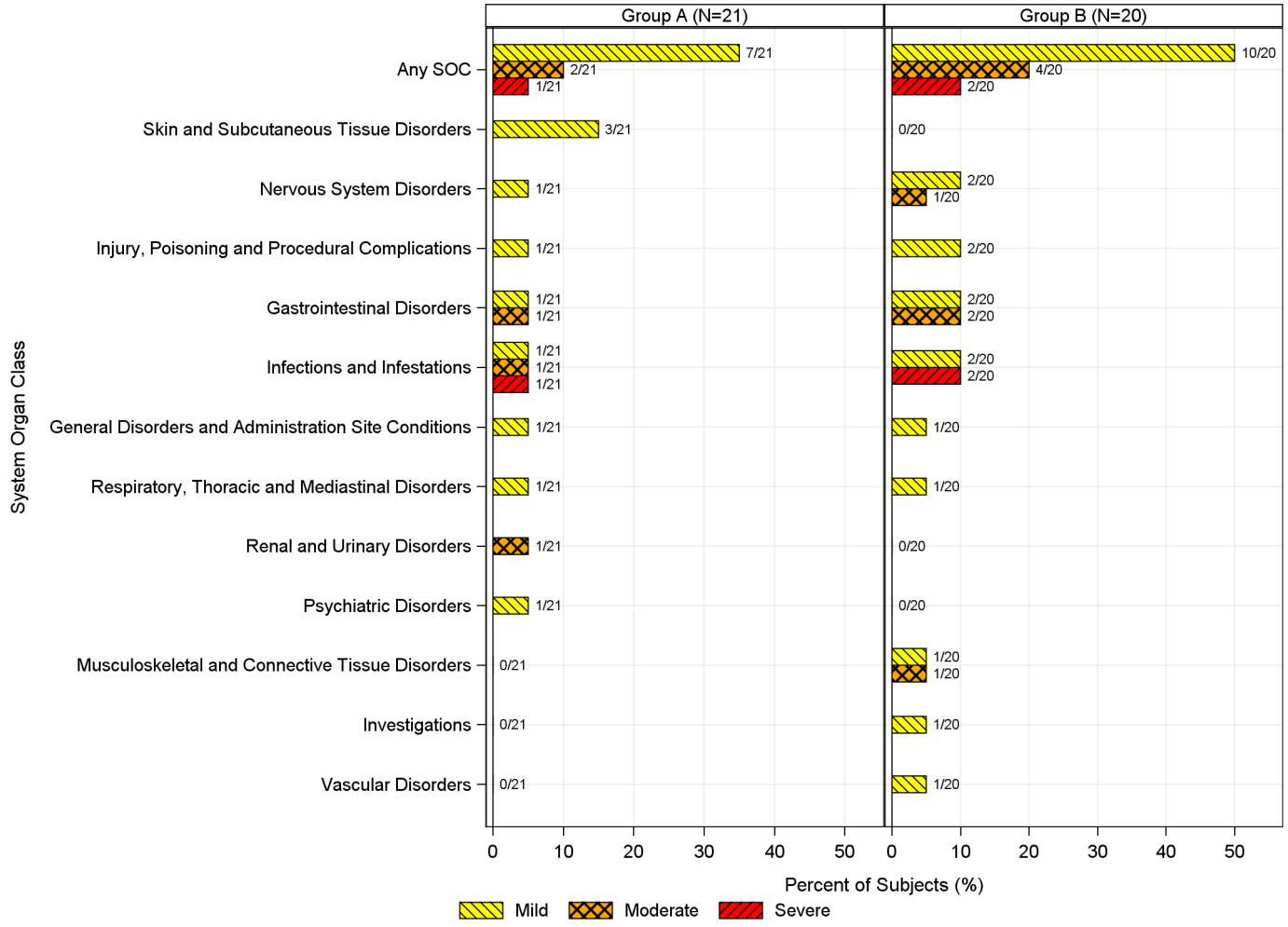


Figure 17: Incidence of Related Adverse Events by MedDRA® System Organ Class and Maximum Severity

[Implementation Note: The figure below is an example only. Groups presented will be Adolescents (Arm 5) and Adults (Arm 4). Severities presented will be mild (yellow with black left-diagonal strip pattern), moderate (orange with black lattice pattern), severe (red with black right-diagonal strip pattern), and life-threatening (solid black).]



14.3.5 Displays of Laboratory Results

Not applicable.

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **Listing of Participants Receiving Investigational Product**

(not included in SAP, but this is a placeholder for the CSR)

16.2 Database Listings by Participant

16.2.1 Discontinued Participants

Listing 2: Early Terminations or Discontinued Participants

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group and Participant ID.]

Age Group	Participant ID	Category	Reason for Early Termination or Vaccination Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: Participant-Specific Protocol Deviations

[Implementation Note: Deviations will be classified as Major or Minor. The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and DV Number.]

Age Group	Participant ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	UP?	Deviation Classification	Deviation Resolution	Comments
Notes: AE = Adverse Event; UP = Unanticipated Problem.													

Listing 4: Non-Participant-Specific Protocol Deviations

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Site, Start Date, and Deviation.]

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Participant Termination?	Deviation Affected Product Stability?	UP?	Deviation Category	Deviation Classification	Deviation Resolution	Comments
Note: UP = Unanticipated Problem.											

16.2.3 Participants Excluded from Analysis

Listing 5: Participants Excluded from Analysis Populations

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will include Stage 1 Arm 3. For Arm 3, only deviations that may impact Day 43 will be assessed. This listing will be sorted by Age Group and Participant ID.]

Age Group	Participant ID	Analyses in which Participant is Included	Analyses from which Participant is Excluded	Results Available?	Reason Participant Excluded
		[e.g., Safety, ITT, PP]	[e.g., Safety, ITT, PP, Day x]		
Notes: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis. Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis. Only deviations that may impact Day 43 were assessed for Stage 1 Arm 3.					

16.2.4 Demographic Data

Listing 6: Demographic Data

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will include Stage 1 Arm 3. This listing will be sorted by Age Group and Participant ID.]

Age Group	Participant ID	Sex at Birth	Age at Enrollment (years)	Ethnicity	Race	HIV Status
Note: Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis.						

Listing 7: Pre-Existing and Concurrent Medical Conditions

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and MH Number.]

Age Group	Participant ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.5 Compliance and/or Drug Concentration Data (if available)

Not applicable.

16.2.6 Individual Immunogenicity Response Data

Listing 8: Individual Immunogenicity Response Data

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will include Stage 1 Arm 3. Arm 3 adults will only include Day 43 results. This listing will be sorted by Age Group, Participant ID, Planned Time Point, and Assay.]

Age Group	Participant ID	HIV Status	Planned Time Point	Actual Study Day	Assay	Titer
Notes: Stage 1 Arm 3 adults were combined with Stage 2 Arm 4 adults as a comparator group for the primary analysis. Only Day 43 titers were assessed for Stage 1 Arm 3.						

16.2.7 Adverse Events

Listing 9: Solicited Events – Systemic Symptoms

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, Dose Number, Post Dose Time Point, and Symptom.]

Age Group	Participant ID	Dose Number	Post Dose Time Point	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?[b]	Alternate Etiology
				MA				
				Clinic				

Notes: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

[a] MA = Data reported by participant on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.

[b] Grade 3 and Grade 4 events only.

Listing 10: Solicited Events – Local Symptoms

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, Dose Number, Post Dose Time Point, and Symptom.]

Age Group	Participant ID	Dose Number	Post Dose Time Point	Assessment[a]	Symptom	Severity
				MA		
				Clinic		

Notes: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.).
MA = Data reported by participant on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.

Listing 11: Unsolicited Adverse Events

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and AE Number.]

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	SUSAR/ MAAE/ UP/ AESI?	Relationship to Study Vaccination	In Not Related, Alternative Etiology	Action Taken with Study Vaccination	Participant Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Age Group: , Participant ID: , AE Number:												
Comments:												
Age Group: , Participant ID: , AE Number:												
Comments:												

Notes: SUSAR = Suspected Unexpected Serious Adverse Reaction; MAAE = Medically Attended Adverse Event; UP = Unanticipated Problem; AESI = Adverse Event of Special Interest.

For additional details about SAEs, see the Listing of Serious Adverse Events.

Listing 12: Injection Site Skin Discoloration and Nodule Measurements

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will include all injection site assessments as recorded in PE form, including skin discoloration and/or nodule(s). This listing will be sorted by Age Group, Participant ID, Dose Number, AE Number, and Post Dose Time Point.]

Age Group	Participant ID	Dose Number	Post Dose Time Point	Parameter	Measurement (mm)	AE Number	Additional Observations
Adolescents (Arm 5)	MPX.1234	1	Day 1	Skin discoloration	21	001	Erythematous discolouration
Note: The maximum severity for the event is listed in listing of Unsolicited Adverse Events.							

Listing 13: Illness Visits

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, Study Day of Illness Onset.]

Age Group	Participant ID	Study Day of Illness Onset	Study Day of Illness Visit	Positive Test for Mpox Infection form Outside Lab	Study Day of Test
				Yes or No	

16.2.8 Individual Laboratory Measurements

Not applicable.

16.2.9 Vital Signs and Physical Exam Findings

Listing 14: Vital Signs

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and Planned Time Point.]

Age Group	Participant ID	Planned Time Point	Actual Study Day	Temperature (°F)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)

Listing 15: Physical Exam Findings

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, and Planned Time Point.]

Age Group	Participant ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 Concomitant Medications

Listing 16: Concomitant Medications

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". This listing will be sorted by Age Group, Participant ID, CM Number.]

Age Group	Participant ID	Concomitant Medication Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

16.2.11 Pregnancy Reports

[Implementation Note: The age groups will specify the study arm in parenthesis, e.g., "Adults (Arm 4)". These listings will be sorted by Age Group and Participant ID.]

Listing 17: Pregnancy Reports – Maternal Information

Age Group	Participant ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
Notes: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 18: Pregnancy Reports – Gravida and Para

			Live Births												
Participant ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Notes: Gravida includes the current pregnancy, para events do not.

[a] Preterm Birth

[b] Term Birth

Listing 19: Pregnancy Reports – Live Birth Outcomes

Participant ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Note: Congenital Anomalies are included in the Adverse Event listing.

Listing 20: Pregnancy Reports – Still Birth Outcomes

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 21: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Participant ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion