CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 17-0089
Study Title:
A Phase 1, Dosage-Escalation Study of the Safety and Immunogenicity of a Novel Rabies Vaccine ChAd155-RG vs. the Comparator RABAVERT Vaccine in Healthy Adult Subjects
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STUDY TITLE

Protocol Number Code:	**DMID Protocol: 17-0089**
Development Phase:	Phase 1
Products:	ChAd155- RG
Form/Route:	Intramuscular
Indication Studied:	Rabies
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
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This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

Ad	Adenovirus
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AST	Aspartate Transaminase
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats per minute
BUN	Blood Urea Nitrogen
C	Celsius
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	Confidence Interval
ChAd	Chimpanzee Adenovirus
CMS	Clinical Materials Services
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CPM	Clinical Project Manager
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CSR	Clinical Study Report
DHHS	Department of Health and Human Services
dL	deciliter
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immuno-sorbent Assay
ELISPOT	Enzyme-linked Immunospot
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
HBsAg	Hepatitis B surface antigen

List of Abbreviations *(continued)*

HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
IDES	Internet Data Entry System
IM	Intramuscular
IU	International Unit
IUD	Intrauterine device
IV	Intravenous
Kg	kilogram
L	Liter
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
mITT	Modified Intention to Treat
mL	Milliliter
mm	millimeter
mM	millimole
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NCBI	National Center for Biotechnology Information
ng	Nanograms
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRR	Office of Clinical Research Resources
PCECV	Purified chick embryo cell vaccine
PEP	Post-Exposure Prophylaxis
PI	Principal Investigator
PP	Per Protocol
PrEP	Pre-Exposure Prophylaxis
PT	Preferred Term
RCD	Reverse Cumulative Distribution

List of Abbreviations *(continued)*

RFFIT	Rapid Fluorescence Focus Inhibition Test
RG	Rabies Protein G
RIG	Rabies Immunoglobulin
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
VNA	Virus neutralizing antibody
VP	Viral Particle
VTEU	Vaccine and Treatment Evaluation Unit
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

This Statistical Analysis Plan (SAP) for "A Phase 1, Dosage-Escalation Study of the Safety and Immunogenicity of a Novel Rabies Vaccine ChAd155-RG vs. the Comparator RABAVERT Vaccine in Healthy Adult Subjects" (DMID Protocol 17-0089) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses and may be used for the interim analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Council 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.

Within the table, figure, and listing mock-ups (Appendix 1, Appendix 2, and Appendix 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

Rabies is an acute, progressive viral encephalitis caused by neurotropic single-stranded RNA viruses (genus Lyssavirus, family Rhabdoviridae). This zoonotic infection is acquired after exposure to the saliva of infected domestic or wild mammals and is almost invariably fatal. Rabies is estimated to cause more than 50,000 deaths annually, mostly in Asia and Africa, but the true disease burden is likely higher due to underreporting and lack of confirmatory testing in many endemic regions [1 and 2].

Highly effective, inactivated viral vaccines against rabies have been available for use as pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) for decades. In the US, two vaccine formulations are currently available, a purified chick embryo cell vaccine (PCECV; RabAvert, GSK Vaccines), and a human diploid cell vaccine (HDCV; Imodex, Sanofi Pasteur) [3 and 4]. It is recommended that both vaccines be administered in a three-dose series (Days 0, 7, and 21 or 28) [3] for PrEP, and a four-dose series (Days 0, 3, 7, and 14; a fifth dose on Day 28 is recommended for immunocompromised individuals) for PEP, with or without rabies immunoglobulin (RIG) depending on the severity of the exposure [4]. Virtually all recipients of a recommended vaccine series mount a seroprotective titer of rabies virus neutralizing antibody (VNA), defined as a post-vaccination VNA concentration ≥0.5 IU/mL, or complete virus neutralization at a 1:5 serum dilution, by a WHO-approved rapid fluorescence focus inhibition test (RFFIT).

Despite the existence of effective vaccines, rabies remains endemic throughout the world. This is largely because RIG and/or rabies vaccines are not readily available, especially in countries with a high animal rabies burden, and because the recommended schedule of vaccine administration is cumbersome and cost-prohibitive. Even in the US, compliance with the recommended PEP vaccine series is suboptimal; for example, in one prospective study of rabies PEP, over one-third of individuals failed to complete the PEP vaccine series at 1 month [5]. Thus, novel vaccines against rabies that are safe, tolerable, economical, and as immunogenic as current formulations, and that can be administered for PrEP in one dose, and for PEP in one or two doses, are urgently needed.

Modified live viral-vectored rabies vaccines – given as a single dose – have been used successfully in animals for decades; thus, a similar approach could be applied against human rabies. For example, RG-canarypox virus and RG-vaccinia virus vaccines are currently in use in the US for vaccination of domestic cats and wildlife, respectively [6]. In humans, replication-defective chimpanzee adenovirus (ChAd) vectors are being increasingly recognized as attractive vaccine vector candidates [7]. Given the lower probability of pre-existing immunity to the ChAd vector in humans, ChAd-vectored vaccines have the potential to elicit high-quality, durable immune responses [8]. In fact, safe and immunogenic ChAd-vectored human vaccines have already been described for Ebola [9, 10, 11, and 12], malaria [13], hepatitis C virus (HCV) [14], and respiratory syncytial virus (RSV) [15].

Ad vaccine carriers have also been shown to be effective for rabies, but only in animals. For example, in Canada, an oral rabies vaccine (ORV) consisting of replication-competent recombinant human adenovirus type 5 (Ad5) expressing RG within an E3 deletion (referred to as AdRG1.3 [16], or ONRAB®) is licensed for use as vaccine bait in animal rabies control efforts [17], and has also been evaluated in multiple US field trials [18, 19, and 20]. More recently, Xiang *et al*. described a novel rabies vaccine consisting of replication-defective recombinant ChAd vector serotype SAd-V24 (referred to as Ad68C) expressing RG using a non-human primate (NHP) model [21]. Notably, after only a single intramuscular (IM) injection in this model, this vaccine elicited sustained levels of seroprotective VNAs through 21 months post-vaccination and provided 100% protection from lethal rabies virus challenge at 22 months post vaccination [21].

ReiThera has recently developed a novel rabies vaccine aimed at extending these findings into humans. The vaccine, ChAd155-RG, consists of a replication-defective group C ChAd 155 (ChAd155) expressing RG

under the control of the CMV promoter. Group C Ad vectors (including human Ad5 and ChAd3) have previously been shown to be safe, tolerable, and highly immunogenic in humans [9, 10, 11, 12, 14, and 15]. A recombinant RSV-ChAd155 vaccine has also been tested successfully in a Phase 1 clinical trial [22]. To increase the cross-protective breadth of ChAd155-RG, the RG sequence is a medoid, a natural viral strain with the highest average percent of amino acid identity among all RG sequences annotated in NCBI's database. The selected RG protein (NCBI strain AGN94271) shares an average 94% percent identity to the RG proteins of current vaccines.

2.1. Purpose of the Analyses

These analyses will assess the immunogenicity and safety of ChAd155-RG (one dose at $5x10^{10}$vp, one dose at $1x10^{11}$vp, and two doses at $1x10^{11}$vp) in comparison with RABAVERT and will be included in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary

- Assessment of the safety, tolerability, and reactogenicity of one dose of ChAd155-RG at $5x10^{10}$vp per dose, or one or two doses of ChAd155-RG at $1x10^{11}$vp per dose.
- Comparison of the safety, tolerability, and reactogenicity of one or two doses of ChAd155-RG, with three doses of RABAVERT.

3.1.2. Secondary

- Assessment of serum rabies VNA levels by a standard, WHO-approved, RFFIT, as assessed by immune response kinetics (through approximately 12 months after first dose of vaccine), seroconversion rates, and peak GMT in each vaccination group.

3.1.3. Exploratory

- Quantification of circulating T-cell responses against RG by ex vivo IFN-gamma ELISpot.
- Characterization of circulating CD4 and CD8 T-cell responses against RG at peak time point by multiparameter ICS.
- Comparison of durability of immune response to ChAd155-RG and RABAVERT at approximately 3, 6, and 12 months after first dose of vaccine by each vaccination group tested.
- Measurement of RG-specific memory B cells by ELISpot.
- Measurement of an antibody response to the vaccine vector (ChAd155).

3.2. Endpoints

3.2.1. Primary

- Frequency and severity of solicited injection site and systemic reactogenicity events from the time of each vaccination through Day 7 after each vaccination, in each vaccination group and overall.
- Frequency and severity of SAEs considered study vaccine-related and reported at any time after the first vaccination through the end of the study, in each vaccination group and overall.
- Frequency and severity of study vaccine-related lab AEs through Day 22 from the time of the first vaccination, in each vaccination group and overall.
- Frequency and severity of unsolicited study vaccine-related AEs from the time of the first vaccination through Day 28 after the last vaccination, in each vaccination group and overall.
- Number of subjects with new onset of a chronic medical condition at any time after the first vaccination, in each vaccination group and overall.
- Frequency and severity of any SAEs at any time after the first vaccination through the end of the study, in each vaccination group and overall.

3.2.2. Secondary

- Proportion of subjects seroconverting to rabies virus at each antibody time point (seroconversion is defined as VNA concentration ≥0.5 IU/mL), in each vaccination group and overall.
- GMT (as measured by rabies VNA using a standard, WHO-approved, RFFIT) at each antibody time point within each vaccination group.
- Peak GMT (as measured by rabies VNA using a standard, WHO-approved, RFFIT; peak GMT is defined as highest GMT measured across all post-vaccination antibody time points) within each vaccination group.

3.2.3. Exploratory

- Frequencies of circulating T cell responses against RG by ex vivo IFN-ELISpot.
- Characteristics of circulating CD4 and CD8 T cell responses against RG by multiparameter ICS.
- Magnitude and durability of RG-specific memory B cells by ELISpot.
- GMT to ChAd155 vector at one month after first vaccination

3.3. Study Definitions and Derived Variables

Seroconversion is defined as a VNA concentration ≥0.5 IU/mL. Peak GMT is defined as the highest GMT measured across all post-vaccination antibody time points per subject.

The baseline value will be defined as the last value obtained prior to the first vaccination.

Vaccination group is defined as the four vaccine and dose combinations:

- Low Dose ChAd155-RG
- High Dose ChAd155-RG (x1)
- High Dose ChAd155-RG (x2)
- RABAVERT

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a single-center, observer-blinded, Phase 1, dosage-escalation trial to evaluate the safety, tolerability, reactogenicity, and immunogenicity of ChAd155-RG compared with RABAVERT in rabies virus-naïve healthy male and non-pregnant female adult subjects. There are 4 vaccination groups (see Table 1).

Since this is a dosage-escalation study, sentinel subjects are used at each dosage level. The first four subjects will be randomized to Group A (Low dose) or D (RABAVERT) (see Table 1). These subjects will be monitored for safety, tolerability, and reactogenicity through 7 days (study day 8) after first study vaccination and if no pre-defined halting rule is met (Section 9 of the protocol), then four additional sentinel subjects will be randomized to Group B (High dose x1) or D (RABAVERT). These subjects will also be monitored for safety, tolerability and reactogenicity through day 7 after first study vaccination. The SMC will review all available safety, reactogenicity, AE and lab data of all the sentinel subjects and will decide whether the remaining non-sentinel subjects may be enrolled.

If the SMC recommends proceeding with the remaining trial enrollments, eligible individuals will be enrolled and randomized to one of the four vaccination groups (Groups A-D). To maintain blinding of study personnel conducting surveillance and assessment of AEs, all subjects in these groups will receive 4 sequential injections, 1 ml per injection, in alternating arms, on the same schedule:

- Subjects randomized to Group A will receive ChAd155-RG at the lower dosage ($5x10^{10}$vp) on Day 1, then placebo injections on Days 8, 15, and 22
- Subjects randomized to Group B will receive ChAd155-RG at the higher dosage ($1x10^{11}$vp) on Day 1, then placebo injections on Days 8, 15, and 22
- Subjects randomized to Group C will receive ChAd155-RG at the higher dosage ($1x10^{11}$vp) on Days 1 and 15, and placebo injections on Days 8 and 22
- Subjects randomized to Group D will receive RABAVERT at the standard dose (1 mL) on Days 1, 8, and 22, and a placebo injection on Day 15

The vaccine administrator is unblinded to vaccine preparation and administration. The investigational vaccine doses are prepared just prior to administration to ensure that the volume of each injection is identical between Groups A-D. Follow-up is double-blinded and the SMC will review all available safety, reactogenicity, AE and lab data collected from all subjects for 15 days after the last vaccination and as needed.

Subjects will be followed using a memory aid, face-to-face scheduled clinic visits and safety lab monitoring as outlined in Section 7 of the protocol and Table 2, Schedule of Study Procedures. Following enrollment and vaccination, safety lab blood samples will be collected on Days 2, 8, 16, and 22. Blood samples for immunologic assays will be collected on Days 1, 2, 8, 15, 16, 22, 29, 91, 181, and 381. The duration of each subject's participation is expected to be approximately 13 months.

This trial is expected to take approximately 30 months to complete, from initiation through availability of a final report on the primary outcomes of safety and the secondary outcomes of VNA levels to RG. Exploratory outcomes are discussed in an addendum. A planned interim safety, reactogenicity, and immunogenicity analysis is detailed in Section 11.3 of the protocol.

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

The active control used in this study is the existing standard rabies vaccine, RABAVERT. All subjects will receive at least one injection of placebo, 0.9% Sodium Chloride, USP, to bring the total number of injections per subject to four for blinding purposes.

4.3. Selection of Study Population

4.3.1. Subject Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for this trial, and for subsequent doses of vaccine/placebo:

1. Must be a male or female aged 18-49 years old (inclusive) at the time of first vaccination.
2. Must be able to provide written informed consent.
3. Must have a body mass index (BMI) ≥18.5 and <35.0 kg/m^2
4. Must be in good health based on physical examination, vital signs[a], medical history, safety labs[b], and the investigator's clinical judgment.

   [a]*Vital signs must be within the normal ranges in* Table 11. *If a subject has elevated systolic or diastolic blood pressure, subject may rest for 10 minutes in a quiet room and the blood pressure may be retaken.*

   [b]*Safety lab normal ranges will be those used by the reference clinical lab and listed, along with toxicity ranges, in* Table 12 *and* Table 13 *Protocol-specific criteria for individual subjects are listed in criteria #5.*

5. Must have acceptable* lab values within 28 days before enrollment.

   **Acceptable values include:*

   -Hemoglobin: women >11.6 g/dL, men >13.1 g/dL

   -White blood cells: >3,700 but <10,900 cells/mm^3

   -Absolute neutrophil count: ≥1,500 cells/mm^3

   -Absolute lymphocyte count: ≥850 cells/mm^3

   -Platelets: >139,000 but <401,000 per mm^3

   -Urine dipstick (clean urine sample): protein <1+, glucose negative

   -Alanine transaminase and aspartate transaminase (ALT, AST) <1.1 x institutional upper limit of normal (ULN)

   -Total bilirubin <1.1x institutional ULN

   -Blood urea nitrogen (BUN) <1 x institutional ULN

   -Serum creatinine <1x institutional ULN

   -If lab screening tests are out of range, repeating them is permitted once, provided there is an alternative explanation for the out-of-range value.

6. Women of childbearing potential* must have a negative serum pregnancy test at screening and negative urine pregnancy tests within 24 hours before each vaccination.

   **Women of non-childbearing potential, defined as postmenopausal (any age with amenorrhea for ≥12 months without other known or suspected cause for amenorrhea), or surgically sterile [hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal*

sterilization)] with documented confirmation test ≥3 months after the procedure), are not required to use contraceptive methods.

7. Women of childbearing potential must use an acceptable method of contraception* from 28 days before the first vaccination until ≥60 days after the last vaccination.

   **Acceptable methods of contraception include: prescription oral contraceptives, contraceptive injections, intrauterine device (IUD), implants, vaginal ring, double-barrier method, contraceptive patch, male partner who had a vasectomy at least 6 months prior to study enrollment, abstinence (defined as refraining from heterosexual intercourse during participation in this trial [from 28 days before the first vaccination until ≥60 days after the last vaccination]).*

8. Female subjects must agree to not donate eggs (ova, oocytes) from the start of screening until ≥60 days after the last vaccination.
9. Male subjects who have not had a vasectomy* and are sexually active with a woman of childbearing potential must agree to use an acceptable method of contraception**.

   **Men who have had a vasectomy must have had the procedure performed at least 6 months prior to study enrollment*

   ***Acceptable methods of contraception must be used from the first vaccination until >60 days after the last vaccination, and include: abstinence (defined as refraining from heterosexual intercourse with a female partner of childbearing potential during participation in this trial [from 28 days before the first vaccination until ≥60 days after the last vaccination]; a double-barrier method, such as condom with spermicidal foam/gel/film/cream/suppository and partner with occlusive cap (diaphragm, cervical/vault caps); if the female partner is using an acceptable method of contraception (see Inclusion Criterion #7), a single-barrier method for the male subject is acceptable.*

10. Male subjects must agree to not donate sperm from the start of screening until ≥60 days after the last vaccination.
11. Must be available and willing to participate for the duration of this trial.
12. Must have a means to be contacted by telephone.

4.3.2. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Was ever vaccinated with a licensed or investigational rabies vaccine* or was diagnosed with rabies exposure, infection, or disease.

   **Includes RABAVERT and Imovax. Subject's verbal history will suffice.*

2. Has a higher risk than the average US resident with regard to exposure to rabies, per the RABAVERT package insert and rabies vaccination recommendations from the CDC*

   **People at high risk of exposure to rabies, such as veterinarians, animal handlers, rabies laboratory workers, spelunkers, and rabies biologics production workers.*

   **People whose activities bring them into frequent contact with rabies virus or with possibly rabid animals.*

   **International travelers who are likely to come in contact with animals in parts of the world where rabies is common.*

3. Was ever vaccinated with a licensed or investigational Ad vector or Ad vaccine.

4. Is currently taking chloroquine or hydroxychloroquine [23].
5. Was diagnosed with laboratory-confirmed COVID-19 (PCR or antigen-based test) in the preceding 28 days.
6. Positive serology for HIV antibody, HCV antibody, or Hepatitis B surface antigen (HBsAg).
7. Has known allergy or history of anaphylaxis or other serious adverse reaction to a vaccine or vaccine products*.

   **Including egg products, aminoglycosides, gelatin, sorbitol, tris (hydroxymethyl)-amino methane (THAM), or any of the constituents of the study vaccines.*
8. Has severe allergy or anaphylaxis to latex.
9. Has an acute illness or temperature ≥38.0ºC on Day 1*.

   **Subjects with fever or acute illness on the day of vaccination may be re-assessed and enrolled if healthy or only minor residual symptoms remain within 3 days.*
10. Female subjects who are pregnant or breastfeeding or planning to become pregnant while enrolled in this trial and at least 60 days after last vaccination.
11. Has history of autoimmune disease, or clinically significant cardiac, pulmonary, hepatic, rheumatologic, or renal disease by history, physical examination, and/or lab studies.
12. Has history of malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision that is considered to have achieved cure*.

    **Subjects with a history of skin cancer must not be vaccinated at the previous tumor site.*
13. Has known or suspected congenital or acquired immunodeficiency, or recent history or current use of immunosuppressive therapy*.

    **Anti-cancer chemotherapy or radiation therapy within the preceding 6 months, or long-term (≥2 weeks within the previous 3 months) systemic corticosteroid therapy (at a dosage of ≥0.5 mg/kg/day). Intranasal or topical prednisone (or equivalent) are allowed.*
14. Is post-organ and/or stem cell transplant, whether or not on chronic immunosuppressive therapy.
15. Had major surgery (per the investigator's judgment) within 4 weeks before study entry or planned major surgery during this trial.
16. Has history of diabetes mellitus type 1 or type 2, including cases controlled with diet alone.

    Note: history of isolated gestational diabetes is not an exclusion criterion.
17. Has history of thyroidectomy, or thyroid disease requiring medication in the last 12 months.
18. Has history of hypertension, even if medically controlled.

    Note: Vital signs must be normal by protocol toxicity grading scale. In the event of an abnormal heart rate or blood pressure due to physiological variation or activity, the subject may rest for 10 minutes in a quiet room, and then blood pressure and/or heart rate re-measured. Repeated vital signs may be used to determine eligibility.
19. Received live attenuated vaccines from 30 days before first vaccination until 30 days after final vaccination.*

**Not including licensed or authorized COVID-19 vaccines*

20. Received killed or inactivated vaccines from 14 days before first vaccination until 30 days after final vaccination.*

    **Not including licensed or authorized COVID-19 vaccines*

21. Received experimental therapeutic agents within 3 months before first vaccination or plans to receive any experimental therapeutic agents during this trial.*

    **That that in the opinion of the investigator would interfere with safety or immunogenicity assessments.*

22. Is currently participating or plans to participate in another clinical study which would involve receipt of the following:*

    **An investigational product, blood drawing, or an invasive medical procedure that would require administration of anesthetics, intravenous (IV) dyes, or removal of tissue during this trial and, in the opinion of the investigator, would interfere with safety or immunogenicity assessments.*

    -Includes endoscopy, bronchoscopy, and administration of IV contrast.

23. Received blood products or immunoglobulin in the 3 months before study entry or planned use during this trial.
24. Donated a unit of blood or blood products within 8 weeks before Day 1 or plans to donate blood or blood products during this trial.
25. Has major psychiatric illness in the past 12 months that in the opinion of the investigator would preclude participation.
26. Has current alcohol use or current or past abuse of recreational or narcotic drugs by history as judged by the investigator to potentially interfere with study adherence.
27. Has a history of chronic urticaria.
28. Has tattoos, scars, or other marks on both deltoid areas which would, in the opinion of the investigator, interfere with assessment of the vaccination site.
29. Is a site employee* or staff who are paid entirely or partially by/through the OCRR contract for this trial, or staff who are supervised by the Principal Investigator (PI) or sub-investigators.

    **Including the PI, sub-investigators listed on Form FDA 1572 or Investigator of Record Form.*

30. In the opinion of the investigator cannot communicate reliably, is unlikely to adhere to the requirements of this trial or has any condition which would limit the ability to complete this trial.
31. Has history of Guillain-Barre syndrome, meningitis, encephalitis, neuroparalysis, transient paralysis, myelitis, retrobulbar neuritis, multiple sclerosis, vertigo, or visual disturbances.
32. Has a history of arterial or venous thrombosis, or thrombocytopenia that required medical attention.

4.4. Treatments

4.4.1. Treatments Administered

Subjects randomized to Group A will receive one dose of the IP at a dosage of $5x10^{10}$vp and subjects randomized to Groups B and C will receive the IP at a dosage of $1x10^{11}$vp in one or two doses, respectively. Subjects randomized to Group D will receive three doses of the licensed RABAVERT vaccine. All subjects

will receive at least one placebo vaccine, 0.9% Sodium Chloride Injection, USP, to bring the total number of doses to four. One milliliter (mL) of study product will be delivered at each study visit and will be administered intramuscularly in the deltoid region of the arm.

4.4.2. Identity of Investigational Product(s)

4.4.2.1. Study Product Description

ChAd155-RG Vaccine

The ChAd155-RG Vaccine consists of a replication-defective group C ChAd, ChAd155, expressing RG under the control of the CMV promoter. The RG sequence cloned into the ChAd155 vector is a medoid, a natural viral strain with the highest average percent of amino acid identity among all RG sequences annotated in the NCBI database. The selected RG (NCBI strain AGN94271) shares an average 94% percent identity to the RGs in current vaccines. The ChAd155-RG candidate vaccine is formulated without preservative and is presented as a sterile suspension in a 3-mL clear glass, stoppered vial, at a concentration of $1.3x10^{11}$ vp/mL.

RABAVERT Vaccine

The RABAVERT Vaccine is an inactivated, purified chick embryo cell vaccine (PCECV). It consists of lyophilized rabies virus equivalent to at least 2.5 International Units of rabies antigen in a 1.0 mL dose. In the United States, RABAVERT is licensed for pre-exposure vaccination and post exposure prophylaxis against rabies in all age groups

Placebo

The placebo is 0.9% Sodium Chloride, USP injection.

4.4.2.2. Acquisition

ChAd155-RG and RABAVERT are provided by GSK Vaccines under agreement with DHHS and are supplied through DMID CMS to the site before the start of this trial upon request and with prior approval from DMID. Should the site PI require additional vaccine during this trial, further instructions are provided in the MOP.

Normal saline is used as the placebo and will be provided by DMID Clinical Materials Services (CMS, Fisher BioServices).

4.4.2.3. Formulation, Packaging, and Labeling

ChAd155-RG Vaccine

The purified ChAd155-RG bulk drug substance is processed as follows to obtain drug product: Purified ChAd155-RG drug substance is diluted in buffer A 195 (Tris base 10mM, NaCl 75 mM, L-Histidine 10mM, $MgCl_2$ 1 mM, EDTA 0.1 mM, Polysorbate 80 0.02% (w/v), sucrose 5% (w/v), ethanol 0.5% (v/v), HCl for adjustment to pH 7.4). It then undergoes sterile filtration and is then transferred into final containers. The ChAd155-RG drug product is a liquid formulation contained in vials. It is presented as a sterile suspension in a 3-mL clear glass, stoppered vial, with a 1-mL extractable volume (nominal single dose).

The vaccine is supplied as a single 1mL-dose and is formulated without preservative.

The study product will be labelled according to manufacturer specifications or regulatory specifications and include the statement “Caution: New Drug-Limited by Federal Law to Investigational Use.”

RABAVERT Vaccine

RABAVERT [24] is a freeze-dried vaccine obtained by growing the fixed-virus strain Flury LEP in primary cultures of chicken fibroblasts. The virus is inactivated with β-propiolactone, processed by zonal centrifugation, and then lyophilized after adding a stabilizer solution consisting of buffered polygeline and potassium glutamate. One dose of reconstituted vaccine contains ≤12 mg polygeline (processed bovine gelatin), ≤0.3 mg human serum albumin, 1 mg potassium glutamate, and 0.3 mg sodium EDTA. Small quantities of bovine serum (originating from the US, Australia, and New Zealand) are used in the cell culture process; ovalbumin content is ≤3 ng/dose (1 mL), based on ELISA. Antibiotics (neomycin, chlortetracycline, amphotericin B) added during cell and virus propagation are largely removed during subsequent steps in the manufacturing process; thus, in the final vaccine, neomycin is present at ≤10 µg, chlortetracycline at ≤200 ng, and amphotericin B at ≤20 ng per dose. RABAVERT is supplied in a package that contains a vial of the freeze-dried vaccine, a syringe containing 1 mL of sterile diluent (sterile water for injection), a sterile needle for reconstitution, and a sterile needle suitable for IM injection.

Placebo

Placebo is supplied as 0.9% Sodium Chloride Injection, USP which is a colorless, sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection (WFI). Each mL contains supplied chloride 9 mg. It contains no bacteriostatic, antimicrobial agent, or added buffer and is supplied only in single-dose containers. The placebo, 0.9% Sodium Chloride, contains no preservatives. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3 [4.5 to 7.0]).

4.4.2.4. Product Storage and Stability

ChAd155-RG Vaccine

The vaccine product requires storage at ≤ -60˚C

The stability of ChAd155-RG final container lots will be followed for up to 60 months at the recommended storage condition of ≤ -60°C.

RABAVERT Vaccine

RABAVERT contains no preservative and should be stored protected from light at 2°C to 8°C (36°F to 46°F). After reconstitution with the supplied sterile diluent (water for injection), the vaccine should be used immediately (as defined in the MOP). The reconstituted vaccine is a clear-to-slightly opalescent, colorless-to-slightly pink suspension. The vaccine may not be used after the expiration date given on package and container.

Placebo

0.9% Sodium Chloride, USP injection must be stored at 20ºC to 25ºC (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°F and 86°F) are permitted]. See protocol-specific MOP for further instructions.

Additional Information

All vaccines will be stored in the site research pharmacy. The temperature of the storage unit will be continuously monitored and recorded during this trial per the site's SOPs, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) will be quarantined at the correct storage temperature and labeled "Do Not Use" (until further notice). The pharmacist will alert the site PI and study coordinator if the temperature fluctuates outside of the required range. If the

temperature fluctuates outside of the required range, including accidental deep-freezing or disruption of the cold chain, the affected vaccine(s) will not be administered. The site PI or responsible person should immediately contact the DMID Product Support Team at DMIDProductSupportTeam@niaid.nih.gov and DMID Clinical Project Manager (CPM) for further instructions before any additional study vaccines are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected vaccine(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected vaccine(s) to DMID CMS or destroy it on site. Additional instructions for quarantine are provided in the MOP.

Stability studies to support study vaccine storage conditions have been conducted. The sponsor will continue to monitor the stability of the vaccines and will alert the site if a lot is nearing the end of its anticipated shelf life.

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

The list of randomized vaccine assignments will be prepared by statisticians at The Emmes Company and included in the enrollment module of The Emmes Company's Internet Data Entry System (IDES). IDES will assign each subject a vaccine code from the list after demographic and eligibility data have been entered. A designated individual at the site will be provided with a vaccine key, which links the vaccine code to the vaccine assignment, which will be kept in a secure place.

Subjects in sentinel group 1 are randomized 3:1 to either Group A or D. If no halting criteria are met through 7 days after the first vaccination (study day 8), then subjects in sentinel group 2 are randomized 3:1 to either Group B or D. The SMC will review safety data from both sentinel groups through Day 15 for sentinel group 1 (Day 8 for sentinel group 2), and if they approve, then the remaining non-sentinel subjects are enrolled and randomized to the 4 vaccination groups (Groups A-D).

4.4.4. Selection of Doses in the Study

The selection of doses in this study is based on previous studies described in the ReiThera ChAd155-RG investigator's brochure. This is a first in human trial of ChAd155-RG. However, other ChAd-based vaccines for Ebola, malaria, and RSV have been tested in humans at similar doses of $1x10^{11}$vp, $2x10^{11}$vp, $5x10^{10}$vp, respectively, and produced favorable safety profiles [12, 25]. Additionally, a large clinical trial of ChAd155-RSV in humans at the maximal human dose of $1x10^{11}$vp was performed without safety issues.

Several pre-clinical studies of ChAd155-RG have been performed in New Zealand White rabbits. The first, a repeated dose trial, demonstrated that two doses of $1x10^{11}$vp is more appropriate than three since the third appeared to be fully neutralized by anti-vector immunity. Another study showed that a single 0.5mL half-dose IM dose of $5x10^{10}$vp ChAd155-RG induces stronger and more durable responses than a single half-dose of RABIPUR (marketed as RABAVERT in the US). A third study showed that repeated IM administration of $1x10^{11}$vp of ChAd155-RG was systemically and locally well-tolerated.

A study in non-human primates demonstrated that a single 0.5mL IM dose of $5x10^{10}$vp of ChAd155-RG induced rabies VNA titers comparable to three doses of RABIPUR that remained stable and above 0.5 IU/mL for ~1 year [25].

4.4.5. Selection and Timing of Dose for Each Subject

For randomization methods, see Section 4.4.3.

The actual time of day of vaccine administration is not specified. Subjects will receive study vaccine or placebo on Days 1, 8, 15, and 22 depending on the vaccination group to which they are randomized (see Table 1).

4.4.6. Blinding

Investigators and study personnel performing any study-related assessments following vaccination will be blinded to study vaccine. Syringes will be labeled with an overlay/blinding tape containing the subject ID, treatment number from the treatment key and expiration time for the syringe, then provided to the unblinded vaccine administrator. Lab personnel performing assays will be blinded to all subjects.

The randomization scheme will be generated by the Statistical and Data Coordinating Center (SDCC) and provided to authorized, unblinded study personnel (i.e., pharmacists preparing vaccines, clinical staff administering vaccines) at the site.

The unblinded vaccine administrator will be credentialed to administer vaccines but not involved in study-related assessments, subject contact, or data collection following vaccination.

4.4.7. Prior and Concomitant Therapy

Administration of any medications, therapies, or vaccines will be documented on the appropriate eCRF. Concomitant medications will include all current medications and non-study vaccinations taken within 30 days before signing the ICF through approximately 28 days after the last study vaccination, and for new-onset chronic medical conditions through approximately 12 months after the last study vaccination for each subject. Subjects who do not receive all vaccinations will have concomitant medications collected through approximately 28 days after the last vaccination, or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements.

Use of any new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Medications that might interfere with the evaluation of the study vaccines should not be used during the trial unless absolutely necessary. Medications in this category include the prohibited medications per the subject exclusion criteria (see Section 4.3.2). In addition, the site PI or appropriate sub-investigator may identify other medications that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity. Use of medications as prophylaxis before study vaccination is prohibited.

To the sponsor's knowledge, there are no known drug-vaccine interactions with the study vaccines and subjects are not being asked to discontinue current medications not listed in the exclusion criteria. In the event medical conditions dictate use of medications, subjects are encouraged to obtain adequate care, comply with the course of therapy as prescribed by their physician, and inform the Investigator as soon as practicable. Details of all medications taken during this trial (date, brand or generic name) will be recorded.

4.4.8. Treatment Compliance

All subjects are to receive 4 doses of study product (see Table 1) administered in the clinic.

4.5. Immunogenicity and Safety Variables

For additional details on study procedures and evaluations by study visits/days, see Table 2.

Safety will be assessed by the frequency and/or severity of:

- Solicited injection site and systemic reactogenicity events from the time of each vaccination through Day 7 after each vaccination, overall and in each vaccination group.
- Serious adverse events (SAEs) considered study vaccine-related and reported at any time after the first vaccination through the end of this trial, overall and in each vaccination group.
- Vaccine-related lab AEs through study Day 22, overall and in each vaccination group.
- Unsolicited vaccine-related AEs from the time of the first vaccination through Day 28 after the last vaccination, overall and in each vaccination group.
- New onset chronic medical conditions at any time after the first vaccination and through the end of this trial, overall and in each vaccination group.
- Local, systemic or lab toxicities after any vaccination, overall and in each vaccination group.
- Local reactogenicity through Day 7 after any vaccination, overall and in each vaccination group.
- Any SAEs, overall and in each vaccination group.

Immunogenicity will be assessed by:

- Proportion of subjects seroconverting to rabies virus at each antibody time point (seroconversion is defined as VNA concentration ≥0.5 IU/mL), in each vaccination group and overall.
- GMT (as measured by rabies VNA using a standard, WHO-approved, RFFIT) at each antibody time point within each vaccination group.
- Peak GMT (as measured by rabies VNA using a standard, WHO-approved, RFFIT; peak GMT is defined as the geometric mean of the highest titer per subject across all post-vaccination antibody time points) within each vaccination group.
- Frequencies of circulating T cell responses against RG by ex vivo IFN-ELISpot.
- Characteristics of circulating CD4 and CD8 T cell responses against RG by multiparameter ICS.
- Magnitude and durability of RG-specific memory B cells by ELISpot.
- GMT to ChAd155 vector at one month after first vaccination.

5. SAMPLE SIZE CONSIDERATIONS

This trial will enroll 50 subjects into four vaccination groups: Group A (N=14) will receive one dose of ChAd155-RG at the lower dosage (5 x 10^{10}vp); Group B (N=14) will receive one dose of ChAd155-RG at the higher dosage (1 x 10^{11}vp); Group C (N=10) will receive two doses of ChAd155-RG at the higher dosage (1x10^{11}vp); and Group D (N=12) will receive three doses of RABAVERT.

The sample size of 10-14 subjects in each vaccination group is small given the early stage (Phase I) of the product's development; thus, the precision of estimates for AEs is limited. Rare AEs associated with dose level or number of doses are not demonstrable in a trial of this size; however, the probabilities of observing one or more AEs within a vaccination group given various true event rates are presented in Table 3. The minimum detectable event rates for various levels of power are displayed in Table 4.

This trial was not designed to formally test any hypotheses associated with the immunogenicity data. The 95% confidence intervals (CIs) for various observed seroconversion rates at various sample sizes were calculated assuming observed seroconversion rates of 90%, 95%, and 100%, as shown in Table 5.

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 (SD), 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 vaccination group and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each vaccination group in the following order: low dose, high dose (x1), high dose (x2), RABAVERT and All Subjects, and will be annotated with the total population size relevant to that table, including any missing observations.

6.2. Timing of Analyses

One interim analysis is planned for this study. It will be performed after at least half the subjects complete Day 91 and after VNA data through Day 91 are received for subjects for whom data are available at the time of database freeze.

The primary CSR will summarize all safety and all primary and secondary protocol-specified humoral immunogenicity endpoint results collected through Day 381.

6.3. Analysis Populations

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

The modified intent-to-treat (mITT) population includes all subjects who received at least one dose of study vaccine and contributed both pre- and at least one post-study vaccination venous blood samples for immunogenicity testing for which valid results were reported. For analyses using the mITT population, subjects will be grouped based on randomized treatment arm.

6.3.2. Per Protocol Population

The per protocol (PP) population includes all subjects in the mITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline, according to the inclusion and exclusion criteria at the time of the subject's enrollment.
- Data from subjects who have a baseline rabies VNA concentration ≥ 0.5 IU/mL (for the immunogenicity analyses).
- Data from all visits subsequent to the following, such as:
  - Study withdrawal or treatment discontinuation
  - Any study vaccination dose received out of window
  - Receipt of non-study licensed live vaccine within 30 days before or after each study vaccination
  - Receipt of non-study licensed inactivated vaccine within 14 days before or after each study vaccination
  - Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after each study vaccination

- Receipt of chloroquine or hydroxychloroquine

- Data from any visit that occurs out of window, as defined in Table 2 "Window for each study visit".

6.3.3. Safety Population

The Safety Population will consist of all subjects who have received at least one dose of vaccine and for whom any data on safety are available. Subjects will be classified according to the vaccine and dosage received. The primary safety analysis will be performed using this population.

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Missing Data

Missing safety and/or immunogenicity data will not be imputed. No search for outliers will be performed. However, the logarithmic transform will be used as appropriate to improve the distributional properties of the data and reduce the impact of potential outliers.

6.6. Interim Analyses and Data Monitoring

For purposes of planning subsequent research and to allow internal and external presentations of data (e.g., national and/or international conferences and early publication of data), there will be one planned interim safety and immunogenicity analysis of subjects in the safety and modified intent to treat populations, respectively. Results of the interim analysis will not be used to make any decisions concerning the conduct of this trial.

Once at least half the subjects complete the Day 91 visit the clinical database will be cleaned, monitored and frozen by the SDCC. Group-unblinded analyses of safety, reactogenicity and available immunogenicity data are planned. The interim report will be prepared by the SDCC after the interim clinical database is frozen and all VNA data through Day 91 for subjects for whom data are available at the time of database freeze are received.

For this interim report, investigators will remain blinded to individual subject treatment assignments and will only be provided with data summaries aggregated by dose-group. Any data listings at the subject level will be blinded to vaccination group.

For the purpose of advancing from each group of sentinel subjects to the enrollment of all remaining subjects, the SMC will review all available safety data. Furthermore, the halting rules described in Section 9.5 of the study protocol will be utilized to pause this trial if certain criteria are met.

6.6.1. Interim Safety Review

Safety data for the first set of four sentinel subjects will not be reviewed by the SMC before enrollment of the second set of four sentinel subjects if no pre-defined halting rule is met. Safety data for all 8 sentinels will be reviewed by the SMC prior to enrollment of the remaining 42 subjects. These sentinel reviews will not involve hypothesis testing and will not be considered in estimating the precision of any estimates made at the conclusion of this trial.

The interim analysis will include all safety and immunogenicity data through Day 91 for subjects in the safety population for whom data are available at the time of database freeze. The interim safety analyses will include tables summarizing demographics, study status and protocol adherence information. Tables and figures will present unsolicited adverse events by MedDRA System Organ Class (SOC) and Preferred Term (PT), severity and relationship to study product. Solicited adverse events will be summarized by symptom, severity, and study day. Laboratory results will be summarized by parameter, severity, and study day. Blinded listings of early terminations, protocol deviations and clinical data may be included. Since this early analysis of the data is not intended to impact the conduct of this trial, it will have no impact on Type I error and adjustments are not planned.

6.6.2. Interim Immunogenicity Review

The interim analysis will include all available immunogenicity (VNA-RFFIT) data through Day 91 for the subjects in the mITT population for whom data are available at the time of database freeze, addressing secondary objectives. The interim immunogenicity analysis will include summaries of geometric mean titers (GMTs) and their associated 95% confidence intervals as well as peak GMT by vaccination group at study timepoints outlined in Table 2. Titer results will also be displayed in reverse cumulative distribution (RCD) curves by visit and vaccination group. No hypothesis tests or modeling will be included in the interim immunogenicity analysis. Since this early analysis of the data is not intended to impact the conduct of this trial, it has no impact on Type I error and adjustments are not planned.

6.7. Multicenter Studies

Not applicable. This study will take place at a single VTEU site (Emory University).

6.8. Multiple Comparisons/Multiplicity

No multiple comparisons correction will be applied for the interim analysis. No adjustments for multiple testing are planned for the final analysis.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

The disposition of subjects in the study will be tabulated by vaccination group (Table 14). The table shows the total number of subjects screened, enrolled/randomized, vaccinated, received all vaccinations, completed Study Day 91, completed Study Day 181, completed final blood draw, completed follow-up (Study Day 381), and completed per protocol.

The composition of analysis populations, including reasons for subject exclusion, by vaccination group, will be presented in Table 15. A listing of subjects excluded from each analysis population will be presented in Listing 5.

Dates of first treatment administration by vaccination group will be presented in Table 16.

Table 17 will present a summary of the reasons that subjects were screened but not enrolled.

A Consort Diagram showing the disposition of study subjects will be included (Figure 1). This figure will present the number of subjects screened, randomized, excluded, discontinued treatment, terminated early, and analyzed, by vaccination group.

A listing of subjects who discontinued dosing or terminated from study follow-up, with reasons, will be included in Listing 2.

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and vaccination group for all subjects (Table 6). Deviations will be reviewed for possible subject exclusion from the per protocol population include: subject ineligibility at baseline (see Section 4.3.2 for subject exclusion criteria), a baseline rabies VNA concentration $\geq$ 0.5 IU/mL, study withdrawal or treatment discontinuation, an out-of-window treatment administration or study visit, receipt of non-study licensed live vaccine within 30 days before and following each study vaccination, receipt of non-study licensed inactivated vaccine within 14 days before and following each study vaccination, receipt of immunosuppressive therapy within 30 days before or following each study vaccination, and receipt of chloroquine or hydroxychloroquine. All subject-specific protocol deviations and non-subject specific protocol deviations will be included in Appendix 3 as data listings (Listing 3 and Listing 4, respectively).

8. IMMUNOGENICITY EVALUATION

8.1. Primary Immunogenicity Analysis

Not applicable.

8.2. Secondary Immunogenicity Analyses

Summaries and analyses of immunogenicity data will be presented for the mITT population. If more than 5% of subjects, overall, would be excluded or have visits excluded from the PP population due to protocol deviations, then a PP analysis will also be performed.

Seroconversion is defined as achieving a serum antibody level post-vaccination that is greater than 0.5 IU/mL, the pre-defined protective titer in the KSU RFFIT assay.

Seroconversion rates and GMT for rabies VNA titers will be calculated for each antibody timepoint by vaccination group and will be summarized graphically.

Seroconversion rates and GMT will be presented with their corresponding 95% confidence interval estimates at each time point and overall peak GMT, and the pair-wise differences between seroconversion rates by treatment arm will be summarized by study day along with 95% CIs.

GMTs will be estimated by computing the geometric mean and 95% confidence interval based on the student's t distribution.

The distribution of antibody titers will also be graphically summarized using the reverse cumulative frequency distribution of titers by study day and vaccination group.

8.2.1. Rabies Virus Neutralizing Antibodies (VNA)

Results from the RFFIT assay will be reported in IU/mL, with a typical range of 1-15 IU/mL. Results beyond 15 IU/mL will require dilution and retesting. The lower limit of quantification for the RFFIT assay is 0.1 IU/mL; values below the LLOQ will be imputed as 1/2 the LLOQ, or 0.05 IU/mL.

Serum samples for rabies VNA will be collected prior to vaccination (Day 1) and on Day 8, Day 15, Day 22, Day 29, Day 91, Day 181, and Day 381.

For each sample time point (and peak post-vaccination value), the GMT and 95% CI of the rabies VNA results will be analyzed and presented as described above, including post-baseline seroconversion rates and exact Clopper-Pearson 95% CI for the mITT and PP populations (Table 21 and Table 22, respectively).

Graphical displays of the reverse cumulative distribution curves, by time point and vaccine group, will be presented for the mITT and PP populations (Figure 2 and Figure 3, respectively). Similarly, graphical box-and-whisker plots will be presented for rabies VNA titers (Figure 4 and Figure 5, respectively) and for the percent seroconversion rate and 95% CIs (Figure 6 and Figure 7, respectively).

The pair-wise differences in seroconversion rates will be computed at each post-vaccination visit, with corresponding 95% CI computed via the Miettinen and Nurminen score method, for the mITT and PP populations (Table 23 and Table 24, respectively). Pair-wise differences and 95% CIs will be based on standard 2 x 2 table analyses and estimated using PROC FREQ and the RISKDIFF option in SAS. See pseudo code below.

```
PROC FREQ DATA=aa;
    TABLE Grp*Response / RISKDIFF(CLTYPE=MN);
```

```
        OUTPUT OUT=bb RISKDIFF;
RUN;
```

A listing of all rabies VNA titers will be presented in Listing 9.

8.3. Exploratory Immunogenicity Analyses

Summaries and analyses of immunogenicity data will be presented for the mITT population. If more than 5% of subjects, overall, would be excluded or have visits excluded from the PP population due to protocol deviations, then a PP analysis will also be performed.

The relationship between proportion of seroconverters and vaccine type, dosage, and number of doses may be examined using mixed-effects logistic regression models for longitudinal data. Also, the relationship between the log-transformed titer values, vaccine type, dosage, and dose number may be modeled using longitudinal regression methods in an exploratory analysis. Results will be summarized in Table 25 and Table 26.

The GMT of neutralizing antibody to the ChAd155 vector will be measured at Day 1 and one month after first vaccination (Day 29). The number of observations, GMT, and 95% CI for GMT will be reported in Table 27 and Table 28.

Analyses of CD4+ and CD8+ T cell and memory B cell data for the remaining exploratory endpoints will be outlined in an addendum to the SAP.

9. SAFETY EVALUATION

All summaries of safety data will be presented for the Safety Population. Summaries will be presented for each vaccination group and for all subjects.

Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage and 95% confidence interval where indicated.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by vaccination group and overall. (Table 18 and Table 19). In accordance with NIH reporting policy, subjects 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 subject listings will be presented for all demographics (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 21.0 or higher. Summaries of subjects' pre-existing or concurrent medical conditions at enrollment will be presented by vaccination group (Table 20).

All pre-existing or concurrent medical conditions will be presented in Listing 7.

9.1.2. Prior and Concomitant Medications

Administration of any medications, therapies, or vaccines will be documented on the appropriate eCRF. Concomitant medications will include all current medications and non-study vaccinations taken within 30 days before signing the ICF through approximately 28 days after the last study vaccination, and for new-onset chronic medical conditions through approximately 12 months after the last vaccination for each subject. Subjects who do not receive all vaccinations will have concomitant medications collected through approximately 28 days after the last vaccination, or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included as well as herbals, vitamins, and supplements.

Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Summaries of medications that were started prior to dosing and possibly continuing at the time of dosing will be presented by WHO Drug Terms 1 and 2 and vaccination group (Table 120). Medications started during the study will also be summarized by WHO Drug Terms 1 and 2 and vaccination group and presented in Table 121). Individual subject listings will be presented for all prior and concomitant medications (Listing 19).

9.2. Measurements of Treatment Compliance

The subject disposition table (Table 14) will summarize by vaccination group the total number of subjects screened, enrolled/randomized, vaccinated, and received all vaccinations. Dates and times of all vaccine administration records will be presented in Listing 8.

9.3. Adverse Events

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once per event and based on maximum reported severity when appropriate. The denominator will be

the safety population size associated with the study period (e.g. those who received at least one dose, those who received the second dose, etc.). All adverse events reported will be included in the summaries and analyses.
An overall summary of solicited and unsolicited adverse events is presented in Table 29. Adverse events occurring in 5% of subjects overall will be presented in Table 30.

9.3.1. Solicited Events and Symptoms

Solicited local and systemic adverse events were collected prior to each vaccination, 30 minutes post-vaccination and through 7 days after each vaccination. Systemic events include: feverishness, fatigue, malaise, myalgia, arthralgia, headache, nausea, and fever (based on temperature). Local injection site events include: pain, tenderness, pruritis, ecchymosis (grade and measurement), erythema (grade and measurement) and induration (grade and measurement). See Table 7, Table 8, Table 9, and Table 10 for grading details. Each solicited AE will be summarized separately for each vaccination and over all vaccinations, by vaccination group. For ecchymosis, erythema, and induration, the severity based on measurement will be presented separately.

The proportion of subjects (and exact 95% CI) reporting at least one solicited AE over each post-vaccination follow-up period will be summarized for each solicited AE, any systemic symptom, any local symptom, and any symptoms (Table 31, Table 32, Table 33, Table 34, and Table 35). The 95% CI will be calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option).

Solicited local injection site and systemic AEs will also be summarized by symptom, dose group, severity, and individual time point (pre-dose, 30 mins post-dose, days 1 to 8). These results will be displayed by dose and dose group in Table 36 through Table 65.

Bar graphs representing the percent of subjects with solicited systemic AEs by dose group, post-vaccination time point, and maximum severity will be presented in Figure 10, Figure 11, Figure 12, Figure 13, and Figure 14. Similar graphs will be presented for solicited local AEs in Figure 15, Figure 16, Figure 17, Figure 18, and Figure 19.

Solicited AEs by subject will be presented in Listing 11 (systemic symptom) and Listing 12 (local symptom).

9.3.2. Unsolicited Adverse Events

Unsolicited AEs are collected from the time of the first vaccination through Day 28 after the last vaccination. Unsolicited AEs are MedDRA coded and classified by system organ class and preferred term. The proportion of subjects reporting at least one unsolicited AE will be summarized by SOC and PT for each vaccination and over all vaccinations. Denominators for percentages are the number of subjects in the Safety Population who received the vaccination being summarized.

A complete listing of unsolicited adverse events by subject will be presented in Listing 13.

The following summaries for unsolicited AE will be presented by MedDRA SOC, PT, study dose, and vaccination group:

- Number and percent (with 95% CI) of subjects with any AEs by dose number, vaccination group, MedDRA SOC/PT and severity (Table 66, Table 67, Table 68, Table 69, and Table 70).
- Number and percent (with 95% CI) of subjects with any AEs related to study product by dose number, vaccination group, MedDRA SOC/PT and severity (Table 71, Table 72, Table 73, Table 74, and Table 75).

- Subject listing of serious adverse events, including deaths (Table 76).
- Subject listing of non-serious AEs of moderate or severe severity (Table 77).
- Subject listing of other significant AEs, such as AEs leading to subject withdrawal, study drug interruption or discontinuation, new onset chronic medical conditions (Table 78).
- Bar chart of total number of unsolicited AEs related to study product, by severity and MedDRA SOC (Figure 20, Figure 21, Figure 22, Figure 23, and Figure 24).
- Bar chart of the proportion of subjects with unsolicited AEs related to study product, by maximum severity and MedDRA SOC (Figure 25, Figure 26, Figure 27, Figure 28, Figure 28, and Figure 29).

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

The following listings will be presented including Subject ID, Vaccination Group, Adverse Event Number, Adverse Event Description, Associated Dose Number, Number of Days Post Dose (Duration), Number of Days Post Dose the Event Became Serious, Reason Reported as an SAE, Severity, Relationship to Treatment, Alternate Etiology if not Related, Action Taken with Study Treatment, Subject Discontinuation, Outcome, MedDRA SOC, MedDRA PT:

- Serious Adverse Events (Table 76).
- Non-Serious, Unsolicited, Moderate or Greater AEs (Table 77).
- Other Significant AEs (Table 78).

9.5. Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt was made to follow these subjects 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 treatment will be presented. In addition, listings of all pregnancy-related outcomes will be presented (Listing 20, Listing 21, Listing 22, Listing 23, and Listing 24).

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory parameters will be evaluated after receipt of each study vaccine (on Days 2, 8, 16, and Day 22) and will include WBC, hemoglobin, platelets, absolute neutrophil count, absolute lymphocyte count, ALT, AST, total bilirubin, BUN and creatinine. Grading scales for safety laboratory parameters are presented in Table 12 and Table 13. Baseline values will be the most recent values obtained prior to receipt of the first dose.

The following summaries for clinical laboratory results will be presented:

- Subject listings of abnormal chemistry and hematology results of Grade 1 severity or higher will be presented in Table 79 and Table 80, respectively.
- Frequency and percent of subjects with abnormal chemistry results over all parameters and for each parameter, by visit, vaccination group and severity (Table 81, Table 82, Table 83, Table 84, Table 85, and Table 86).

- Frequency and percent of subjects with abnormal chemistry results related to study product, over all parameters and for each parameter, by visit, vaccination group and severity (Table 87, Table 88, Table 89, Table 90, Table 91, and Table 92,).
- Descriptive statistics (mean, standard deviation, median, minimum, and maximum) of each chemistry parameter, including change from baseline, by time point and vaccination group (Table 93, Table 94, Table 95, Table 96, and Table 97).
- Frequency and percent of subjects with abnormal hematology results over all parameters and for each parameter, by visit, vaccination group, and severity (Table 98, Table 99, Table 100, Table 101, Table 102, and Table 103).
- Frequency and percent of subjects with abnormal hematology results related to Study Product, over all parameters and for each parameter, by visit, vaccination group, and severity (Table 104, Table 105, Table 106, Table 107, Table 108, and Table 109).
- Descriptive statistics (mean, standard deviation, median, minimum and maximum) of each hematology parameter, including change from baseline, by time point and vaccination group (Table 110, Table 111, Table 112, Table 113, and Table 114).
- Median change from baseline of each lab parameter will be displayed by gender and vaccination group in Figure 30 (WBC), Figure 31 (HgB), Figure 32 (Platelets), Figure 33 (ALC), Figure 34 (ANC), Figure 35 (AST), Figure 36 (ALT), Figure 37 (Total Bilirubin), Figure 38 (BUN), and Figure 39 (Creatinine).

Listing 14 will provide a complete listing of individual chemistry laboratory results with applicable reference ranges. Listing 15 will provide a complete listing of individual hematology laboratory results with applicable reference ranges. Listing 16 will provide a complete listing of individual urinalysis laboratory results.

9.7. Vital Signs and Physical Evaluations

Vital signs measurements include systolic and diastolic blood pressure, oral temperature and pulse and will be assessed on Days 1, 2, 8, 15, 16, 22, 29, 91, 181 and 381. Vital signs will be tabulated by visit and vaccination group and classified by severity (Table 115, Table 116, Table 117, Table 118, and Table 119) and listed per subject in Listing 17. All temperatures recorded within 7 days of vaccination will be included in assessments of solicited fever AE.

Targeted physical examinations will be performed at study visits if indicated based on review of complete medical history. Any physical examination findings will be presented per subject in Listing 18.

9.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification (ATC) using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented (Listing 19). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and vaccination group for the Safety population (Table 120 and Table 121).

9.9. 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, median, standard deviation, GMT, 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".
- 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".
- Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients,) will be reported to 3 significant figures
- Estimated correlation coefficients will be reported to 3 decimal places.
- Confidence intervals will use the same number of decimal places as the corresponding statistic

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

15.1. Changes to Planned Interim Analyses

The protocol was amended (Protocol v6.0, 11FEB2022) to have only one interim analysis of safety and immunogenicity after a sufficient number of subjects completed Day 91, due to enrollment progressing more slowly than anticipated.

15.2. Changes from Version 1.0 to Version 2.0 of the SAP

The protocol was amended (Protocol v7.0, 19JAN2022) to correct the group sizes in Section 11.2 of the protocol to be consistent with Table 1 of the protocol. The group sizes in Section 5 (Sample Size Considerations) of Version 2.0 of the SAP were similarly corrected to be consistent with Table 1.

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17. LISTING OF TABLES, FIGURES, AND LISTINGS

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

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

[Implementation note: tables to be included in the interim analysis are noted with an asterisk, '*']

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Study Design

Study Group	N	Vaccine	Dosage of Vaccine	Number of Vaccine Doses	Schedule of Vaccine and Placebo Injections	Route	Description of Study Group
A	14 including 3 sentinels[#]	ChAd155-RG	$5x10^{10}$vp*	1	Day 1 vaccine; Days 8, 15, and 22 placebo	IM	Lower dosage, 1 dose
B	14 including 3 sentinels	ChAd155-RG	$1x10^{11}$vp	1	Day 1 vaccine; Days 8, 15, and 22 placebo	IM	Higher dosage, 1 dose
C	10	ChAd155-RG	$1x10^{11}$vp	2	Days 1 and 15 vaccine; Days 8 and 22 placebo	IM	Higher dosage, 2 doses
D	12 including 2 sentinels	RABAVERT	1 mL	3	Days 1, 8, and 22 vaccine; Day 15 placebo	IM	Active comparator (licensed vaccine)

*Abbreviations: vp, viral particles; IM, intramuscular

#Groups A, B and D each include sentinel subjects as indicated. Note: Two of the sentinels will receive a three-dose series of RABAVERT. To maintain blinding, the other sentinels will receive placebo injections on Days 8, 15, and 22 as indicated in the table.

Table 2: Schedule of Study Procedures

Study Visit		1st Screen (D-28 to -1)	2nd Screen (D -28 to -1)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Early termination	Unscheduled
Study Day post Vaccination #1 (D1)				**Enrollment Dose 1 D1**	**D2 +2d**	**D8 +2d**	**D15 +2d**	**D16 +2d**	**D22 +2d**	**D29+14d**	**D50+ 7d**	**D91 ± 14d**	**D181± 14d**	**D381± 14d**		
Study Day post Vaccination #2						**Dose 2 D1**	**D8 +2d**	**D9 +2d**	**D15 +2d**	**D22+14d**	**D43+ 7d**	**D84 ± 14d**	**D174± 14d**	**D374± 14d**		
Study Day post Vaccination #3							**Dose 3 D1**	**D2 +2d**	**D8 +2d**	**D15+14d**	**D36+ 7d**	**D77 ± 14d**	**D167± 14d**	**D367± 14d**		
Study Day post Vaccination #4									**Dose 4 D1**	**D8+14d**	**D29+ 7d**	**D70 ± 14d**	**D160± 14d**	**D360± 14d**		
Signed ICF		X														
Assessment of Eligibility Criteria		X	X	X		X	X		X							
Symptom Screen		X	X	X	X	X	X	X	X	X	X	X	X	X		
Review of Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Review of Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X[a]	X[a]	X[a]	X	(X)
Vaccinations (X) Placebo (P)	A			X		P	P		P							
	B			X		P	P		P							
	C			X		P	X		P							
	D			X		X	P		X							
Physical Exam	Complete	X														
	Symptom-Directed		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)	(X)	(X)	(X)	(X)
	Vital Signs	X[b]	X[b]	X	X	X	X	X	X	X		X	X	X	X	(X)

Table 2: Schedule of Procedures (*continued)*

Study Visit		1st Screen (D-28 to -1)	2nd Screen (D -28 to -1)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Early termination	Unscheduled
Study Day post Vaccination #1 (D1)				**Enrollment Dose 1 D1**	**D2 +2d**	**D8 +2d**	**D15 +2d**	**D16 +2d**	**D22 +2d**	**D29+14d**	**D50+ 7d**	**D91 ± 14d**	**D181± 14d**	**D381± 14d**		
Study Day post Vaccination #2						**Dose 2 D1**	**D8 +2d**	**D9 +2d**	**D15 +2d**	**D22+14d**	**D43+ 7d**	**D84 ± 14d**	**D174± 14d**	**D374± 14d**		
Study Day post Vaccination #3							**Dose 3 D1**	**D2 +2d**	**D8 +2d**	**D15+14d**	**D36+ 7d**	**D77 ± 14d**	**D167± 14d**	**D367± 14d**		
Study Day post Vaccination #4									**Dose 4 D1**	**D8+14d**	**D29+ 7d**	**D70 ± 14d**	**D160± 14d**	**D360± 14d**		
Assessment of Adverse Events and New Onset Chronic Medical Conditions				X	X	X	X	X	X	X	X	X[c]	X[c]	X[c]	X	X
Examine Vaccination Site for Local Reactions (before vaccination on injection visits) and Review Memory Aid					X	X	X	X	X	X					X[d]	X[e]
Pre-vaccine Administration Reactogenicity Assessment				X		X	X		X							
Post-vaccination Observation (for 30 minutes) to Assess Acute Reactions				X		X	X		X							
Evaluation of Vaccination Site to Assess for Reactogenicity and AE/SAEs after 30 minutes				X		X	X		X							
Subject provided with Memory Aid to Enter Reactogenicity Information				X		X	X		X							
Pregnancy test	Serum	X														
	Urine			X		X	X		X							

Table 2: Schedule of Procedures (*continued)*

Study Visit		1st Screen (D-28 to -1)	2nd Screen (D -28 to -1)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Early termination	Unscheduled
Study Day post Vaccination #1 (D1)				Enrollment Dose 1 D1	D2 +2d	D8 +2d	D15 +2d	D16 +2d	D22 +2d	D29+14d	D50+ 7d	D91 ± 14d	D181± 14d	D381± 14d		
Study Day post Vaccination #2						Dose 2 D1	D8 +2d	D9 +2d	D15 +2d	D22+14d	D43+ 7d	D84 ± 14d	D174± 14d	D374± 14d		
Study Day post Vaccination #3							Dose 3 D1	D2 +2d	D8 +2d	D15+14d	D36+ 7d	D77 ± 14d	D167± 14d	D367± 14d		
Study Day post Vaccination #4									Dose 4 D1	D8+14d	D29+ 7d	D70 ± 14d	D160± 14d	D360± 14d		
Blood draw		X	(X)	X	X	X	X	X	X	X		X	X	X	X	(X)
Clinical Laboratory	Chemistry	X[f]	(X)		X	X		X	X						X	(X)
	Hematology	X	(X)		X	X		X	X						X	(X)
	Urine dipstick	X	(X)													
Research Assay	SARS-CoV-2 test				(X)	(X)	(X)	(X)	(X)	(X)						
Immunology (all samples on vaccination days will be collected before the vaccine dose is given)	Rabies nAb (RFFIT)			X		X	X		X	X		X	X	X	X	
	T cell (IFNγ ELISpot) ($5x10^6$ $10x10^6$ PBMCs)			X			X			X		X		X		
	T cell (ICS) ($10x10^6$ PBMCs)						X[g]			X[g]						
	MBC ELISpot ($5x10^6$ $10x10^6$ PBMCs)			X								X	X	X		

Table 2: Schedule of Procedures (*continued)*

Study Visit		1st Screen (D-28 to -1)	2nd Screen (D -28 to -1)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Early termination	Unscheduled
Study Day post Vaccination #1 (D1)				**Enrollment Dose 1 D1**	**D2 +2d**	**D8 +2d**	**D15 +2d**	**D16 +2d**	**D22 +2d**	**D29+14d**	**D50+ 7d**	**D91 ± 14d**	**D181± 14d**	**D381± 14d**		
Study Day post Vaccination #2						**Dose 2 D1**	**D8 +2d**	**D9 +2d**	**D15 +2d**	**D22+14d**	**D43+ 7d**	**D84 ± 14d**	**D174± 14d**	**D374± 14d**		
Study Day post Vaccination #3							**Dose 3 D1**	**D2 +2d**	**D8 +2d**	**D15+14d**	**D36+ 7d**	**D77 ± 14d**	**D167± 14d**	**D367± 14d**		
Study Day post Vaccination #4									**Dose 4 D1**	**D8+14d**	**D29+ 7d**	**D70 ± 14d**	**D160± 14d**	**D360± 14d**		
	PBMCs for future use			X			X			X		X	X	X		
	Blood for developer assays[h]			X	X	X	X	X	X	X						

[a]Concomitant medications associated with new onset chronic medical condition(s)

[b]Height and weight will also be measured at the 1st and 2nd screening visits to calculate BMI

[c]Only SAEs

[d]Vaccination site will be examined for local reactions if early termination visit occurs ≤28 days after last injection; memory aid will be reviewed if early termination visit occurs ≤15 days after last injection

[e]Vaccination site will be examined for local reactions if unscheduled visit occurs ≤28 days after any vaccination, and if so, determine whether information recorded by subject on the memory aid conforms to examination

[f]Clinical labs drawn at 1st screening visit will also include HIV-1/2 antibody, HBsAg, and HCV antibody

[g]Assay will be done only for those with positive IFNγ response by T cell ELISpot assay

[h]Detailed in Appendix B of the protocol.

9.7.1 Sample Size

Table 3: Probability of Observing an Adverse Event for Various Event Rates and Sample Sizes

N	"True" Event Rate	Probability of Observation (%)	N	"True" Event Rate	Probability of Observation (%)
8	0.1 %	0.8	12	0.1%	1.2
	0.5 %	3.9		0.5%	5.8
	1.0 %	7.7		1.0%	11.4
	2.0 %	14.9		2.0%	21.5
	3.0 %	21.6		3.0%	30.6
	4.0 %	27.9		4.0%	38.7
	5.0 %	33.7		5.0%	46.0
	10.0 %	57.0		10.0%	71.8
	20.0 %	83.2		20.0%	93.1
10	0.1%	1.0	14	0.1%	1.4
	0.5%	4.9		0.5%	6.8
	1.0%	9.6		1.0%	13.1
	2.0%	18.3		2.0%	24.6
	3.0%	26.3		3.0%	34.7
	4.0%	33.5		4.0%	43.5
	5.0%	40.1		5.0%	51.2
	10.0%	65.1		10.0%	77.1
	20.0%	89.3		20.0%	95.6

Table 4: Minimum Detectable Event Rates for Various Levels of Power and Sample Size

N	Desired Power Level	Detectable Event Rate (%)	N	Desired Power Level	Detectable Event Rate (%)
8	0.80	18.2	12	0.80	12.6
	0.90	25.0		0.90	17.5
	0.95	31.2		0.95	22.1
	0.99	43.8		0.99	31.9
10	0.80	14.9	14	0.80	10.9
	0.90	20.6		0.90	15.2
	0.95	25.9		0.95	19.3
	0.99	36.9		0.99	28.0

Table 5: 95% Confidence Intervals for Seroconversion Rate for Various Rates and Sample Sizes

N	Seroconversion Rate	95% CI	N	Seroconversion Rate	95% CI
8	90%	(50 %, 100%)	12	90%	(59 %, 100%)
	95%	(56 %, 100%)		95%	(66 %, 100%)
	100%	(63 %, 100%)		100%	(74 %, 100%)
10	90%	(55 %, 100%)	14	90%	(62 %, 99%)
	95%	(62 %, 100%)		95%	(69 %, 100%)
	100%	(69 %, 100%)		100%	(77 %, 100%)

10.2 Protocol Deviations

Table 6: Distribution of Protocol Deviations by Category, Type, and Vaccination Group*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Category	Deviation Type	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type										
	Did not meet inclusion criterion	x	x	x	x	x	x	x	x	x	x
	Met exclusion criterion										
	ICF not signed prior to study procedures										
	Other										
Treatment 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										
	Urine not collected										
	Other specimen not collected										

Table 6: Schedule of Procedures (*continued)*

Category	Deviation Type	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
	Too few aliquots obtained										
	Specimen result not obtained										
	Required procedure not conducted										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Specimen temperature excursion										
	Other										
Treatment administration	Any type										
	Required procedure done incorrectly										
	Study product temperature excursion										
	Other										
Blinding policy/procedure	Any type										
	Treatment unblinded										
	Other										

Note: N = Number of subjects in the Safety Population.

12.2.2 Displays of Adverse Events

Table 7: Local (Injection Site) Reactogenicity Grading

Local (Injection Site) Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity, **and** it does not require pain medication or it requires use of a non-narcotic pain reliever ≤24hours	Subject is aware of pain; there is interference with daily activity **or** it requires repeated use of a non-narcotic pain reliever for >24 hours	Subject is aware of pain, **and** it prevents daily activity or requires any use of a narcotic pain reliever
Tenderness – hurts only when injection site is touched or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, **and** it does **not** interfere with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it prevents daily activity
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Swelling*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
*Size will also be measured in mm but will not be used as a halting criterion			

Table 8: Local (Injection Site) Reactogenicity Measurements

Local (Injection Site) Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Ecchymosis (Bruising)*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Erythema (Redness)*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
Induration (Hardness)/Swelling*	25 mm – 50 mm	51 mm – 100 mm	>100 mm
*Will not be used as halting criteria			

Table 9: Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Fatigue (Tiredness)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise (General Unwell Feeling)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia (Body Aches/Muscular Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Arthralgia (Joint Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
*Not at injection site			

Table 10: Quantitative Systemic Reactogenicity Grading

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever* - oral†	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	>38.9°C >102.0°F

Note: Oral temperature assessed on Day 1 prior to the first study vaccination will be considered as baseline.
*A fever can be considered not related to the vaccine if an alternative etiology can be documented.
†Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature

Table 11: Pulse and Blood Pressure Grading

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bradycardia - beats per minute	50 – 54	45 – 49	<45
Tachycardia - beats per minute	101 – 115	116 – 130	>130
Hypotension (systolic) mmHg	85 – 89	80 – 84	<80
Hypotension (diastolic) mmHg	50 – 54	45 – 49	<45
Hypertension (systolic) mmHg	141 – 150	151 – 155	>155
Hypertension (diastolic) mmHg	91 – 95	96 – 100	>100
Note: Pulse and blood pressure assessed on Day 1 prior to the first study vaccination will be considered as baseline.			

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 12: Laboratory Adverse Event Grading Scale - Hematology

Hematology	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
WBC $10^3/\mu L$ (Decrease)	3.8 – 10.8	2.5 – 3.7	1.5 – 2.4	<1.5
WBC $10^3/\mu L$ (Increase)	3.8 – 10.8	10.9 – 15.0	15.1 – 20.0	>20.0
Hgb g/dL (Decrease) (Female)	11.7 – 15.5	11.0 – 11.6	9.5 – 10.9	<9.5
Hgb g/dL (Decrease) (Male)	13.2 – 17.1	12.0 – 13.1	10.0 – 11.9	<10.0
Platelets $10^3/\mu L$ (Decrease)	140 – 400	125 – 139	100 – 124	<100
Platelets $10^3/\mu L$ (Increase)	140 – 400	401 – 550	551– 750	>750
Absolute Lymphocyte Count $10^3/\mu L$	0.85 – 3.9	0.65 – 0.84	0.5 – 0.64	<0.5
Absolute Neutrophil Count $10^3/\mu L$	1.5 – 7.8	1.2 – 1.49	1.0 – 1.19	<1.0
Note: Clinical laboratory evaluations assessed at the screening visit will be considered as baseline.				

Table 13: Laboratory Adverse Event Grading Scale - Chemistry

Chemistry	Normal Range	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
AST IU/L (increase) (Male)	10 – 40	1.1 – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 10 x ULN
AST IU/L (increase) (Female)	10 – 30	1.1 – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 10 x ULN
ALT IU/L (increase) (Male)	9 – 46	1.1 – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 10 x ULN
ALT IU/L (increase) (Female)	6 – 29	1.1 – 2.5 x ULN	> 2.5 – 5.0 x ULN	> 5.0 – 10 x ULN
Total Bilirubin mg/dL (Increase) – when accompanied by any increase in ALT	0.2 – 1.2	1.1 – 1.25 x ULN	> 1.25 – 1.5 x ULN	> 1.5 – 1.75 x ULN
Total Bilirubin mg/dL (Increase) – when ALT is normal	0.2 – 1.2	1.1 – 1.5 x ULN	> 1.5 – 2.0 x ULN	> 2.0 – 3.0 x ULN
Blood urea nitrogen (BUN) mg/dL (increase)	7 – 25	26 – 29	30 – 34	>34
Creatinine mg/dL (Increase) (Male)	0.60 – 1.35	1.36 – 1.70	1.71 – 2.00	>2.00
Creatinine mg/dL (Increase) (Female)	0.50 – 1.10	1.11 – 1.70	1.71 – 2.00	>2.00
*Clinical laboratory evaluations assessed at the screening visit will be considered as baseline				

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 14: Subject Disposition by Vaccination Group*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Subject Disposition	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%	n	%
Screened	--	--	--	--	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100	x	100	x	100
Vaccinated										
Received All Vaccinations[a]										
Completed Study Day 91										
Completed Study Day 181										
Completed Final Blood Draw										
Completed Follow-up (Study Day 381)[a]										
Completed Per Protocol[b]										

Note: N = Number of subjects in the Safety Population; n = number of subjects completing the milestone.
[a]Refer to Listing 2 for reasons subjects discontinued or terminated early.
[b]Refer to Listing 5 for reasons subjects are excluded from the analysis populations.

Table 15: Analysis Populations by Vaccination Group*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date for the safety and mITT populations only. For timepoint-specific exclusions from the Per Protocol population, record each subject's exclusions at all time points for a given reason.]

Analysis Populations	Reason Subjects Excluded	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%
Safety	Did not receive vaccination	x	xx	x	xx	x	xx	x	xx	x	xx
Modified Intent to Treat	Any Reason										
	Did not receive vaccination										
	Did not contribute a valid pre-study vaccination blood sample										
	Did not contribute any valid post-study vaccination blood samples										
Per Protocol	**Any Time Point:**										
	Any Reason										
	Found to be ineligible at baseline										
	Baseline rabies VNA concentration ≥ 0.5 IU/mL										
	Visit occurs out of window										
	Study withdrawal[a,b]										
	Treatment discontinuation[b]										
	Study vaccination dose received out of window[b]										
	Receipt of non-study licensed live vaccine within 30 days before or after study vaccination[b]										
	Receipt of non-study licensed inactivated vaccine within 14 days before or after study vaccination[b]										
	Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after study vaccination[b]										
	Receipt of chloroquine or hydroxychloroquine[b]										
	Prior to or at Day 8 visit:										
	Any Reason										
	Found to be ineligible at baseline										
	Baseline rabies VNA concentration ≥ 0.5 IU/mL										

Table 15: Analysis Populations by Vaccination Group (*continued)*

Analysis Populations	Reason Subjects Excluded	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%
	Visit occurs out of window										
	Study withdrawal[a,b]										
	Treatment discontinuation[b]										
	Study vaccination dose received out of window[b]										
	Receipt of non-study licensed live vaccine within 30 days before or after study vaccination[b]										
	Receipt of non-study licensed inactivated vaccine within 14 days before or after study vaccination[b]										
	Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after study vaccination[b]										
	Receipt of chloroquine or hydroxychloroquine[b]										
	Repeat Day 8 for:										
	Prior to or at Day 15 visit:										
	Prior to or at Day 22 visit:										
	Prior to or at Day 29 visit:										
	Prior to or at Day 91 visit:										
	Prior to or at Day 181 visit:										

Note: N=Number of subjects enrolled; n=number of subjects meeting the criteria.
[a]Subjects visits may be included in the PP population up to study withdrawal.
[b]Subjects are excluded from per protocol analyses at all timepoints subsequent to the occurrence of the protocol deviation. Subjects are summarized in this table at all affected timepoints.

Table 16: Dates of First Vaccination by Vaccination Group

Dates of First Dosing	Low Dose ChAd155-RG (N=X)	High Dose ChAd155-RG (x1) (N=X)	High Dose ChAd155-RG (x2) (N=X)	RABAVERT (N=X)	All Subjects (N=X)
Total (Entire period of enrollment)					
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x
Note: N = Number of subjects in the Safety Population					

Table 17: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	Must be a male or female aged 18-49 years old (inclusive) at the time of first vaccination.	x	xx
	Must be able to provide written informed consent.	x	xx
	Must have a body mass index (BMI) ≥18.5 and <35.0 kg/m^2.		
	Must be in good health based on physical examination, vital signs, medical history, safety labs, and the investigator's clinical judgment.		
	Must have acceptable lab values within 28 days before enrollment.		
	Women of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy tests within 24 hours before each vaccination.		
	Women of childbearing potential must use an acceptable method of contraception from 28 days before the first vaccination until ≥60 days after the last vaccination.		
	Female subjects must agree to not donate eggs (ova, oocytes) from the start of screening until ≥60 days after the last vaccination.		
	Male subjects who have not had a vasectomy and are sexually active with a woman of childbearing potential must agree to use an acceptable method of contraception.		
	Male subjects must agree to not donate sperm from the start of screening until ≥60 days after the last vaccination.		
	Must be available and willing to participate for the duration of this trial.		
	Must have a means to be contacted by telephone.		
Exclusion	Any exclusion criterion	x	xx
	Was ever vaccinated with a licensed or investigational rabies vaccine[8] or was diagnosed with rabies exposure, infection, or disease.	x	xx
	Has a higher risk than the average US resident with regard to exposure to rabies, per the Rabavert package insert and rabies vaccination recommendations from the CDC.	x	xx
	Was ever vaccinated with a licensed or investigational Ad vector or Ad vaccine.	x	xx
	Is currently taking chloroquine or hydroxychloroquine.		
	Was diagnosed with laboratory-confirmed COVID-19 (PCR or antigen-based test) in the preceding 28 days.		
	Positive serology for HIV antibody, HCV antibody, or Hepatitis B surface antigen (HBsAg).		
	Has known allergy or history of anaphylaxis or other serious adverse reaction to a vaccine or vaccine products.		
	Has severe allergy or anaphylaxis to latex.		
	Has an acute illness or temperature ≥38.0°C on Day 1.		

Table 17: Ineligibility Summary of Screen Failures (*continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
	Female subjects who are pregnant or breastfeeding or planning to become pregnant while enrolled in this trial and at least 60 days after last vaccination.		
	Has history of autoimmune disease, or clinically significant cardiac, pulmonary, hepatic, rheumatologic, or renal disease by history, physical examination, and/or lab studies.		
	Has history of malignancy other than squamous cell or basal cell skin cancer, unless there has been surgical excision that is considered to have achieved cure.		
	Has known or suspected congenital or acquired immunodeficiency, or recent history or current use of immunosuppressive therapy.		
	Is post-organ and/or stem cell transplant, whether or not on chronic immunosuppressive therapy.		
	Had major surgery (per the investigator's judgment) within 4 weeks before study entry or planned major surgery during this trial.		
	Has history of diabetes mellitus type 1 or type 2, including cases controlled with diet alone.		
	Has history of thyroidectomy, or thyroid disease requiring medication in the last 12 months.		
	Has history of hypertension, even if medically controlled.		
	Received live attenuated vaccines from 30 days before first vaccination until 30 days after final vaccination.		
	Received killed or inactivated vaccines from 14 days before first vaccination until 30 days after final vaccination.		
	Received experimental therapeutic agents within 3 months before first vaccination or plans to receive any experimental therapeutic agents during this trial.		
	Is currently participating or plans to participate in another clinical study which would involve receipt of certain investigational products or procedures[c]		
	Received blood products or immunoglobulin in the 3 months before study entry or planned use during this trial.		
	Donated a unit of blood or blood products within 8 weeks before Day 1 or plans to donate blood or blood products during this trial.		
	Has major psychiatric illness in the past 12 months that in the opinion of the investigator would preclude participation.		
	Has current alcohol use or current or past abuse of recreational or narcotic drugs by history as judged by the investigator to potentially interfere with study adherence.		
	Has a history of chronic urticaria.		
	Has tattoos, scars, or other marks on both deltoid areas which would, in the opinion of the investigator, interfere with assessment of the vaccination site.		
	Is a site employee or staff who are paid entirely or partially by/through the OCRR contract for this trial, or staff who are supervised by the Principal Investigator (PI) or sub-investigators.		
	In the opinion of the investigator cannot communicate reliably, is unlikely to adhere to the requirements of this trial or has any condition which would limit the ability to complete this trial.		

Table 17: Ineligibility Summary of Screen Failures (*continued)*

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
	Has history of Guillain-Barre syndrome, meningitis, encephalitis, neuroparalysis, transient paralysis, myelitis, retrobulbar neuritis, multiple sclerosis, vertigo, or visual disturbances.		
	Has a history of arterial or venous thrombosis, or thrombocytopenia that required medical attention.		
Eligible but Not Enrolled	Any Reason		
	Time commitment		
	Concern of potential risk		
	Number of procedures/blood draws		
	Unable to contact subject		
	Other		

n = number of subjects meeting the criteria.
[a]More than one criterion may be marked per subject.
[b]Denominator for percentages is the total number of screen failures.
[c]See section 4.3.2 for specification of exclusionary clinical studies.

14.1.2 Demographic Data by Study Group

Table 18: Summary of Categorical Demographic and Baseline Characteristics by Vaccination Group - All Enrolled Subjects*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

		Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
Variable	**Characteristic**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Male	x	xx	x	xx	x	xx	x	xx	x	xx
	Female										
Ethnicity	Not Hispanic or Latino										
	Hispanic or Latino										
	Not Reported										
	Unknown										
Race	American Indian or Alaska Native										
	Asian										
	Native Hawaiian or Other Pacific Islander										
	Black or African American										
	White										
	Multi-Racial										
	Unknown										
Note: N = Number of subjects enrolled; n = number of subjects in the demographic characteristic group.											

Table 19: Summary of Continuous Demographic and Baseline Characteristics by Vaccination Group - All Enrolled Subjects*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Variable	Statistic	Low Dose ChAd155-RG (N=X)	High Dose ChAd155-RG (x1) (N=X)	High Dose ChAd155-RG (x2) (N=X)	RABAVERT (N=X)	All Subjects (N=X)
Age (years)	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x
BMI (kg/m^2)	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	Standard Deviation	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	x.x	x.x	x.x	x.x	x.x
	Minimum	x	x	x	x	x
	Maximum	x	x	x	x	x
Note: N = Number of subjects enrolled.						

14.1.3 Prior and Concurrent Medical Conditions

Table 20: Summary of Subjects with Pre-Existing or Concurrent Medical Conditions by MedDRA System Organ Class and Vaccination Group

	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]										
[SOC 2]										

Note: N = Number of subjects in the Safety Population; n = number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.
Includes all medical conditions with onset prior to the first vaccination.

14.2 Immunogenicity Data

Table 21: Rabies VNA Geometric Mean Titer and Seroconversion Rate with 95% Confidence Intervals by Time Point and Vaccination Group - Modified Intent to Treat Population*

Time Point (day relative the vaccination)	Statistic	Low Dose ChAd155-RG (N=X)	High Dose ChAd155-RG (x1) (N=X)	High Dose ChAd155-RG (x2) (N=X)	Combined High Dose ChAd155-RG (N=X)	RABAVERT (N=X)
Day 1 (Baseline, Pre-Dose 1)[a]	n	x	x	x	x	x
	GMT	x.x	x.x	x.x	x.x	x.x
	95% CI for GMT	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Day 8 (Pre-Dose 2)[a]	n					
	GMT					
	95% CI for GMT					
	Seroconversion (%)[b]					
	95% CI for Seroconversion					
Day 15 (Pre-Dose 3)[a]	n					
	GMT					
	95% CI for GMT					
	Seroconversion (%)[b]					
	95% CI for Seroconversion					
Day 22 (Pre-Dose 4)[a]	n				NA	
	GMT				NA	
	95% CI for GMT				NA	
	Seroconversion (%)[b]				NA	
	95% CI for Seroconversion				NA	
Repeat Day 22 for the following visits						
Day 29 (7 Days Post-Dose 4)					NA	
Day 91 (69 Days Post-Dose 4)					NA	
Day 181 (159 Days Post-Dose 4)[c]					NA	
Day 381 (359 Days Post-Dose 4)[c]					NA	
Peak Response, Post-Vaccination					NA	

Note: N = Number of subjects in the mITT population; n = number of subjects in the study population with data available at timepoint.
Exact (Clopper-Pearson) 95% CIs are presented for proportions.
[a]Day of study vaccination. Sample collected prior to vaccination.
[b]Seroconversion is defined as VNA ≥ 0.5 IU/mL post-vaccination.
[c]Day 181 time point will not be presented in the first interim immunogenicity analysis and Day 381 time point will not be presented in either interim immunogenicity analysis

Table with similar format:

Table 22: Rabies VNA Geometric Mean Titer and Seroconversion Rate with 95% Confidence Intervals by Time Point and Vaccination Group - Per Protocol Population

Table 23: Rabies VNA Pairwise Differences in Seroconversion Rates by Time Point - Modified Intent to Treat Population*

Group 1	Group 2	Difference and 95% CI (Group 1 - Group 2) in Proportion with Seroconversion						
		Day 8 (Pre-Dose 2)	Day 15 (Pre-Dose 3)	Day 22 (Pre-Dose 4)	Day 29 (7 Days Post-Dose 4)	Day 91 (69 Days Post-Dose 4)	Day 181 (159 Days Post-Dose 4)[a]	Day 381 (359 Days Post-Dose 4)[a]
Low Dose ChAd155-RG (N=X)	Combined High Dose ChAd155-RG (N=X)	x xx – xx	x xx – xx					
Low Dose ChAd155-RG (N=X)	High Dose ChAd155-RG (x1) (N=X)							
Low Dose ChAd155-RG (N=X)	High Dose ChAd155-RG (x2) (N=X)							
Low Dose ChAd155-RG (N=X)	RABAVERT (N=X)							
Combined High Dose ChAd155-RG (N=X)	RABAVERT (N=X)							
High Dose ChAd155-RG (x1) (N=X)	RABAVERT (N=X)							
High Dose ChAd155-RG (x2) (N=X)	RABAVERT (N=X)							

Note: N = Number of subjects in the mITT Population for the appropriate group.
95% CIs of pairwise differences calculated via the Miettinen and Nurminen score method.
[a] Day 181 time point will not be presented in the first interim immunogenicity analysis and Day 381 time point will not be presented in either interim immunogenicity analysis.

Table with similar format:

Table 24: Rabies VNA Pairwise Differences in Seroconversion Rates by Time Point - Per Protocol Population

Exploratory Immunology Analyses

Table 25: Rabies VNA Regression Analyses of GMT and Seroconversion Rate - Modified Intent to Treat Population

Table 26: Rabies VNA Regression Analyses of GMT and Seroconversion Rate - Per Protocol Population

The format of these tables will be decided based on the results.

Table 27: Geometric Mean Titer of Neutralizing Antibody Titer to ChAd155 Vector – Modified Intent to Treat Population

Time Point	Statistic	Low Dose ChAd155-RG (N=X)	High Dose ChAd155-RG (x1) (N=X)	High Dose ChAd155-RG (x2) (N=X)	Combined High Dose ChAd155-RG (N=X)	RABAVERT (N=X)
Day 1 (Pre-Dose 1)[a]	n	x	x	x	x	x
	GMT	x.x	x.x	x.x	x.x	x.x
	95% CI for GMT	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
Day 29 (7 Days Post-Dose 4)	n				NA	
	GMT				NA	
	95% CI for GMT				NA	

Note: N = Number of subjects in the mITT population; n = number of subjects in the study population with data available at timepoint.
[a] Day of study vaccination. Sample collected prior to vaccination.

Table with similar format:

Table 28: Geometric Mean Titer of Neutralizing Antibody Titer to ChAd155 Vector –Per Protocol Population

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 29: Overall Summary of Adverse Events*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		Combined High Dose ChAd155-RG (N = X)		RABAVERT (N = X)		All Subjects (N = X)	
Subjects[a] with	n	%	n	%	n	%	n	%	n	%	n	%
At least one local solicited adverse event	x	x	x	x	x	x	x	x	x	x	x	x
At least one systemic solicited adverse event												
At least one unsolicited adverse event												
At least one related unsolicited adverse event												
Mild (Grade 1)												
Moderate (Grade 2)												
Severe (Grade 3)												
At least one severe (Grade 3) unsolicited adverse event												
Related												
Unrelated												
At least one serious adverse event[b]												
At least one related, serious adverse event												
At least one adverse event leading to early termination[c]												
At least one new onset chronic medical condition												

Note: N = Number of subjects in the Safety Population; n = number of subjects reporting event.
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Table 84.
[c] As reported on the Adverse Event eCRF.

Table 30: Adverse Events Occurring in 5% of Subjects in Any Vaccination Group by MedDRA System Organ Class and Preferred Term, and Vaccination Group - Safety Population

Preferred Term	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		Combined High Dose ChAd155-RG (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Serious Adverse Events												
All	x (xx)	x	x (xx)	x	x (xx)	x	x (xx)	x	x (xx)	x	x (xx)	x
[SOC 1]												
Any PT												
[PT 1]												
[PT 2]												
Other (Non-Serious) Adverse Events												
All												
[SOC 1]												
Any PT												
[PT 1]												
[PT 2]												

Note: N = number of subjects in the Safety Population; n= number of subjects reporting event; Events = total frequency of events reported.

14.3.1.1 Solicited Adverse Events

Table 31: Number and Percentage of Subjects Experiencing Solicited Adverse Events by Symptom, Maximum Severity, and Vaccination Group - Post Dose 1

Symptom/ Severity	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		Combined High Dose ChAd155-RG[a] (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Symptom												
Any Severity	x (xx)	xx, xx										
None												
Mild												
Moderate												
Severe												
Repeat for:												
Any Systemic Symptom												
Feverishness												
Fatigue												
Malaise												
Myalgia												
Arthralgia												
Nausea												
Headache												
Fever												
Any Local Symptom												
Pain												
Tenderness												
Pruritis												
Ecchymosis Grade												
Ecchymosis Measurement												
Erythema Grade												
Erythema Measurement												
Induration Grade												
Induration Measurement												

Note: N = Number of subjects in the Safety Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject; n = Number of subjects reporting event.
[a] Both high dose groups combined.

Table 32: Number and Percentage of Subjects Experiencing Solicited Adverse Events by Symptom, Maximum Severity, and Vaccination Group - Post Dose 2

Symptom/ Severity	Low Dose Placebo (N=X)		High Dose (x1) Placebo (N=X)		High Dose (x2) Placebo (N=X)		All Placebo[a] (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Symptom												
Any Severity	x (xx)	xx, xx										
None												
Mild												
Moderate												
Severe												
Repeat for:												
Any Systemic Symptom												
Feverishness												
Fatigue												
Malaise												
Myalgia												
Arthralgia												
Nausea												
Headache												
Fever												
Any Local Symptom												
Pain												
Tenderness												
Pruritis												
Ecchymosis Grade												
Ecchymosis Measurement												
Erythema Grade												
Erythema Measurement												
Induration Grade												
Induration Measurement												

Note: N = Number of subjects in the Safety Population who received the specified dose; n = Number of subjects reporting event.
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.
[a] Low dose and both high dose groups combined.

Table 33: Number and Percentage of Subjects Experiencing Solicited Adverse Events by Symptom, Maximum Severity, Dose, and Vaccination Group - Post Dose 3

Symptom/ Severity	Low Dose Placebo (N=X)		High Dose (x1) Placebo (N=X)		High Dose (x2) ChAd155-RG (N=X)		RABAVERT Placebo (N=X)		All Placebo[a] (N=X)		All Subjects (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Symptom												
Any Severity	x (xx)	xx, xx										
None												
Mild												
Moderate												
Severe												
Repeat for:												
Any Systemic Symptom												
Feverishness												
Fatigue												
Malaise												
Myalgia												
Arthralgia												
Nausea												
Headache												
Fever												
Any Local Symptom												
Pain												
Tenderness												
Pruritis												
Ecchymosis Grade												
Ecchymosis Measurement												
Erythema Grade												
Erythema Measurement												
Induration Grade												
Induration Measurement												

Note: N = Number of subjects in the Safety Population who received the specified dose; n = Number of subjects reporting event.
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.
[a] Low dose, high dose (x1) and RABAVERT combined.

Table 34: Number and Percentage of Subjects Experiencing Solicited Adverse Events by Symptom, Maximum Severity, Dose, and Vaccination Group - Post Dose 4

Symptom/ Severity	Low Dose Placebo (N=X)		High Dose (x1) Placebo (N=X)		High Dose (x2) Placebo (N=X)		All Placebo[a] (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Symptom												
Any Severity	x (xx)	xx, xx										
None												
Mild												
Moderate												
Severe												
Repeat for:												
Any Systemic Symptom												
Feverishness												
Fatigue												
Malaise												
Myalgia												
Arthralgia												
Nausea												
Headache												
Fever												
Any Local Symptom												
Pain												
Tenderness												
Pruritis												
Ecchymosis Grade												
Ecchymosis Measurement												
Erythema Grade												
Erythema Measurement												
Induration Grade												
Induration Measurement												

Note: N = Number of subjects in the Safety Population who received the specified dose; n = Number of subjects reporting event.
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.
[a] Low dose, and both high dose combined.

Table 35: Number and Percentage of Subjects Experiencing Solicited Adverse Events by Symptom, Maximum Severity, Dose, and Vaccination Group - Post Any Dose

Symptom/ Severity	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any Symptom										
Any Severity	x (xx)	xx, xx	x (xx)	xx, xx	x (xx)	xx, xx	x (xx)	xx, xx	x (xx)	xx, xx
None										
Mild										
Moderate										
Severe										
Repeat for:										
Any Systemic Symptom										
Feverishness										
Fatigue										
Malaise										
Myalgia										
Arthralgia										
Nausea										
Headache										
Fever										
Any Local Symptom										
Pain										
Tenderness										
Pruritis										
Ecchymosis Grade										
Ecchymosis Measurement										
Erythema Grade										
Erythema Measurement										
Induration Grade										
Induration Measurement										

Note: N = Number of subjects in the Safety Population who received the specified dose; n = Number of subjects reporting event.
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

Table 36: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 1*

Treatment Received = ChAd155-RG (N = X)											
		Pre-Dose (N*=X)	30 Mins. Post-Dose (N*=X)	Day 1[a] (N*=X)	Day 2 (N*=X)	Day 3 (N*=X)	Day 4 (N*=X)	Day 5 (N*=X)	Day 6 (N*=X)	Day 7 (N*=X)	Day 8 (N*=X)
	Severity	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Solicited Symptom	Any Severity	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Any Systemic Symptom	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Feverishness	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Fatigue	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Malaise	Any Severity										
	None										

Table 36: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 1* ***(continued)***

	Mild										
	Moderate										
	Severe										
	Not Reported										
Myalgia	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Arthralgia	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Nausea	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Headache	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Fever	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										

Table 36: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 1* ***(continued)***

	Not Reported										
Any Local Symptom	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Pain	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Tenderness	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Pruritus	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Ecchymosis	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Ecchymosis Measurement	Any Severity										

Table 36: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 1* ***(continued)***

	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Erythema	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Erythema Measurement	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Induration	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										
Induration Measurement	Any Severity										
	None										
	Mild										
	Moderate										
	Severe										
	Not Reported										

Note: N = Number of subjects in the Safety Population who received the specified dose; N*=Number of subjects in the Safety Population with data available for at least one measure at the specified time point, and the denominator for percentages.
[a] Day of vaccination (excluding 30 minute assessment)

Table 37: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 2*

Table 38: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 3*

Table 39: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 4*

Table 40: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Dose 2, 3, 4*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

Table 41: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - Low Dose ChAd155-RG, Any Dose*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

Table 42: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x1) ChAd155-RG, Dose 1*

Table 43: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x2) ChAd155-RG, Dose 1*

Table 44: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – Combined High Dose ChAd155-RG, Dose 1*

Table 45: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x1) ChAd155-RG, Dose 2*

Table 46: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x2) ChAd155-RG, Dose 2*

Table 47: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – Combined High Dose ChAd155-RG, Dose 2*

Table 48: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x1) ChAd155-RG, Dose 3*

Table 49: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x2) ChAd155-RG, Dose 3*

Table 50: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x1) ChAd155-RG, Dose 4*

Table 51: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x2) ChAd155-RG, Dose 4*

Table 52: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – Combined High Dose ChAd155-RG, Dose 4*

Table 53: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x1) ChAd155-RG, Any Dose*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

Table 54: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - High Dose (x2) ChAd155-RG, Any Dose*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

Table 55: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – RABAVERT, Dose 1*

Table 56: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – RABAVERT, Dose 2*

Table 57: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – RABAVERT, Dose 3*

Table 58: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – RABAVERT, Dose 4*

Table 59: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – RABAVERT, Dose 1, 2, 4*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

Table 60: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing – RABAVERT, Any Dose*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

Table 61: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - All Subjects, Dose 1*

Table 62: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - All Subjects, Dose 2*

Table 63: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - All Subjects, Dose 3*

Table 64: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - All Subjects, Dose 4*

Table 65: Number and Percentage of Subjects Experiencing Any Solicited Adverse Event by Maximum Severity and Day Post Dosing - All Subjects, Any Dose*

[Implementation note: The maximum severity of each symptom reported by each subject each day over all specified doses is reported.]

14.3.1.2 Unsolicited Adverse Events

Table 66: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Post-Dose 1 and Prior to Dose 2 by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

MedDRA Classification	Severity	Low Dose ChAd155-RG (N=X)			High Dose ChAd155-RG (x1) (N=X)			High Dose ChAd155-RG (x2) (N=X)			Combined High Dose ChAd155-RG (N=X)			RABAVERT (N=X)			All Subjects (N=X)		
Preferred Term		Events	n (%)	95% CI	Events	n (%)	95% CI	Events	n (%)	95% CI	Events	n (%)	95% CI	Events	n (%)	95% CI	Events	n (%)	95% CI
Any SOC																			
Any PT	Any Severity	x	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	x (xx)	xx, xx
	Mild																		
	Moderate																		
	Severe																		
SOC 1																			
Any PT	Any Severity																		
	Mild																		
	Moderate																		
	Severe																		
[PT 1]																			
etc																			
Repeat for other reported SOCs																			
Any PT																			
[PT 1]																			
etc																			

Note: Includes all AEs post-dose 1 and prior to dose 2, or within 7 days of dose 1 if dose 2 not received
N = Number of subjects in the safety population who received the specified dose; n = number of subjects experiencing an AE within the SOC and PT combination. Severity is the maximum severity reported post dosing for each subject for each SOC and PT combination.

Table with similar format:

Table 67: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Post-Dose 2 and Prior to Dose 3 by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

Table 68: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Post-Dose 3 and Prior to Dose 4 by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

MedDRA Classification		Low Dose ChAd155-RG (N=X)			High Dose ChAd155-RG (x1) (N=X)			High Dose ChAd155-RG (x2) (N=X)			RABAVERT (N=X)			All Subjects (N=X)		
Preferred Term	**Severity**	**Events**	**n (%)**	**95% CI**	**Events**	**n (%)**	**95% CI**	**Events**	**n (%)**	**95% CI**	**Events**	**n (%)**	**95% CI**	**Events**	**n (%)**	**95% CI**
Any SOC																
Any PT	Any Severity	x	x (xx)	xx, xx	x	x (xx)	xx, xx	x	x (xx)	xx, xx	x	x (xx)	xx, xx	x	x (xx)	xx, xx
	Mild															
	Moderate															
	Severe															
SOC 1																
Any PT	Any Severity															
	Mild															
	Moderate															
	Severe															
[PT 1]																
Etc.																
Repeat for other reported SOCs																
Any PT																
[PT 1]																
etc																

Note: Includes all AEs post-dose 3 and prior to dose 4, or within 7 days of dose 3 if dose 4 not received.
N = Number of subjects in the safety population who received the specified dose; n = number of subjects experiencing an AE within the SOC and PT combination. Severity is the maximum severity reported post dosing for each subject for each SOC and PT combination.

Tables with similar format:

Table 69: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Post-Dose 4 by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

Table 70: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Through 28 Days Post-Dose 4 by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

[Implementation note: Includes all AEs reported following each dose and no later than 28 days following dose 4. If a subject does not receive a dose, then events only through 7 days following the last dose received will be included.]

Related AEs:

Table 71: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Related to Study Product Post-Dose 1 and Prior to Dose 2, by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

Table 72: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Related to Study Product Post-Dose 2 and Prior to Dose 3, by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

Table 73: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Related to Study Product Post-Dose 3 and Prior to Dose 4, by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

Table 74: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Related to Study Product Post-Dose 4 by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

Table 75: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Related to Study Product Through 28 Days Post-Dose 4, by MedDRA System Organ Class, Preferred Term, and Severity - Safety Population*

[Implementation note: Includes all AEs reported following each dose and no later than 28 days following dose 4. If a subject does not receive a dose, then events only through 7 days following the last dose received will be included.]

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 76: Listing of Serious Adverse Events*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

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	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Subject ID: , Vaccination Group: , AE Number:												
Comments:												
Subject ID: , Vaccination Group: , AE Number:												
Comments:												

Table 77: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

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

Table 78: Listing of Other Significant Adverse Events*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date. Events will include, but are not limited to, AEs leading to subject withdrawal, study drug interruption or discontinuation, and new onset chronic medical conditions.]

Adverse Event	Number of Doses Received at Time of Event	No. of Days Post Associated Dose	Duration of Event	Severity	MedDRA System Organ Class	NOCMC?	Relationship	Outcome
Subject ID: , Vaccination Group: , AE Number:								
Comments:								
Subject ID: , Vaccination Group: , AE Number:								
Comments:								

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 79: Listing of Abnormal Laboratory Results of Grade 1 or Greater – Chemistry*

Subject ID	Vaccination Group	Sex	Age (Years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

Table with similar format:

Table 80: Listing of Abnormal Laboratory Results of Grade 1 or Greater – Hematology*

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 81: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group - Any Chemistry Parameter*

Time Point	Vaccination Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Any Severity	
			n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Baseline (Pre-Dose 1)	Low Dose ChAd155-RG	x	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)
	High Dose ChAd155-RG (x1)											
	High Dose ChAd155-RG (x2)											
	Combined High Dose[a] ChAd155-RG											
	RABAVERT											
	Total											
Repeat for:												
Day 2 (1 Day Post Dose 1)												
Day 8 (Pre-Dose 2)												
Day 16 (2 Days Post Dose 3)												
Day 22 (Pre-Dose 4)												
Max Severity Post Baseline												

Note: The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in the Safety Population; n = number of subjects with laboratory values in the respective category.
[a] Both high dose groups combined.

Tables with similar format:

Abnormal Labs Related to Study Product:

Table 87: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Any Chemistry Parameter

Table 88: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - AST

Table 89: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - ALT

Table 90: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Total Bilirubin

Table 91: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Blood Urea Nitrogen

Table 92: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Creatinine

Table 93: Laboratory Summary Statistics by Time Point and Vaccination Group - AST

	Vaccination Group	N	Mean	Standard Deviation	Median	Min, Max
Baseline						
Results	Low Dose ChAd155-RG	x	xx.x	xx.x	xx.x	xx, xx
	High Dose ChAd155-RG (x1)					
	High Dose ChAd155-RG (x2)					
	Combined High Dose[a] ChAd155-RG					
	RABAVERT					
	Total					
Day 2 (1 Day Post Dose 1)						
Results	Low Dose ChAd155-RG					
	High Dose ChAd155-RG (x1)					
	High Dose ChAd155-RG (x2)					
	Combined High Dose[a] ChAd155-RG					
	RABAVERT					
	Total					
Change from baseline	Low Dose					
	High Dose ChAd155-RG (x1)					
	High Dose ChAd155-RG (x2)					
	Combined High Dose[a] ChAd155-RG					
	RABAVERT					
	Total					
Repeat for						
Day 8 (Pre-Dose 2)						
Day 16 (2 Days Post Dose 3)						
Day 22 (Pre-Dose 4)						
Max Severity Post Baseline						

Note: N = Number of subjects in the Safety Population with available results at specified time point.
[a] Both high dose groups combined.

Tables with similar format:

14.3.5.2 Hematology Results

Table 98: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group - Any Hematology Parameter*

Time Point	Vaccination Group	N	None		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Any Severity	
			n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Baseline (Pre-Dose 1)	Low Dose ChAd155-RG	x	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)
	High Dose ChAd155-RG (x1)											
	High Dose ChAd155-RG (x2)											
	Combined High Dose[a] ChAd155-RG											
	RABAVERT											
	Total											
Repeat for:												
Day 2 (1 Day Post Dose 1)												
Day 8 (Pre-Dose 2)												
Day 16 (2 Days Post Dose 3)												
Day 22 (Pre-Dose 4)												
Max Severity Post Baseline												

Note: The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in the Safety Population; n = number of subjects with laboratory values in the respective category.
[a] Both high dose groups combined.

Table 99: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group – WBC*

Time Point and Vaccination Group		Overall						Abnormal Low						Abnormal High					
	Missing	Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Mild/ Grade 1		Moderate/ Grade 2		Severe/ Grade 3	
	n (%)	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Baseline (Pre-Dose 1)																			
Low Dose ChAd155-RG (N = X)	x (xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)	x (xx)	(xx, xx)
High Dose ChAd155-RG (x1) (N = X)																			
High Dose ChAd155-RG (x2) (N = X)																			
Combined High Dose[a] ChAd155-RG																			
RABAVERT (N=X)																			
Total																			
Repeat for:																			
Day 2 (1 Day Post Dose 1)																			
Dose 8 (Pre-Dose 2)																			
Day 16 (2 Days Post Dose 3)																			
Day 22 (Pre-Dose 4)																			
Max Severity Post Baseline																			

Note: The "Max Post Baseline" rows indicate the maximum severity of abnormal laboratory results experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in the Safety Population; n = number of subjects with laboratory values in the respective category.
[a]Both high dose groups combined.

Tables with similar format to Table 99:

Table 100: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group – Platelets*

Tables with similar format to Table 98:

Table 101: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group – Hemoglobin*

Table 102: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group - Absolute Lymphocyte Count*

Table 103: Abnormal Laboratory Results by Maximum Severity, Time Point, and Vaccination Group - Absolute Neutrophil Count*

Abnormal Labs Related to Study Product – Excluding Baseline
Table with similar format to Table 98:

Table 104: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Any Hematology Parameter

Table with similar format to Table 99:

Table 105: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - WBC

Table 106: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Platelets

Table with similar format to Table 98:

Table 107: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Hemoglobin

Table 108: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Absolute Lymphocyte Count

Table 109: Abnormal Laboratory Results Related to Study Product by Maximum Severity, Time Point, and Vaccination Group - Absolute Neutrophil Count

Tables with similar format as Table 93:

14.3.6 Displays of Vital Signs

Table 115: Vital Signs by Maximum Severity, Time Point, and Vaccination Group - Any Vital Sign Parameter*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Time Point and Vaccination Group	N	None n (%)	Mild/ Grade 1 n (%)	Moderate/ Grade 2 n (%)	Severe/ Grade 3 n (%)	Any Severity n (%)
Baseline (Pre-Dose 1)						
Low Dose ChAd155-RG	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
High Dose ChAd155-RG (x1)						
High Dose ChAd155-RG (x2)						
Combined High Dose [a] ChAd155-RG						
RABAVERT						
Total						
Day 2 (1 Day Post Dose 1)						
Low Dose ChAd155-RG						
High Dose ChAd155-RG (x1)						
High Dose ChAd155-RG (x2)						
Combined High Dose [a] ChAd155-RG						
RABAVERT						
Total						
Repeat for						
Day 8 (Pre-Dose 2)						
Day 15 (Pre-Dose 3)						
Day 16 (2 Days Post Dose 3)						
Day 22 (Pre-Dose 4)						
Day 29 (7 Days Post-Dose 4)						
Day 91 (69 Days Post-Dose 4)						
Day 181 (159 Days Post-Dose 4)						

Time Point and Vaccination Group	N	None n (%)	Mild/ Grade 1 n (%)	Moderate/ Grade 2 n (%)	Severe/ Grade 3 n (%)	Any Severity n (%)
Day 381 (359 Days Post-Dose 4)						
Max Severity Post Baseline						

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in the Safety Population; n = number of subjects with vital signs values in the respective category.
Any vital sign includes heart rate, systolic and diastolic BP and temperature.
[a] Both high dose groups combined.

Table 116: Vital Signs by Maximum Severity, Time Point, and Vaccination Group - Heart Rate (Pulse)*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Time Point and Vaccination Group	N	Any Severity n (%)	Overall			Bradycardia			Tachycardia		
			Mild/ Grade 1 n (%)	Moderate/ Grade 2 n (%)	Severe/ Grade 3 n (%)	Mild/ Grade 1 n (%)	Moderate/ Grade 2 n (%)	Severe/ Grade 3 n (%)	Mild/ Grade 1 n (%)	Moderate/ Grade 2 n (%)	Severe/ Grade 3 n (%)
Baseline (Pre-Dose 1)											
Low Dose ChAd155-RG	x	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)	x (xx)
High Dose ChAd155-RG (x1)											
High Dose ChAd155-RG (x2)											
Combined High Dose[a] ChAd155-RG											
RABAVERT											
Total											
Repeat for:											
Day 2 (1 Day Post Dose 1)											
Day 8 (Pre-Dose 2)											
Day 15 (Pre-Dose 3)											
Day 16 (2 Days Post Dose 3)											
Day 22 (Pre-Dose 4)											
Day 29 (7 Days Post-Dose 4)											
Day 91 (69 Days Post-Dose 4)											
Day 181 (159 Days Post-Dose 4)[a]											
Day 381 (359 Days Post-Dose 4)											
Max Severity Post Baseline											

Notes: The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.
N = Number of subjects in the Safety Population. n = Number of subjects with vital signs values in the respective category.
[a] Both high dose groups combined.

Tables with similar format: (Overall/Hypotension/Hypertension)

Table 117: Vital Signs by Maximum Severity, Time Point, and Vaccination Group - Systolic Blood Pressure*

Table 118: Vital Signs by Maximum Severity, Time Point, and Vaccination Group - Diastolic Blood Pressure*

Tables with similar format as Table 115:

Table 119: Vital Signs by Maximum Severity, Time Point, and Vaccination Group – Fever*

14.4 Summary of Concomitant Medications

Table 120: Number and Percentage of Subjects Taking Prior Medications by WHO Drug Classification and Vaccination Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Low Dose ChAd155-RG (N=X)		High Dose ChAd155-RG (x1) (N=X)		High Dose ChAd155-RG (x2) (N=X)		RABAVERT (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]										
	[ATC 2 - 1]										
	[ATC 2 - 2]										
	[ATC 2 - 3]										
[ATC Level 1 – 2]	[ATC 2 - 1]										
	[ATC 2 - 2]										
	[ATC 2 - 3]										

N= Number of subjects in the Safety Population; n = number of subjects reporting taking at least one medication in the specific WHO Drug Class
Includes medications started prior to enrollment.

Table with similar format:

Table 121: Number and Percentage of Subjects Taking Concomitant Medications by WHO Drug Classification and Vaccination Group

[Implementation Note: Includes medications started after enrollment.]

APPENDIX 2. FIGURE MOCK-UPS

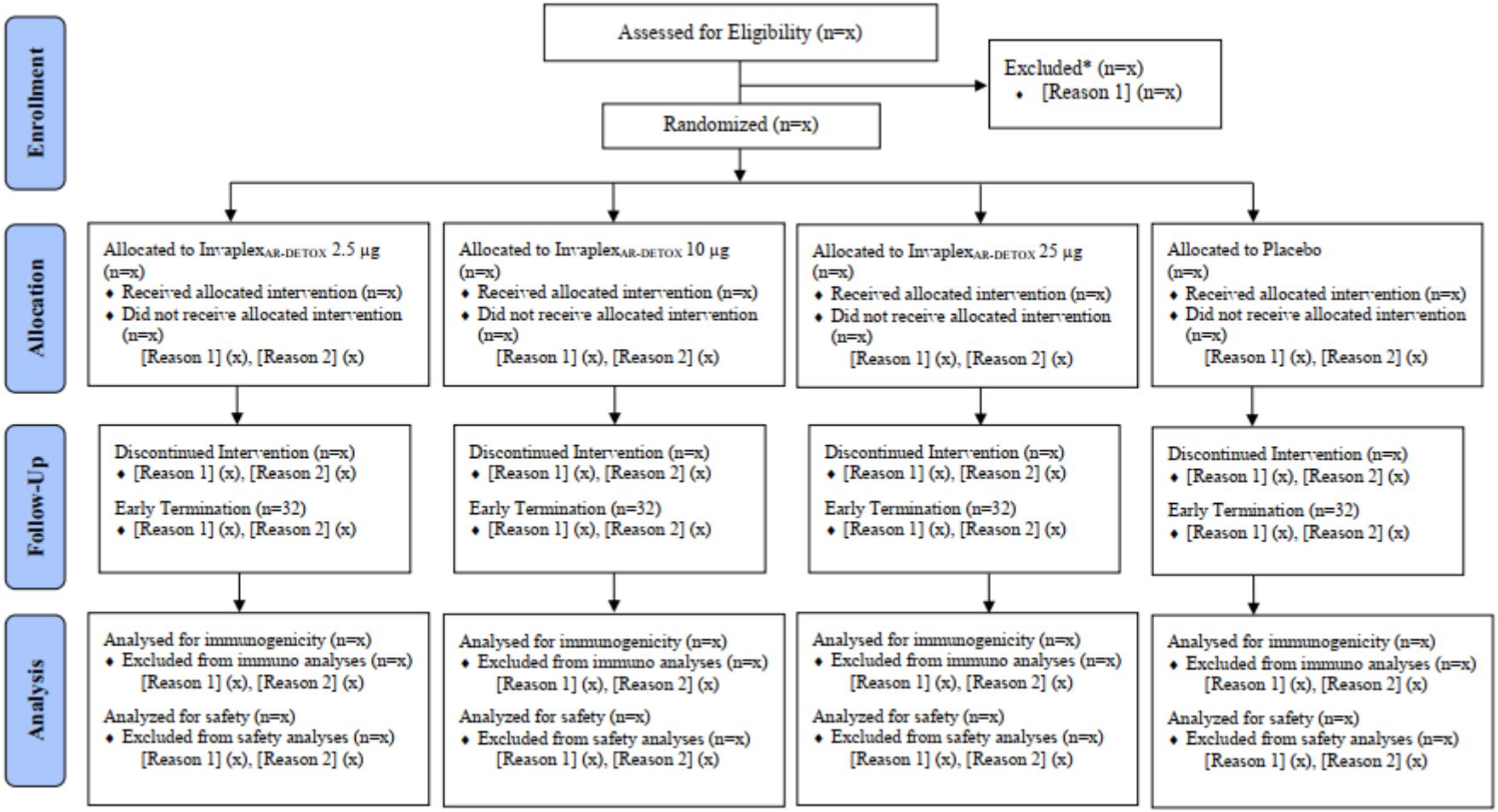
LIST OF FIGURES

[Implementation note: figures to be included in the interim analysis are noted with an asterisk, '*']

10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram

[Implementation note: A generic figure is shown. The 4 columns will represent study groups A – D.]



14.2.2 Immunogenicity Response Figures by Measure, Vaccination, and Time Point

Figure 2: Reverse Cumulative Distribution of Rabies Neutralizing Antibodies (VNA) by Time Point and Vaccination Group - Modified Intent to Treat Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed. Prior to day 22 the high dose groups are the same, so results are combined. All scheduled time points will be presented in actual figure.]

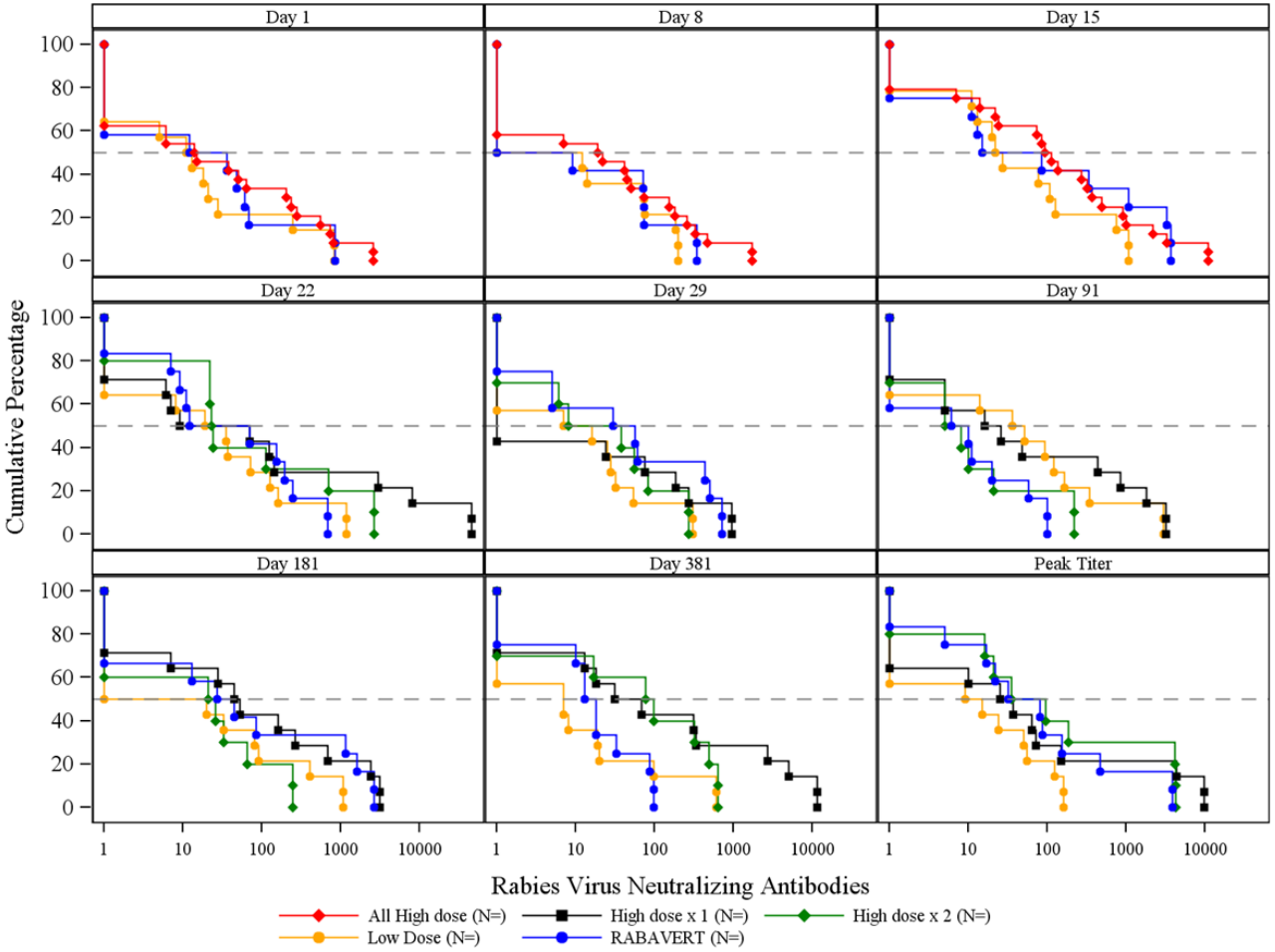
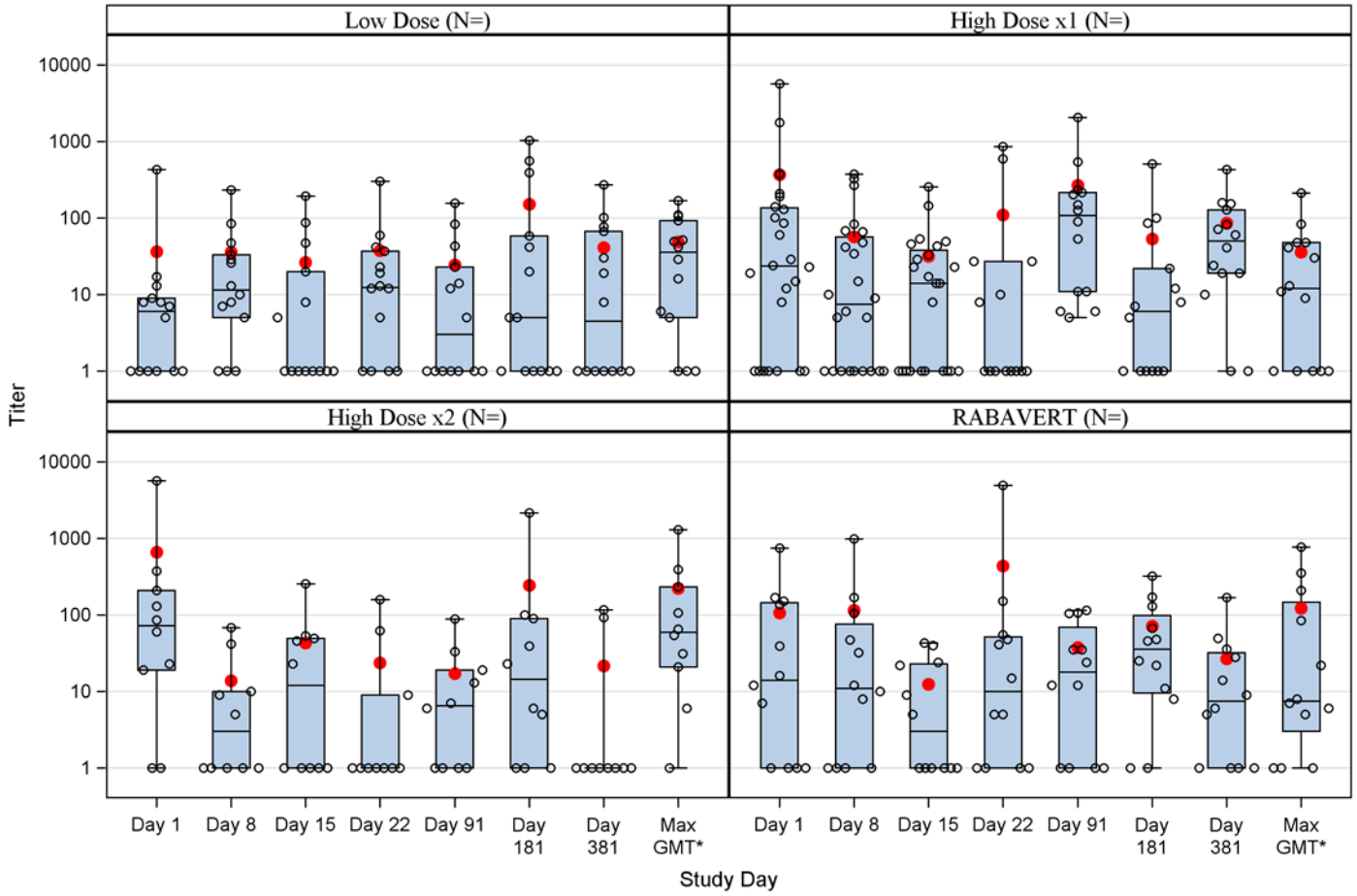


Figure with Similar Format:

Figure 3: Reverse Cumulative Distribution of Rabies Neutralizing Antibodies (VNA) by Time Point and Vaccination Group - Per Protocol Population

Figure 4: Rabies VNA Titer Over Time by Vaccination Group - Modified Intent to Treat Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed and individual observations will be excluded. Prior to day 22 the high dose groups are the same, so results are combined. All scheduled time point will be presented in actual figure.]



Red dot = Mean. Horizontal line within a box = Median
Box represents 25th and 75th percentiles (i.e., 50% of the observations).
Whiskers extend to the minimum and maximum values.
* Maximum post-baseline response.

Figure with Similar Format:

Figure 5: Rabies VNA Titer Over Time by Vaccination Group – Per Protocol Population

Figure 6: Rabies VNA Geometric Mean Titer and 95% CI Over Time Point by Vaccination Group - mITT Population*

Implementation note: an example figure is shown below. The x-axis will include all study days for which RFFIT titer data is available, along with an "Any Time" at end of x-axis that represents the peak titers for each subject across all post-baseline visits. Different colors and symbols will be used for each study arm representing each individual titer value. The GMT will be represented as a black diamond and 95% CIs by black error bars. The y-axis label should be "RFFIT Geometric Mean Titer (IU/mL)" and the x-axis label should be "Study Visit Day". A black dotted reference line will be drawn to represent the LLOQ of the RFFIT assay and a grey dashed reference line will represent the seroconversion titer limit of 0.5 IU/mL. "All High Dose" study arm data will be included but only up to Day 22.

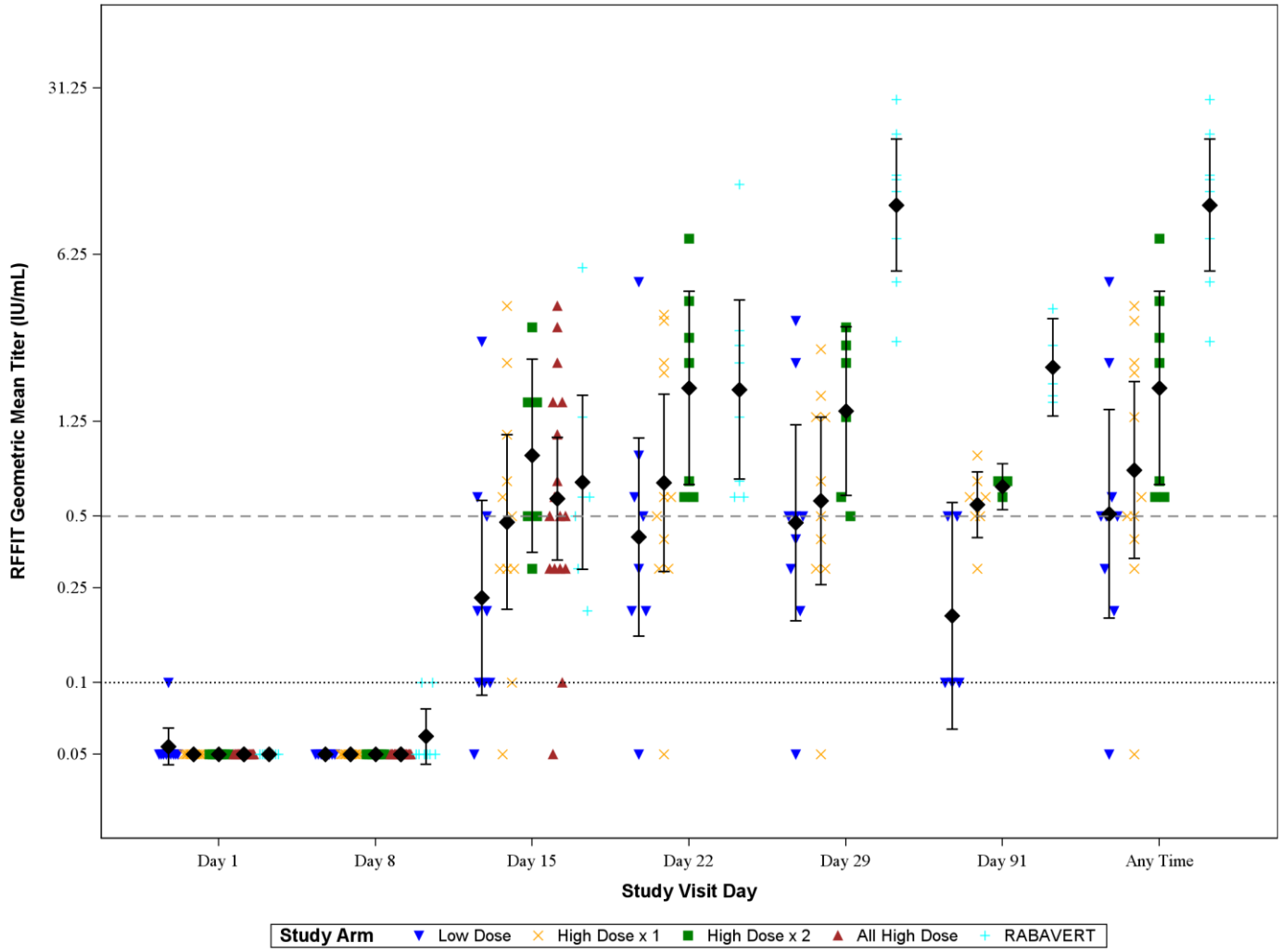
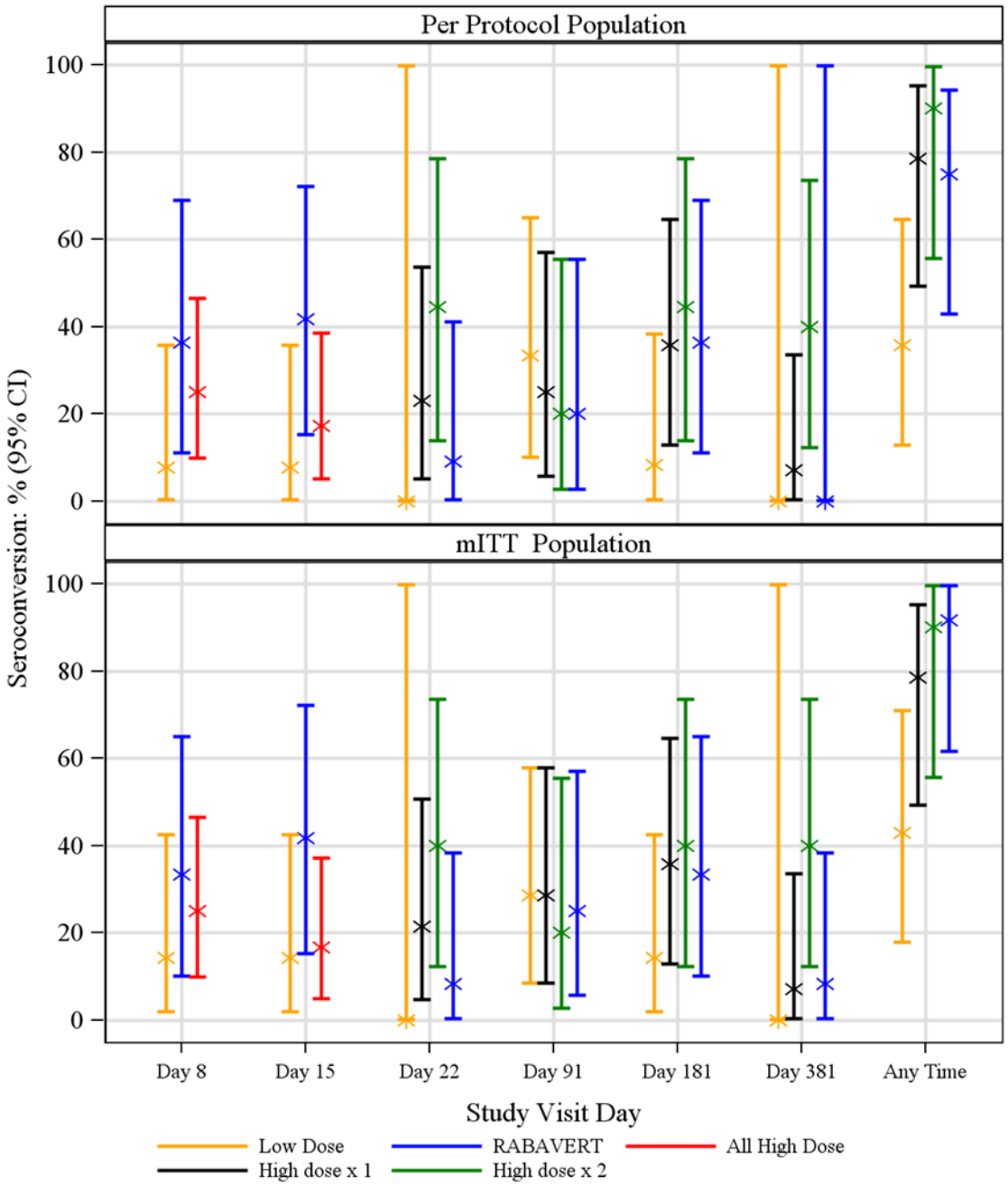


Figure with Similar Format:

Figure 7: Rabies VNA Geometric Mean Titer and 95% CI Over Time Point by Vaccination Group - Per Protocol Population

Figure 8: Proportion of Subjects Seroconverting to Rabies Virus by Time Point and Vaccination Group - Modified Intent to Treat Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed. Seroconversion is a post-vaccination serum antibody level > 0.5 IU/mL.]



Asterisks = Proportion (%) of seroconverters.
Bars represent the exact, Clopper-Pearson, 95% CIs.
Any Time indicates proportion who seroconverted at any time.

Figure with similar format:

Figure 9: Proportion of Subjects Seroconverting to Rabies Virus by Time Point and Vaccination Group – Per Protocol Population

14.3.1.1 Solicited Adverse Events

Figure 10: Maximum Severity Per Subject Over All Solicited Systemic Symptoms by Day (Post Dose 1) - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

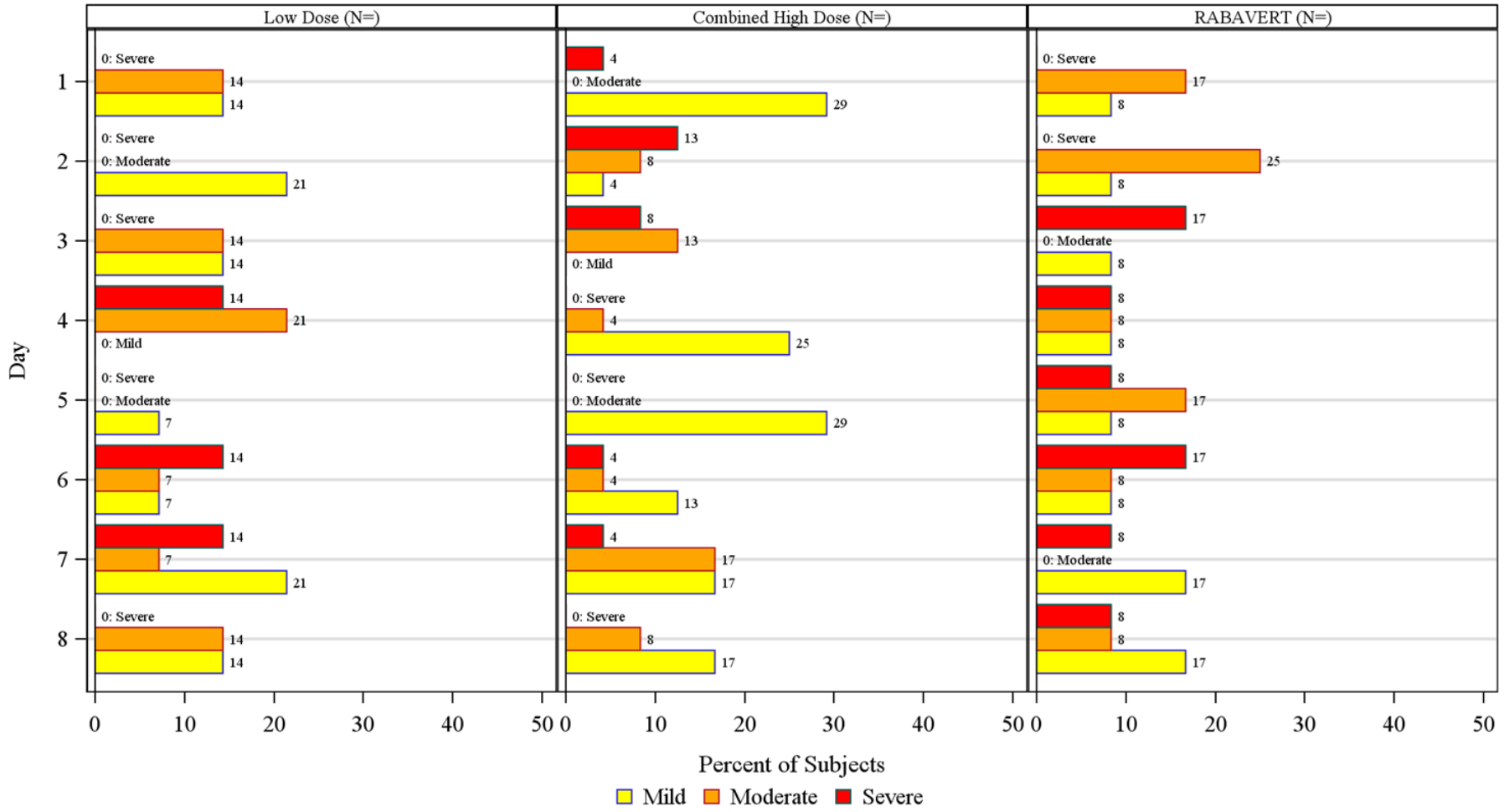


Figure 11: Maximum Severity Per Subject Over All Solicited Systemic Symptoms by Day (Post Dose 2) - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

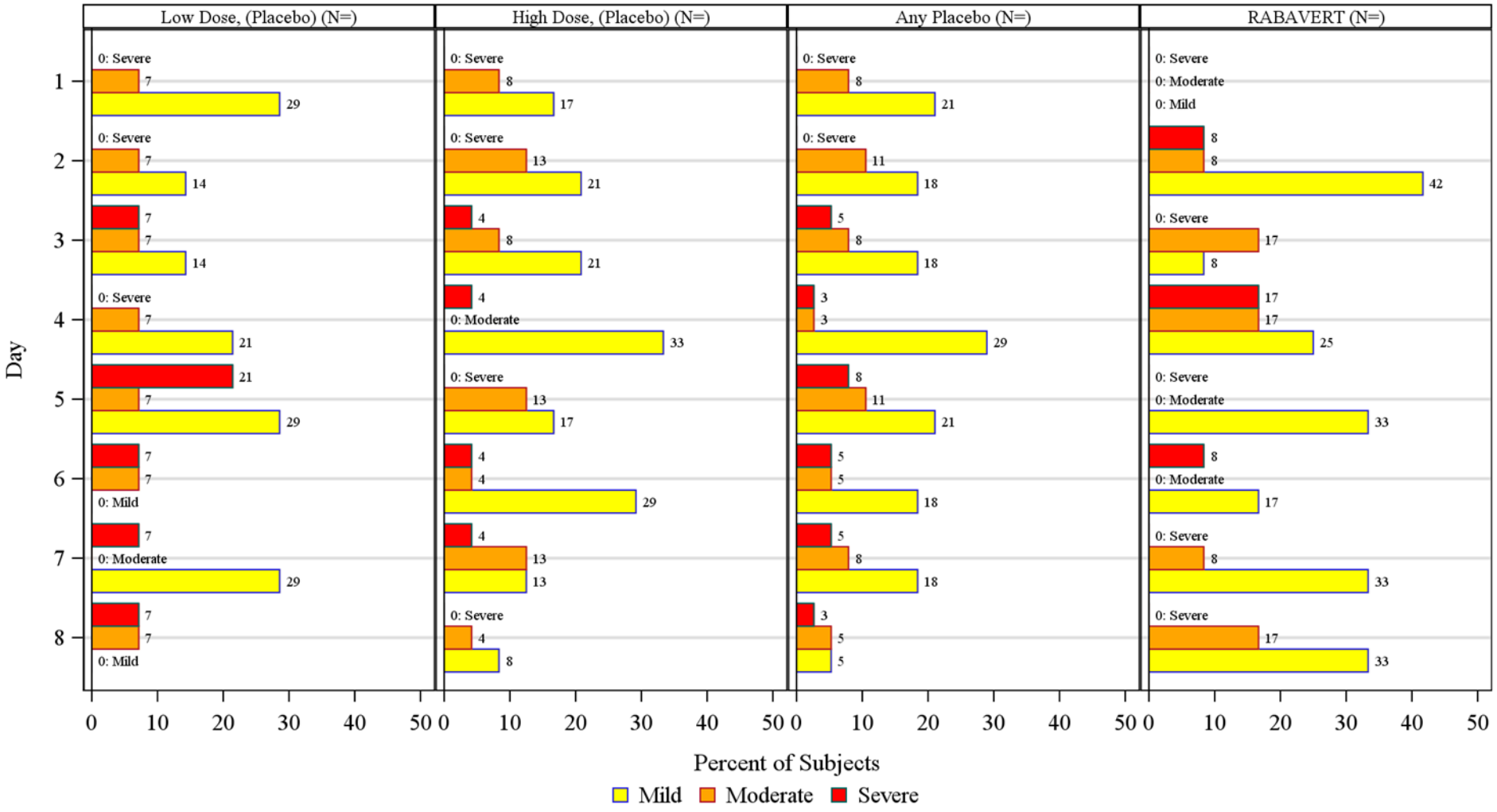


Figure 12: Maximum Severity Per Subject Over All Solicited Systemic Symptoms by Day (Post Dose 3) - Safety Population*

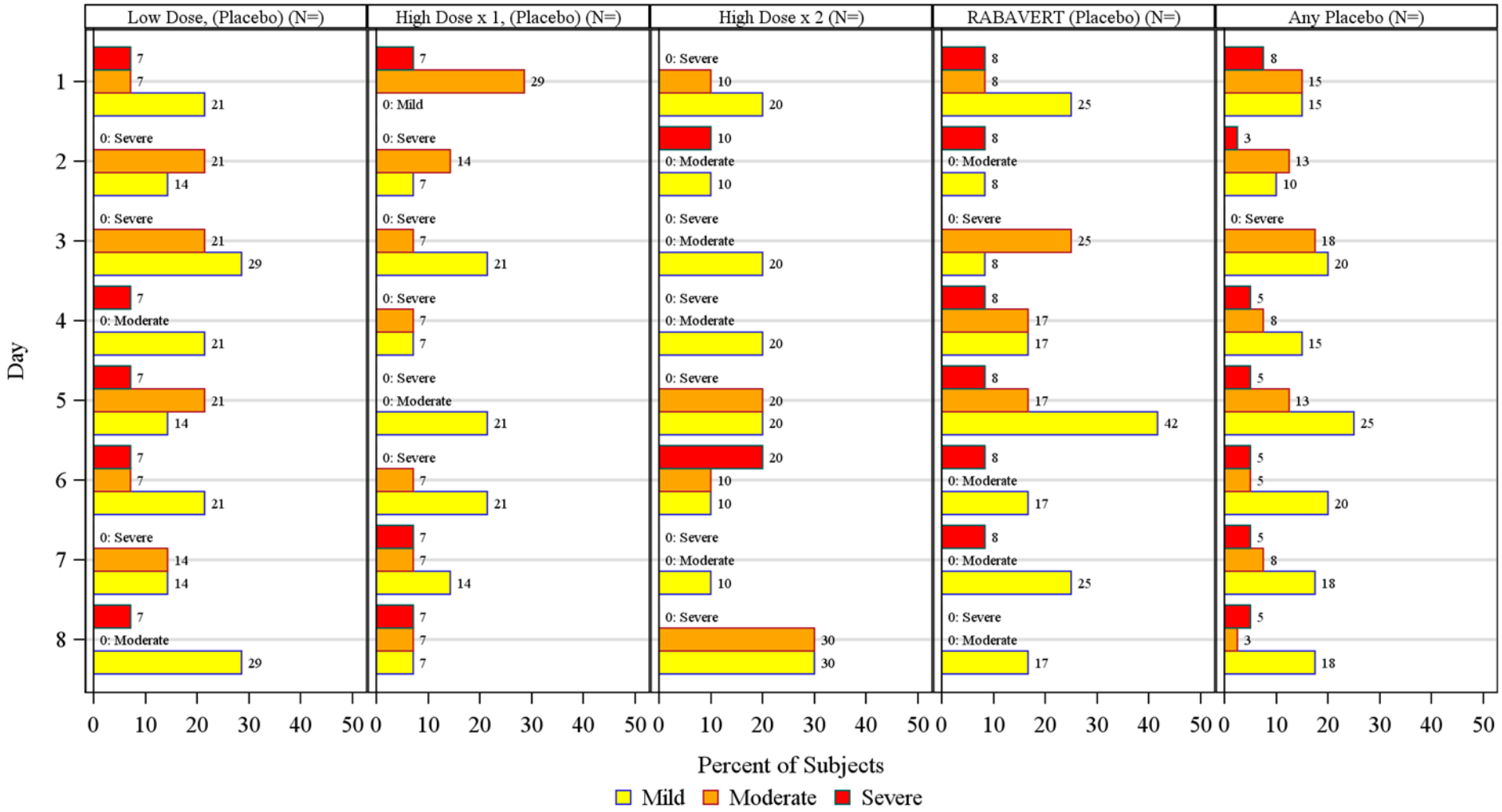


Figure 13: Maximum Severity Per Subject Over All Solicited Systemic Symptoms by Day (Post Dose 4) - Safety Population*

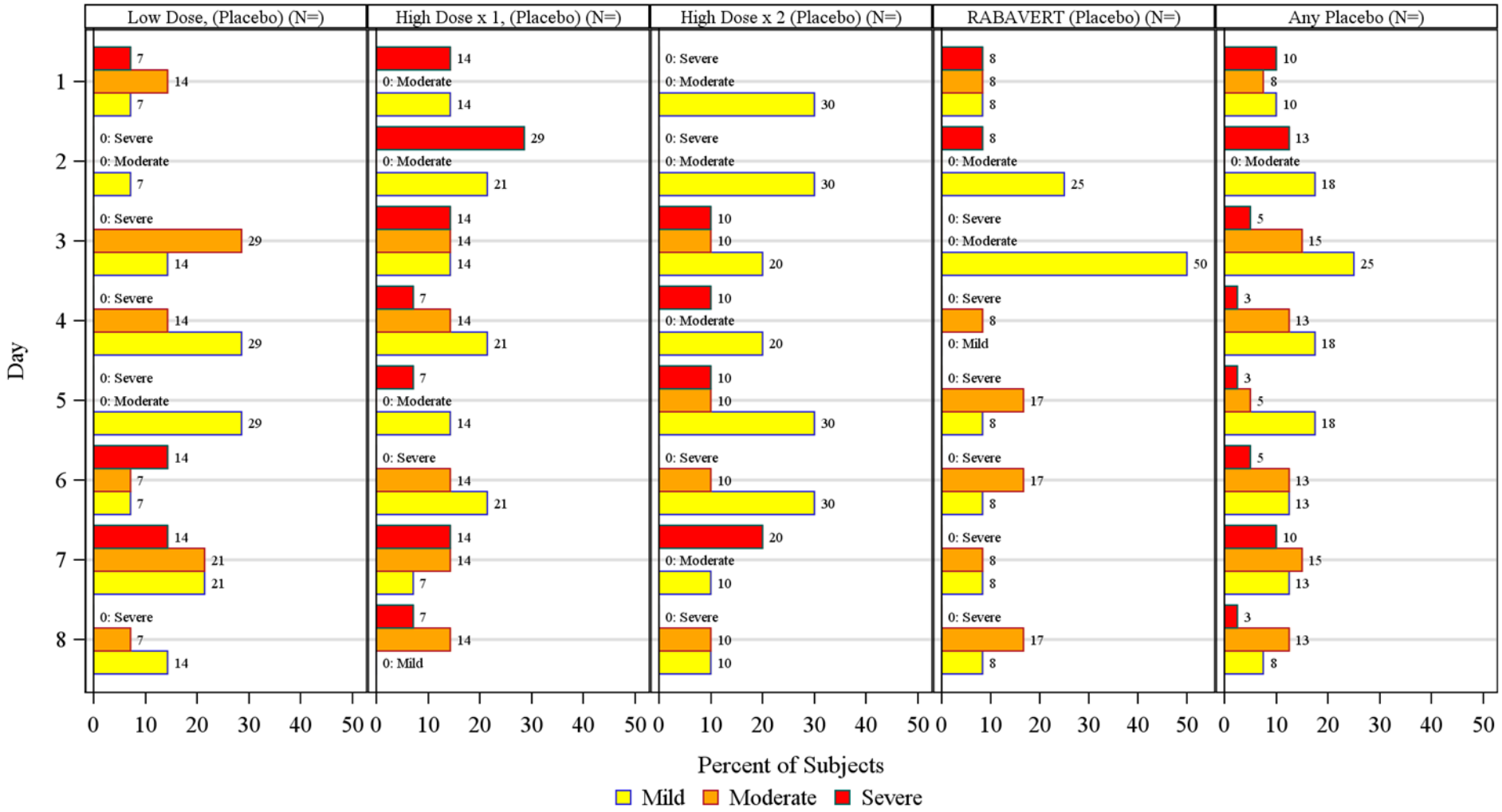
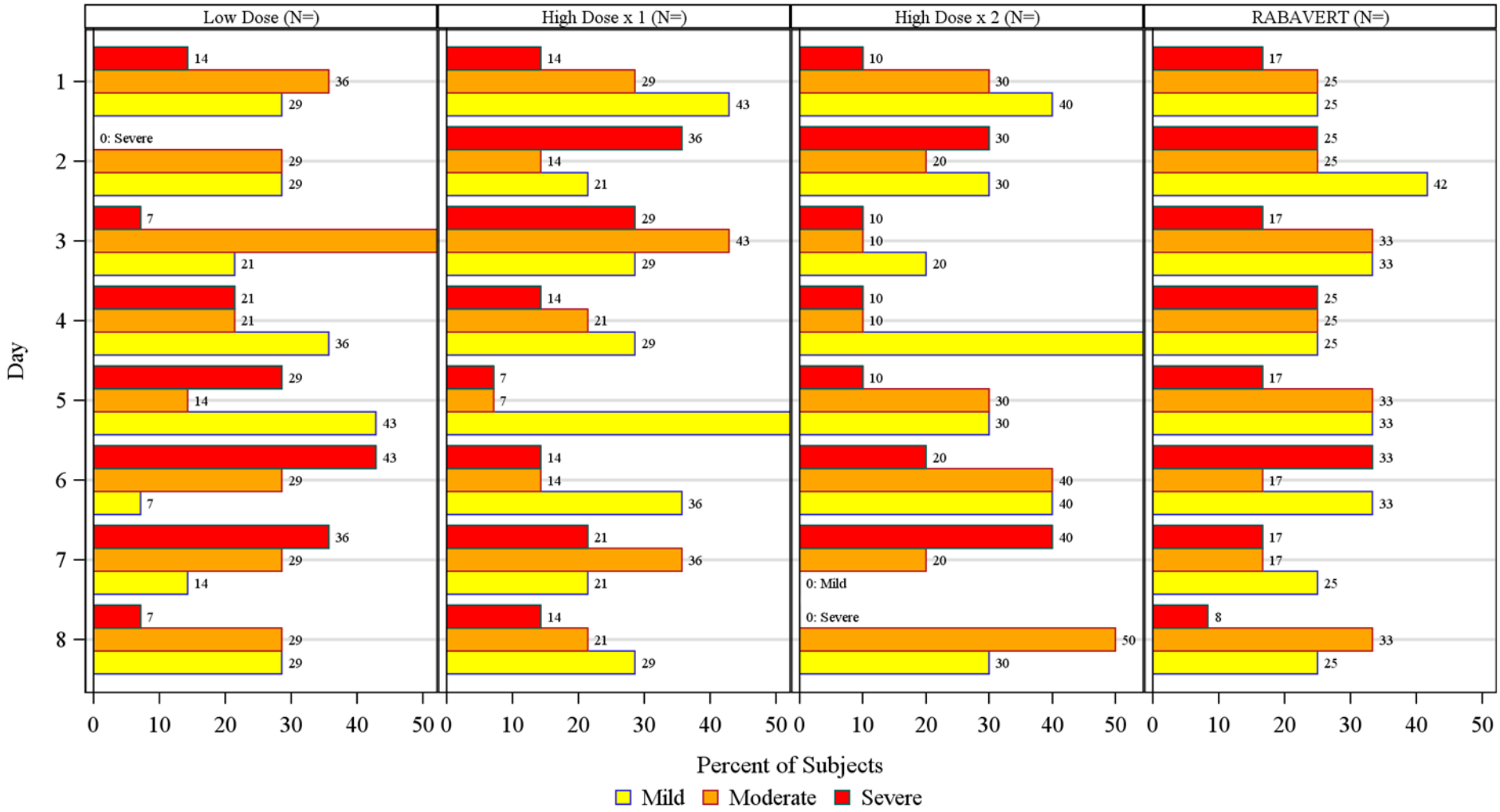


Figure 14: Maximum Severity Per Subject Over All Solicited Systemic Symptoms by Day (Post Any Dose) - Safety Population*



Local Reactions

Similar Formats to Figures 10 to 14, respectively:

Figure 15: Maximum Severity Per Subject Over All Solicited Local Symptoms by Day (Post Dose 1) - Safety Population*

Figure 16: Maximum Severity Per Subject Over All Solicited Local Symptoms by Day (Post Dose 2) - Safety Population*

Figure 17: Maximum Severity Per Subject Over All Solicited Local Symptoms by Day (Post Dose 3) - Safety Population*

Figure 18: Maximum Severity Per Subject Over All Solicited Local Symptoms by Day (Post Dose 4) - Safety Population*

Figure 19: Maximum Severity Per Subject Over All Solicited Local Symptoms by Day (Post Any Dose) - Safety Population*

14.3.1.2 Unsolicited Adverse Events

Figure 20: Frequency of Adverse Events Related to Study Product Post Dose 1 and Prior to Dose 2, or Through Day 8 Post Dose 1 if Dose 2 Not Received, by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

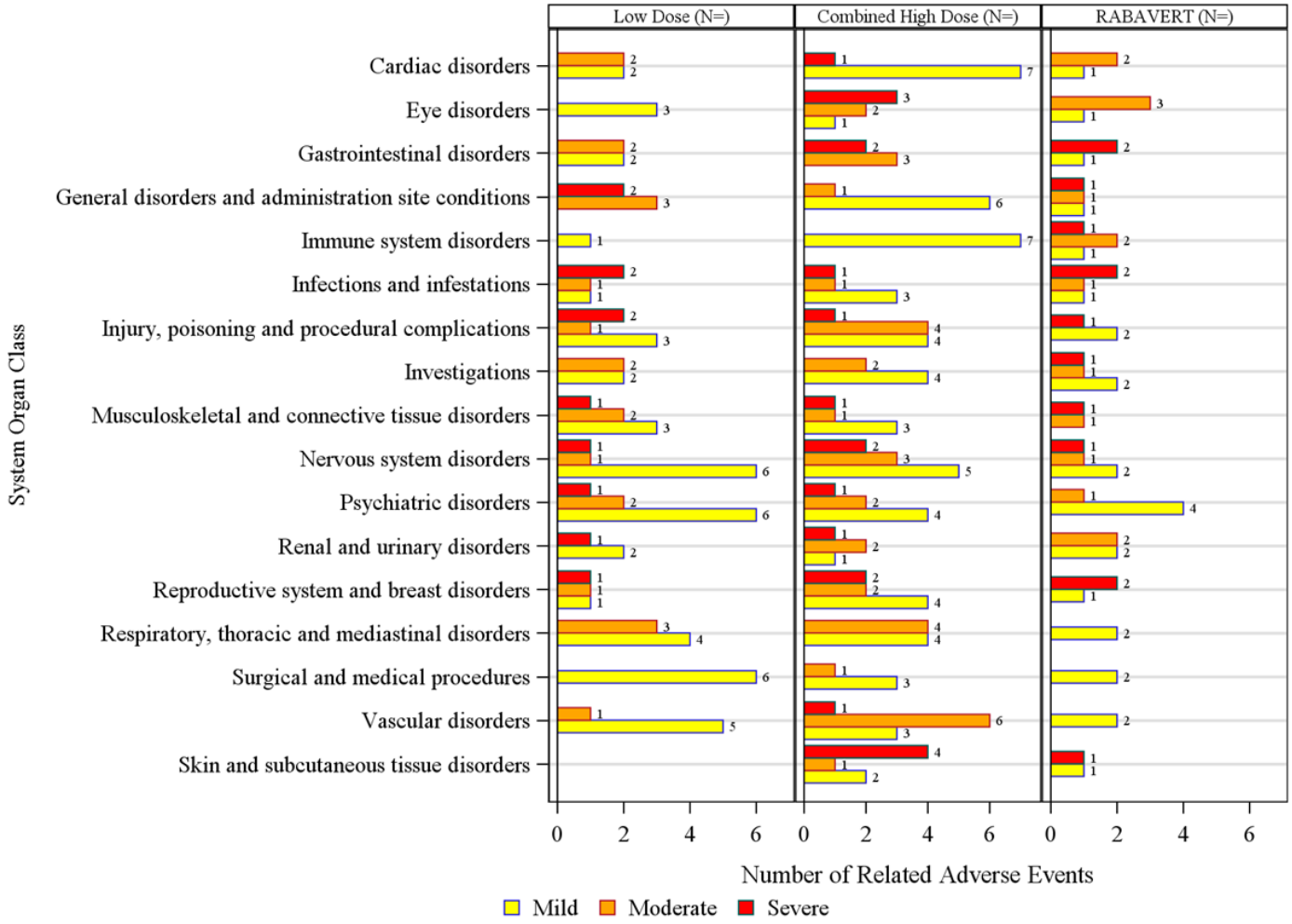


Figure 21: Frequency of Adverse Events Related to Study Product Post Dose 2 and Prior to Dose 3, or Through Day 8 Post Dose 2 if Dose 3 Not Received, by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

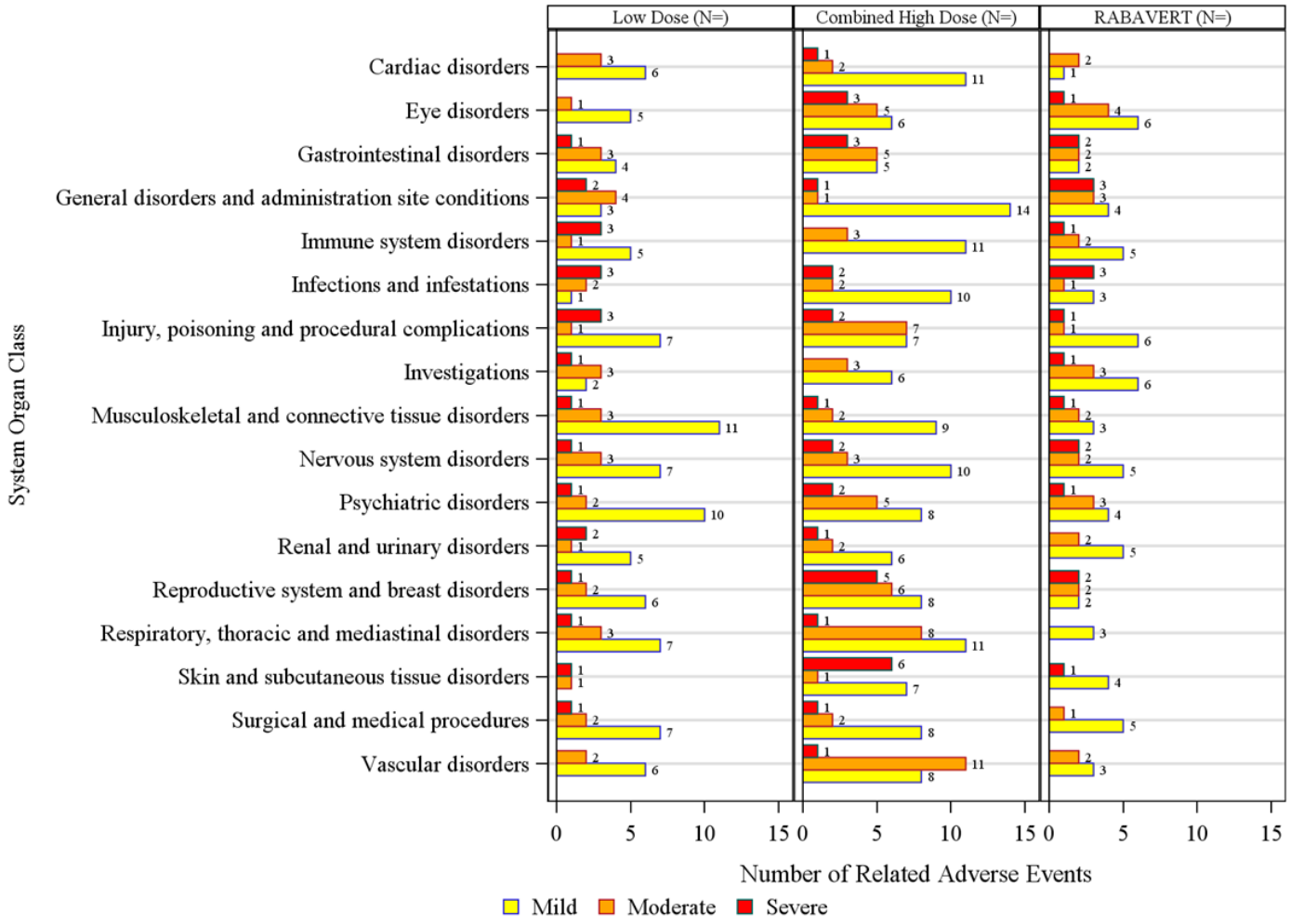
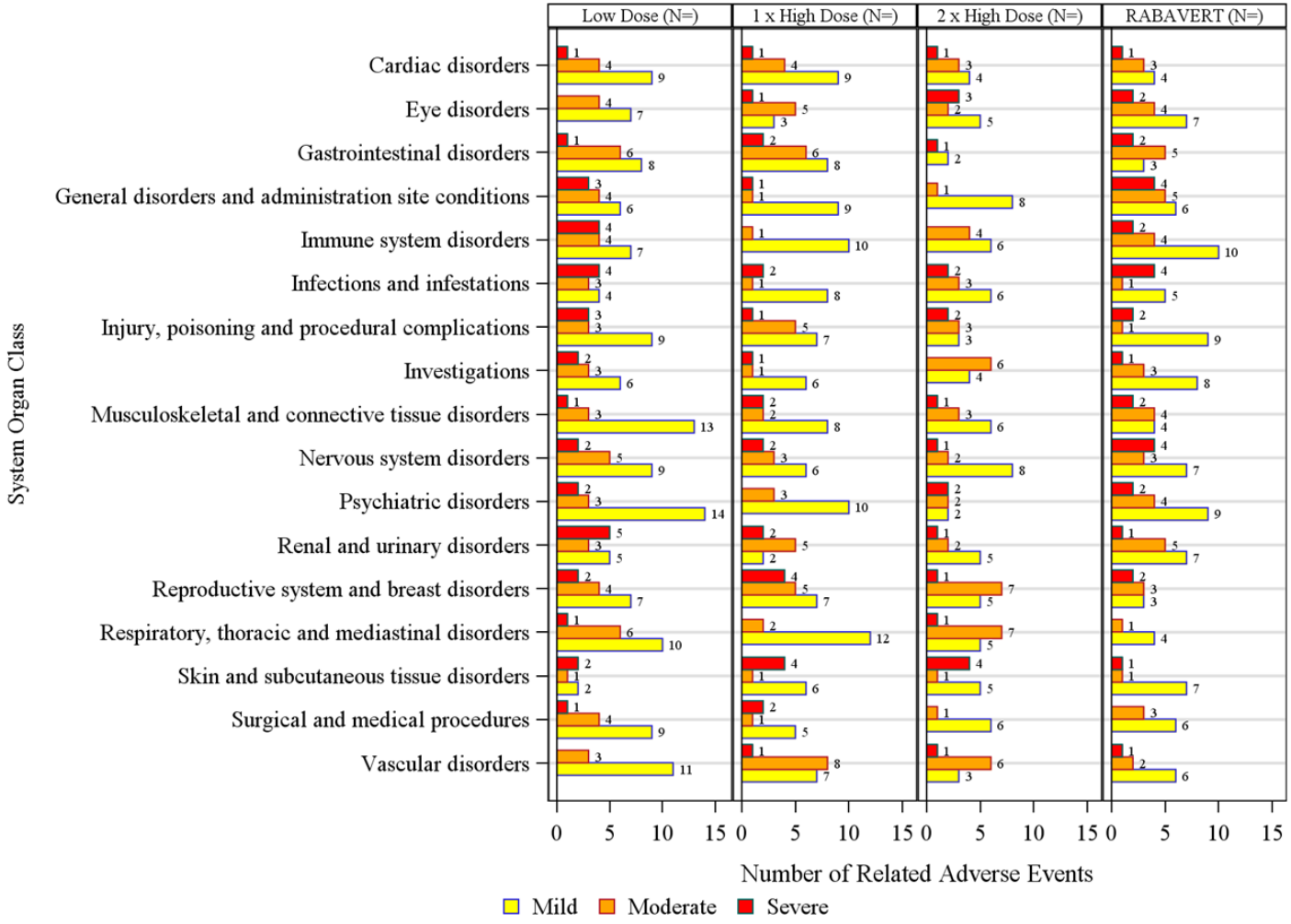


Figure 22: Frequency of Adverse Events Related to Study Product Post Dose 3 and Prior to Dose 4, or Through Day 8 Post Dose 3 if Dose 4 Not Received, by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]



Figures with Similar Format:

Figure 23: Frequency of Adverse Events Related to Study Product Within 28 Days Post Dose 4 by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

Figure 24: Overall Frequency of Adverse Events Related to Study Product From Dose 1 Through 28 Days Post Final Dose by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

Figure 25: Incidence of Adverse Events Related to Study Product Post Dose 1 and Prior to Dose 2, or Through Day 8 Post Dose 1 if Dose 2 Not Received, by MedDRA System Organ Class and Severity*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

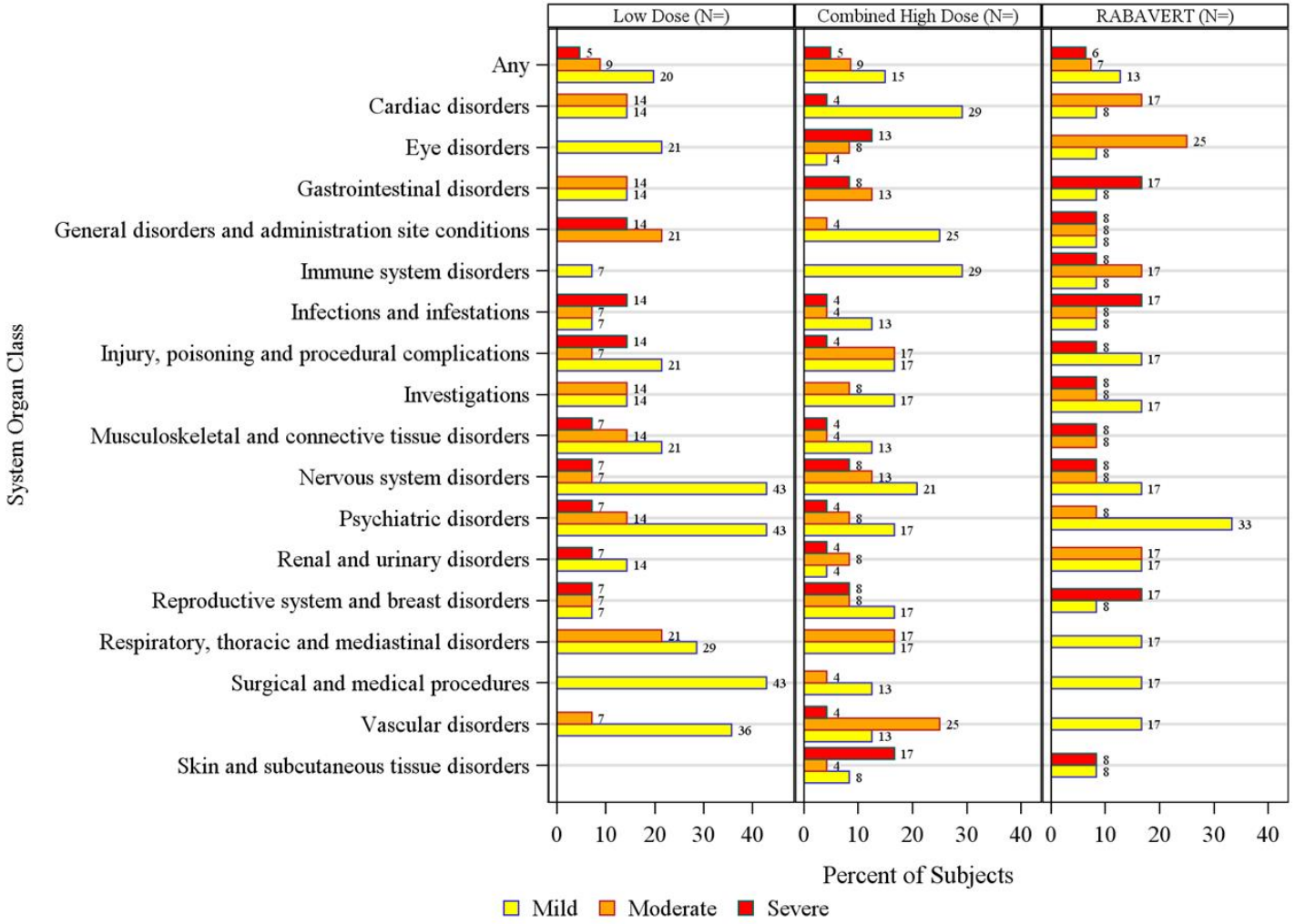


Figure 26: Incidence of Adverse Events Related to Study Product Post Dose 2 and Prior to Dose 3, or Through Day 8 Post Dose 2 if Dose 3 Not Received, by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

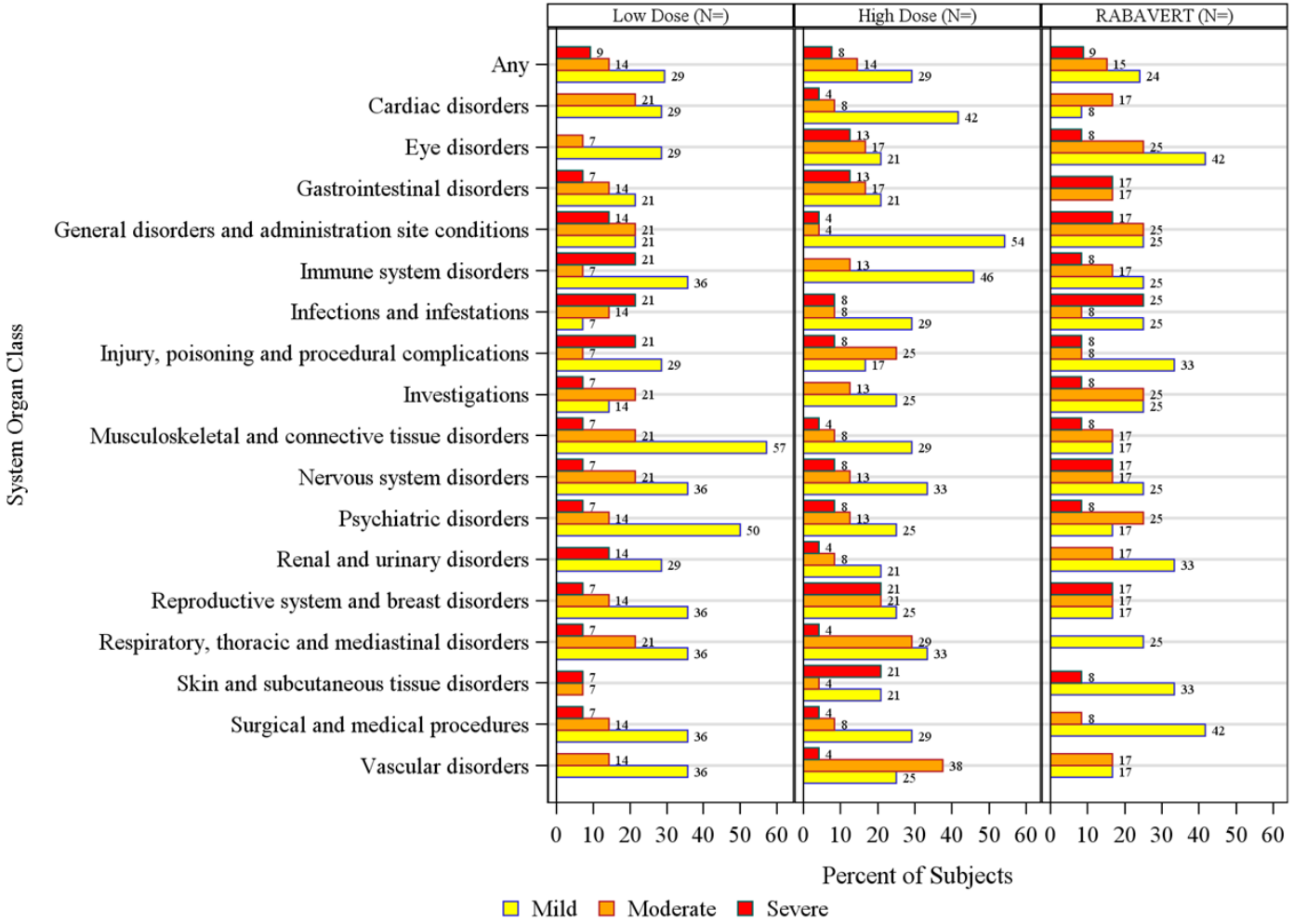


Figure 27: Incidence of Adverse Events Related to Study Product Post Dose 3 and Prior to Dose 4, or Through Day 8 Post Dose 3 if Dose 4 Not Received, by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

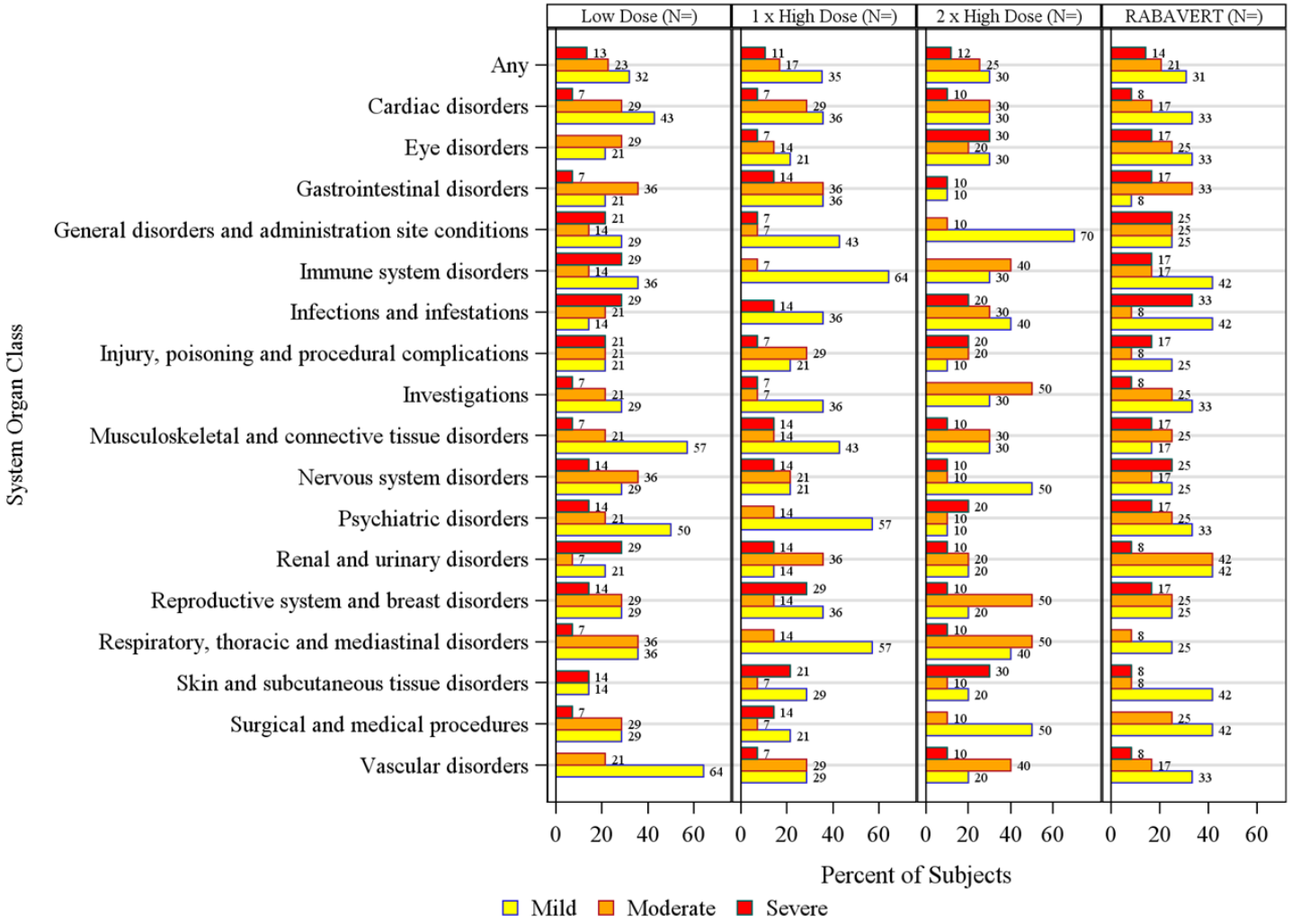


Figure with Similar Format to Figure 23:

Figure 28: Incidence of Adverse Events Related to Study Product Within 28 Days Post-Dose 4 by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

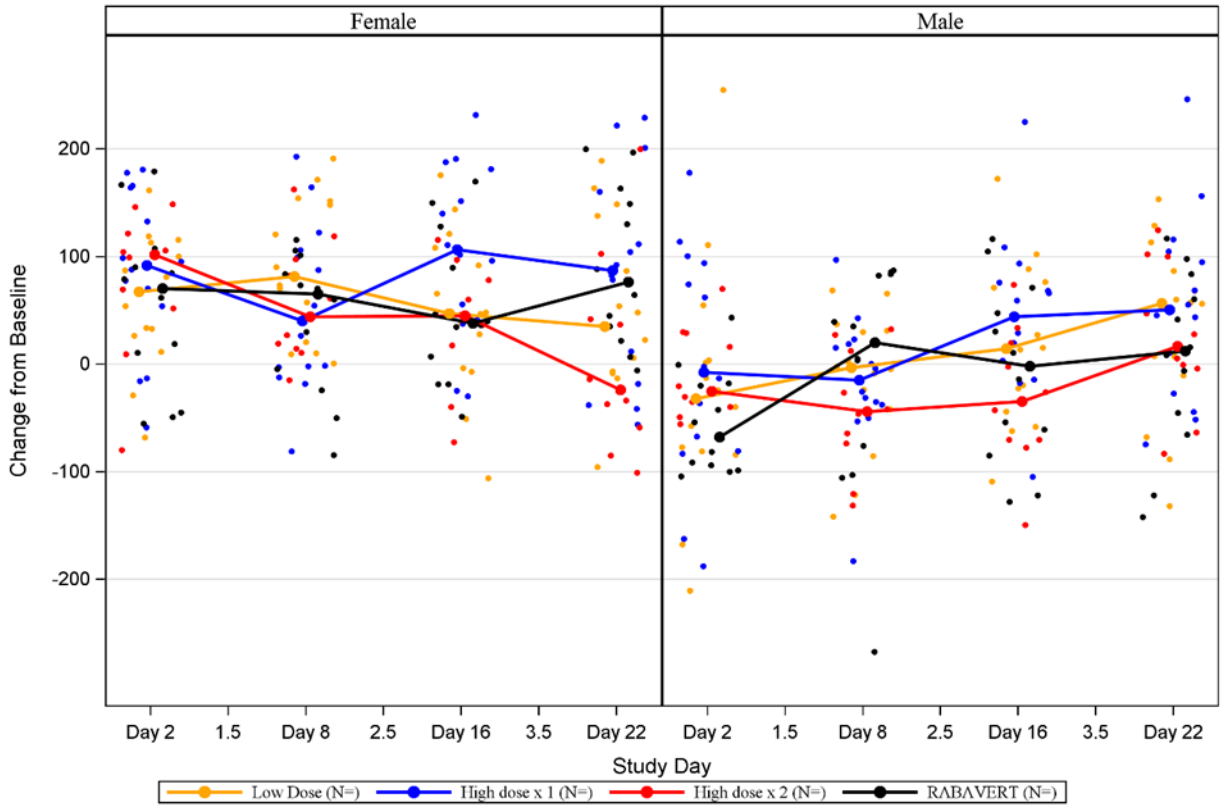
Figure 29: Incidence of Adverse Events Related to Study Product From Dose 1 Through 28 Days Post Final Dose by MedDRA System Organ Class and Severity - Safety Population*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]

14.3.5 Displays of Laboratory Results

Figure 30: Laboratory Results by Scheduled Visits: Median Change from Baseline by Parameter and Vaccination Group – WBC*

[Implementation Note: For preliminary analyses, data collected through the data cut-off date will be displayed.]



Figures with Similar Format:

Figure 31: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter, Sex, and Vaccination Group – Hemoglobin*

Figure 32: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter and Vaccination Group – Platelets*

Figure 33: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter and Vaccination Group - Absolute Lymphocyte Count*

Figure 34: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter and Vaccination Group - Absolute Neutrophil Count*

Figure 35: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter, Sex, and Vaccination Group – AST*

Figure 36: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter, Sex, and Vaccination Group – ALT*

Figure 37: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter and Vaccination Group - Total Bilirubin*

Figure 38: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter and Vaccination Group - Blood Urea Nitrogen*

Figure 39: Laboratory Results by Scheduled Visits: Median Changes from Baseline by Parameter, Sex, and Vaccination Group – Creatinine*

APPENDIX 3. LISTINGS MOCK-UPS

[Implementation note: listings to be included in the interim analysis are noted with an asterisk, '*'. Listings for the interim analysis will be blinded with respect to subject-level treatment assignment.]

LISTINGS

Listing 1: Listing of Subjects Receiving Investigational Product

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

16.2 Database Listings by Subject

[Implementation Note: All listings will be sorted by treatment group, subject id, and visit number or date, whichever is appropriate.]

16.2.1 Discontinued Subjects

Listing 2: 16.2.1: Early Terminations or Discontinued Subjects*

[Implementation Note: For preliminary analyses, blinded data will be reported through the data cut-off date.]

Vaccination Group	Subject ID	Most Recent Dose	Category	Reason for Early Termination or Treatment Discontinuation	Day* Post Most Recent Vaccination

*If on day of most recent vaccination then day=0

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Subject-Specific Protocol Deviations*

[Implementation Note: For preliminary analyses, blinded data will be reported through the data cut-off date.]

Vaccination Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Most Recent Dose	Day* Post Most Recent Vaccination	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

*If on day of most recent vaccination then day=0

Listing 4: 16.2.2.2: Non-Subject-Specific Protocol Deviations*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Immunogenicity Analysis

Listing 5: 16.2.3: Subjects Excluded from Analysis Populations*

[Implementation Note: results will show "Y" if subject excluded. Visit number is only for immunogenicity. Put 'All' if excluded from all visits. Reason excluded could be "Not vaccinated", "Missed Vaccination", "Early termination", "Missing data", etc.

For the interim analysis, this listing will only include information for exclusions from the mITT population and Rabies VNA results.]

			Immunogenicity				
Vaccination Group	**Subject ID**	**Safety**	**Visit Number/Day**	**Rabies VNA**	**T-Cells**	**ICS**	**Reason Subject Excluded**

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographic Data

Vaccination Group	Subject ID	Sex	Age at Enrollment (years)	Height (cm)	Weight (kg)	Ethnicity	Race
Low Dose ChAd155-RG							
Repeat for							
High Dose ChAd155-RG (x1)							
High Dose ChAd155-RG (x2)							
RABAVERT							

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

Vaccination Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term
Low Dose ChAd155-RG							
Repeat for							
High Dose ChAd155-RG (x1)							
High Dose ChAd155-RG (x2)							
RABAVERT							

16.2.5 Compliance

Listing 8: 16.2.5: Compliance

		Study Product and Date Received			
Vaccination Group	**Subject ID**	**Dose 1**	**Dose 2**	**Dose 3**	**Dose 4**
Low Dose ChAd155-RG		**ChAd155-RG**	**Placebo**	**Placebo**	**Placebo**
High Dose ChAd155-RG (x1)		**ChAd155-RG**	**Placebo**	**Placebo**	**Placebo**
High Dose ChAd155-RG (x2)		**ChAd155-RG**	**Placebo**	**ChAd155-RG**	**Placebo**
RABAVERT		**RABAVERT**	**RABAVERT**	**Placebo**	**RABAVERT**

16.2.6 Individual Immunogenicity Response Data

Listing 9: 16.2.6.1: Individual Immunogenicity Response Data - Rabies VNA, IFNγ ELISpot, and MBC ELISpot*

[Implementation Note: For preliminary analyses, blinded RFFIT data will be reported through the data cut-off date.]

Vaccination Group	Subject ID	Planned Study Day	Actual Study Day	Rabies nAb (RFFIT)	IFNγ ELISpots (/10^6 PBMCs)	MBC ELISpots (/10^6 PBMCs)
Low Dose ChAd155-RG						
Repeat for						
High Dose ChAd155-RG (x1)						
High Dose ChAd155-RG (x2)						
RABAVERT						

Listing 10: 16.2.6.2: Individual Immunogenicity Response Data - Percent of Cells Expressing Each Cytokine as Measured by ICS

Vaccination Group	Subject ID	Planned Study Day	Actual Study Day	IFN-γ (%)	IL-2 (%)	TNF-α (%)
Low Dose ChAd155-RG						
Repeat for						
High Dose ChAd155-RG (x1)						
High Dose ChAd155-RG (x2)						
RABAVERT						

16.2.7 Adverse Events

Listing 11: 16.2.7.1: Solicited Events - Systemic Symptoms*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Dose Number	Product Received	Date Received	Post Dose Timepoint[a]	Time Post-Dose (mins)[b]	Ongoing After Day 8[c]	Symptom	Severity	Attributed to Alternate Etiology?[d]	Alternate Etiology
Low Dose ChAd155-RG									
Subject ID									
	Vaccine/Placebo				Yes (stop date)				
Comments:									
High Dose ChAd155-RG (x1)									
High Dose ChAd155-RG (x2)									
RABAVERT									
Subject ID									
Comments:									

[a] If day of vaccination then "Pre-Dose" and "30 mins" are in-clinic assessments, all others are from subject memory aids ("Day 0" is day of vaccination).
[b] Actual time (minutes) post-vaccination for the 30 minute assessments only.
[c] If "Yes" then stop date is included.
[d] Grade 3 events only.

Listing 12: 16.2.7.2: Solicited Events – Local Symptoms*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Dose Number	Product Received	Date Received	Post Dose Timepoint[a]	Time Post-Dose (mins)[b]	Ongoing After Day 8[c]	Symptom	Severity
Low Dose ChAd155-RG							
Subject ID							
	Vaccine/Placebo				Yes (stop date)		
Comments:							
High Dose ChAd155-RG (x1)							
High Dose ChAd155-RG (x2)							
RABAVERT							
Subject ID							
Comments:							

[a] If day of vaccination then "Pre-Dose" and "30 mins" are in-clinic assessments, all others are from subject memory aids ("Day 0" is day of vaccination).
[b] Actual time (minutes) post-vaccination for the 30 minute assessments only.
[c] If "Yes" then stop date is included.

Listing 13: 16.2.7.3: Unsolicited Adverse Events*

[Implementation Note: For preliminary analyses, data will be reported through the data cut-off date.]

Adverse Event	Associated with Dose No. and Product	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment[a]	Subject Discontinued Due to AE	Outcome[b]	New Onset Chronic Medical Condition	MedDRA System Organ Class	MedDRA Preferred Term
Vaccination Group: , Subject ID: , AE Number:												
Comments:												
Vaccination Group: , Subject ID: , AE Number:												
Comments:												

[a] Action Taken with Study Treatment: INC = Dose not changed. INT = Drug interrupted. WD = Drug withdrawn. NA = Not applicable.
[b] Outcome: R = Recovered/resolved. RS = Recovered/resolved with sequelae. O = Recovering/resolving. NR = Not recovered/not resolved. F = Fatal.
Note: For additional details about SAEs, see Table: 106.

16.2.8 Individual Laboratory Measurements

Listing 14: 16.2.8.1: Clinical Laboratory Results – Chemistry*

[Implementation note: For preliminary analyses, blinded data will be reported through the data cut-off date. Include all unscheduled/early termination visits with "--" as the planned study day. Indicate severity by shading.]

Subject ID, Sex, Age (years)	Study Visit	Planned Study Day	Actual Study Day	Chemistry Collection Date	Were Tests Performed?	Reason Not Performed	Creatinine (mg/dL)	Blood Urea Nitrogen (mg/dL)	ALT (IU/L)	AST (IU/L)	Total Bilirubin (mg/dL)
Low Dose ChAd155-RG											
XXXXXX Female/Male xx	00A	-28 to -1									
	00B	-7 to -1									
	02	2									
	03	8									
	05	16									
	06	22									
High Dose ChAd155-RG (x1)											
High Dose ChAd155-RG (x2)											
RABAVERT											
Yellow, Orange and Red indicate Grade 1, 2 and 3, respectively.											

Listing 15: 16.2.8.2: Clinical Laboratory Results – Hematology*

[Implementation note: For preliminary analyses, blinded data will be reported through the data cut-off date. Include all unscheduled/early termination visits with "--" as the planned study day. Indicate severity by shading.]

Subject ID, Sex, Age (years)	Study Visit	Planned Study Day	Actual Study Day	Hematology Collection Date	Were Tests Performed?	Reason Not Performed	Platelets (10^3/µL)	Hemoglobin (g/dL)	WBC (10^3/µL)	Neutrophils (10^3/µL)	Lymphocytes (10^3/µL)
Low Dose ChAd155-RG											
XXXXXX Female/Male xx	00A	-28 to -1									
	00B	-7 to -1									
	02	2									
	03	8									
	05	16									
	06	22									
High Dose ChAd155-RG (x1)											
High Dose ChAd155-RG (x2)											
RABAVERT											
Yellow, Orange and Red indicate Grade 1, 2 and 3, respectively.											

Listing 16: 16.2.8.3: Clinical Laboratory Results – Urine Dipstick and Pregnancy Tests

				Urine Dipstick					Pregnancy Test				
Subject ID, Sex, Age (years)	**Study Visit**	**Planned Study Day**	**Actual Study Day**	**Test Performed?**	**Reason Not Performed**	**Collection Date**	**Protein**	**Glucose**	**Test Type**	**Test Performed?**	**Reason Not Performed**	**Collection Date**	**Result**
Low Dose ChAd155-RG													
XXXXXX Female/Male xx	00A	-28 to -1							N/A, Serum, Urine				Negative, Positive
	00B	-7 to -1								N/A			
	01	1		N/A									
	03	8		N/A									
	04	15		N/A									
	06	22		N/A									
High Dose ChAd155-RG (x1)													
High Dose ChAd155-RG (x2)													
RABAVERT													
Yellow, Orange and Red indicate Grade 1, 2 and 3, respectively.													

16.2.9 Vital Signs and Physical Exam Findings

Listing 17: 16.2.9.1: Vital Signs*

Vaccination Group	Subject ID	Planned Study Day	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)
Low Dose ChAd155-RG							
Repeat for							
High Dose ChAd155-RG (x1)							
High Dose ChAd155-RG (x2)							
RABAVERT							
Yellow, Orange and Red indicate Grade 1, 2 and 3, respectively.							

Listing 18: 16.2.9.2: Physical Exam Findings

Vaccination Group	Subject ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)
Low Dose ChAd155-RG						
Repeat for						
High Dose ChAd155-RG (x1)						
High Dose ChAd155-RG (x2)						
RABAVERT						

16.2.10 Concomitant Medications

Listing 19: 16.2.10: Concomitant Medications

Vaccination Group	Subject ID	CM 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)
Low Dose ChAd155-RG									
Repeat for									
High Dose ChAd155-RG (x1)									
High Dose ChAd155-RG (x2)									
RABAVERT									

16.2.11 Pregnancy Reports

Listing 20: 16.2.11.1: Pregnancy Reports – Maternal Information

Vaccination Group	Subject 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?
Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.											

Listing 21: 16.2.11.2: Pregnancy Reports – Gravida and Para

				Live Births												
Vaccination Group	**Subject 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?**

Note: Gravida includes the current pregnancy, para events do not.
[a] Preterm Birth
[b] Term Birth

Listing 22: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Vaccination Group	Subject 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 23: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Vaccination Group	Subject 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 24: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Vaccination Group	Subject 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