NCT03031912

A Phase 2 Randomized, Multi-Center Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of 1 or 2 doses of the V920 (rVSVΔG-ZEBOV-GP) Ebola Virus Vaccine Candidate in HIV-Infected Adults and Adolescents

Short Title: African-Canadian Study of HIV-Infected Adults and a Vaccine for Ebola – ACHIV-Ebola (Merck Study V920-015)

SPONSOR:
Dalhousie University
(Institution representing Canadian Immunization Research Network –CIRN)
MANUFACTURER:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

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Protocol-specific Sponsor, Manufacturer and Investigator Contact information can be found in the Investigator Trial File Binder (or equivalent).

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AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.2	02Aug2016	Dr. Joanne Langley	**Cover page of protocol**: Short Title: African-Canadian Study of HIV-Infected Adults and a Vaccine for Ebola – (ACHIV-Ebola) has been added.
1	2.2	02Aug2016	Dr. Joanne Langley	Headers and footers changed to reflect new protocol version number and date.
1	2.2	02Aug2016	Dr. Joanne Langley	**Section 4.2.3.2 Safety Endpoints**. Changes have been made to reflect the collection of some solicited AE's until 14 days, and some for the full 42 day post vaccination period. **1. a. i.** The occurrence of each solicited local and systemic AE, during a 14-day follow-up period following vaccination, and fever, arthritis, arthralgia, rash and blisters/vesicular lesions during a 42-day follow –up period following vaccination. Clarification to what constitutes D0-D42 is added in the first paragraph. "The Memory Aid will prompt the subject to record his/her temperature for 42 days following vaccination starting with the day of vaccination (D0-D42). Injection site and systemic reactions will be monitored for 14-days post-vaccination (D0-D14). In addition subjects will be prompted for joint pain, joint swelling, rashes, and blisters or vesicular lesions during the 42-day post-vaccination period as these events have been reported in the development program."

				Table 4: Evaluating Adverse Events-Maximum Intensity-Day 5 changed to Day 14. " Injection site redness or swelling from the day of vaccination through Day 14 post-vaccination will be evaluated by maximum size.
1	2.2	02Aug2016	Dr. Joanne Langley	**5.1.2. Subject Inclusion Criteria**. Inclusion Criteria #8 has been changed from "14 days" to "6 weeks".
2	2.3	26Aug2016	Dr. Joanne Langley	Various grammatical and formatting edits. Headers and footers changed to reflect new protocol version number and date.
2	2.3	26Aug2016	Dr. Joanne Langley	**Section 5.2.3 Preparation, Administration, and Dosage of V920 and Section 9.3, Clinical Supplies Disclosure**-clarification throughout that administration of vaccine/placebo may be done by blinded or unblinded personnel.
2	2.3	26Aug2016	Dr. Joanne Langley	**Section 5.9 Beginning and End of the Trial**-The original wording has been replaced with the following, for greater detail. "The overall trial begins when the first subject signs the informed consent form. The subject participation portion of the overall trial ends when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall trial ends when the Sponsor receives the last serology assay result or subject data from the last study-related phone call or visit and the database has been cleaned and locked."
2	2.3	26Aug2016	Dr. Joanne Langley	**Section 6. Trial Flow Chart.** Blood volumes have been added to the flow chart.

2	2.3	26Aug2016	Dr. Joanne Langley	**Section7.1.4.3. Blinding/ Unblinding**. Paragraph explaining emergency unblinding added.
3	2.4	18Nov2016	Dr. Joanne Langley	Headers and footers changed to reflect new protocol version number and date. Table of Contents updated
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 2.1 Trial Design** (P11). Dakar site name has been updated to Institut de Recherche en Santé,de Surveillance Epidemiologique et de Formations
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 5.1.2 Subject Inclusion Criteria**. Inclusion criteria 7 and 8a have been modified by removing the word 'female' from the statement Inclusion criteria 7a"if the female partner" and then removing inclusion criteria 8a. so the criteria are inclusive of contraception for all sexual persuasions and inclusive of timelines for both contraception and viral shedding.
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 5.2.3 Preparation, Administration, and Dosage of V920.**(p29) and **Section 9.3 Clinical Supplies Disclosure** (p 53) Clarification only BLINDED personnel will administer the study product, to protect the blind. Need length recommendation changed from 23G 1.5 inches to 23 G 1 inch, for harmonization throughout the protocol.
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 7.1.1.4 Medical History** (p36) Clarification on collection of medical history to include all pre-existing conditions or signs and/or symptoms present in the participant prior to the first study injection.
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 7.1.3 Laboratory Procedures/Assessments** (p37) 3mls/kg in an 8 week period has been replaced with the NIH recommendation of no more than 10.5mls/kg or 550mls,

				whichever is less, in an eight week period. The following statement has been clarified regarding the option nature of these samples and reworded as: In addition to anti-Ebola immune assessments blood samples, optional blood samples will be drawn at visits 1, 5, 7, & 8 if subjects sign a separate consent form. These samples will be conserved in a biobank for future research studies. Names and locations of labs have been added.
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 7.3.1.1 Laboratory Evaluations (Hematology, Chemistry and Urinalysis)** (p38) Clarifications to table for destination of study samples to different labs.
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 7.2 Assessing and Recording Adverse Events** (p40) Added for clarification: Pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection are not considered to be adverse events. These events will be recorded in the participants' medical history.
3	2.4	18Nov2016	Dr. Joanne Langley	**Section 7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)** Hematocrit removed from the table as it will not be collected for analysis
4	2.5	14Dec2016	Dr. Joanne Langley	Various grammatical and formatting edits. Headers and footers changed to reflect new protocol version number and date.
4	2.5	14Dec2016	Dr. Joanne Langley	Summary of changes added (p10)

4	2.5	14Dec2016	Dr. Joanne Langley	Axillary temperature added throughout as option for assessing for a fever, as this is the route used by the African sites.
4	2.5	14Dec2016	Dr. Joanne Langley	**Section 2.1 Trial Design** (p11) 4th paragraph, second sentence, removed 'and immunogenicity' form the monitoring done by the DSMB. They are monitoring safety, not immunogenicity.
4	2.5	14Dec2016	Dr. Joanne Langley	**Section 7.2.2Events Specific to Post Vaccination.** This section added for guidance in assessment and work-up of arthralgia/arthritis, rashes and vesicular lesions.
5	2.6	12Jan2017	Dr. Joanne Langley	Table numbers have been corrected.
5	2.6	12Jan2017	Dr. Joanne Langley	**Section 5.1.2 Subject Inclusion Criteria** #8: '6 weeks after vaccination' changed to '8 weeks after vaccination' for harmonization within the protocol.
5	2.6	12Jan2017	Dr. Joanne Langley	**Section 5.1.3 Subject Exclusion Criteria** #6:Correction of '…or any other cytotoxic or immunosuppressive drug within six months' to **'**or any other cytotoxic or immunosuppressive drug within **….12 months'**.
5	2.6	12Jan2017	Dr. Joanne Langley	**Section 5.1.3 Subject Exclusion Criteria** #13: Range given for axillary temperature (37.8^0C)
5	2.6	12Apr2017	Dr. Joanne Langley	**Cover Page** Nicholas Meda, MD removed and Innocent Valea, MD added to Co-Investigator list
6	2.7	11May17	Dr. Joanne Langley	Replaced 'Group/s with Cohort/s throughout the document for consistency
6	2.7	11May17	Dr. Joanne Langley	**Section 1.0 Trial Summary:** Added Cohort 5 details: 50 adults and adolescents CD4 ≥ 200 cells/mm^3, increased total number of trial participants to 250; Changed the

				duration of enrollment to 30 months; changed the duration of participation to include cohort 5.
6	2.7	11May17	Dr. Joanne Langley	**Section 2.0 Trial Design:** Added cohort 5 details: 50 adults and adolescents CD4 ≥ 200 cells/mm^3, increased total number of trial participants to 250; first dose of vaccine or placebo at D0 and second dose of matching vaccine or placebo at D56. The fourth safety analysis will be conducted when the fourth cohort (adolescents CD4 ≥ 200 cells/mm^3) will have completed 42 days of follow-up post vaccination
6	2.7	11May17	Dr. Joanne Langley	**Section 2.1 Trial Design:** Removed (160:40 and 40:10) as the ratio of 4:1 is mentioned
6	2.7	11May17	Dr. Joanne Langley	**Section 2.2 Trial Diagram:** Added cohort 5
6	2.7	11May17	Dr. Joanne Langley	**Section 3.0 Objectives(s) and Hypotheses** Added cohort 5 primary objective (s) 1. Added 'combined' at the end of objective. 2. The geometric mean titer (GMT) of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults and adolescents Day 28 after the last dose of vaccine (equivalent to Day 84 from first dose) in Cohort 5 Added cohort 5 secondary objective (s)

				4. **Objective:** Evaluate the safety and tolerability of two doses of V920 in HIV-infected adults and adolescents administered 56 days apart. **5. Objective:** Evaluate the immunogenicity of two doses of V920 administered 56 days apart via ZEBOV-specific antibody responses induced by V920 at D28 post-dose 2 in HIV-infected adults and adolescents.
6	2.7	11May17	Dr. Joanne Langley	**Section 4.1 Background** Table 1: Ebolavirus Outbreaks Updated the above table with information on Ebolavirus outbreaks from 2014-2017
6	2.7	11May17	Dr. Joanne Langley	**Section 4.2.2.2 Vaccine Dose for This Trial:** Added: 'or placebo' to the first sentence Added following to the statement in this section. 'in all Cohorts 1-5. In Cohort 5, at Day 56 a second dose of matching vaccine ($\geq 2 \times 10^7$ pfu/ml) or placebo will be administered. Added the following: The rationale for assessing a second dose in HIV positive subjects is to assess whether a second dose will provide a greater immune response or a response in a greater proportion of subjects in case one dose is less immunogenic in HIV positive subjects than in non-HIV positive subjects assessed in other studies. The 56 day interval is based on the interval utilized in

				other studies that include non-HIV positive adults and children.
6	2.7	11May17	Dr. Joanne Langley	**Section 4.2.3.1 Immunogenicity Endpoints** Added the following to the Primary End points: a. Added 'in Cohorts 1-5 combined'. b. ZEBOV-specific antibody responses measured by ELISA and neutralization on Day 28 after the last dose of vaccine (equivalent to Day 84 from first dose) in Cohort 5. Added the following to the Secondary endpoints: a. ZEBOV-specific antibody responses measured by ELISA and neutralization on Day 28 in Cohort 5. b. added 'after the first dose of vaccine'
6	2.7	11May17	Dr. Joanne Langley	**Section 4.2.3.2 Safety Endpoints:** Added 'each vaccination' to primary endpoint 'iii' Added 'following each vaccination, to secondary endpoint 'a' Replaced post-vaccination with first vaccination for clarity in reporting SAEs

6	2.7	11May17	Dr. Joanne Langley	**Section 4.3.1.3 Reactions to V920** Changed Phase I-III to 2-3 for consistency with title
6	2.7	11May17	Dr. Joanne Langley	**Section 4.3.1.4** Added 'the last' to abstinence and contraception precautions
6	2.7	11May17	Dr. Joanne Langley	**Section 5.2 Trial Vaccination** Updated Table 2 to reflect cohort 5 receipt of 2 doses, under Randomization/Vaccination to add 'and Visit 7 (Day 56), where applicable'
6	2.7	11May17	Dr. Joanne Langley	**Section 5.2 Trial Vaccination** Updated Table 2, under Randomization/Vaccination to add 'and Visit 7 (Day 56), where applicable' and 'Subjects in Cohort 5 will receive two doses of V920 $\geq 2x10^7$ PFU or two doses of normal saline placebo (0.9%) on D0 and D56.'
6	2.7	11May17	Dr. Joanne Langley	**Section 5.2.5 Timing of Dose Administration** Added: Subjects in Cohort 5 will also receive on D56 a matching dose of either the V920 at a dose of $\geq 2x10^7$ PFU in 1mL IM, or normal saline (0.9%) placebo control in 1mL volume.
6	2.7	11May17	Dr. Joanne Langley	**Section 5.4 Stratification** Updated as follows: To satisfy the requirement that each site enrolls at least one placebo subject in each cohort, enrollment will proceed until treatments have been randomized

				to at least one complete block of subjects (consisting of four subjects receiving treatment and one receiving placebo) at each site. Treatment allocation/randomization will be stratified by the 5 cohort groups: Cohort 1: Screening CD4 cell counts for adults: CD4 cells/mm3 ≥ 500 Cohort 2: Screening CD4 cell counts for adults: CD4 cells/mm3 >350 and < 500 Cohort 3: Screening CD4 cell counts for adults: CD4 cells/mm3 ≥ 200 and ≤ 350 Cohort 4: Screening CD4 cell counts for adolescents, age 13 to 17: CD4 cells/mm3 ≥ 200 Cohort 5: Screening CD4 cell counts for adults and adolescents, age 13 to 17: CD4 cells/mm3 ≥ 200 with 2 doses. All sites are stratified by site Cohort 5 is stratified by site, and by age group (adolescent vs. adult). Once three blocks of five adolescents have been enrolled, with at least one block at each site, the requirement to enroll at least 12 adolescents in Cohort 5 will be met.
6	2.7	11May17	Dr. Joanne Langley	**Section 6.0 Trial Flow Chart** **Added: (COHORTS 1 TO 4)** Added to footnote b: Specimens should be obtained for ZEBOV-specific Serum Antibodies and ZEBOV-specific Serum Antibodies before vaccination
6	2.7	11May17	Dr. Joanne Langley	**Section 6.0 Trial Flow Chart** Added: (Cohort 5) as a separate Flow Chart for cohort 5

6	2.7	11May17	Dr. Joanne Langley	**Section 7.1.3 Laboratory Procedures/Assessments** Added the following for optional laboratory blood collection: (cohorts 1-4) and at visits 1, 5, 7, 11, 13 & 14 (cohort 5).
6	2.7	11May17	Dr. Joanne Langley	**Section 7.2 Clinical Procedures/Assessments** Separated the procedures for Cohorts 1-4 and Cohort 5 for clarity**.** Added: Cohort 5: At visit 1 (Randomization /vaccination), the inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject still qualifies for the trial. At visit 1 (first dose of vaccine or placebo) and visit 7 (second dose of matching vaccine or placebo), vital Signs will be taken (including heart rate, blood pressure, oral/tympanic/axillary temperature, respiratory rate) Participant will be coming to the center at day 3 (visit 2), day 7 (visit 3), day 14 (visit 4), day 28 (visit 5), day 42 (visit 6), day 56 (visit 7), 3 days post dose 2 (visit 8), 7 days post dose 2 (visit 9), 14 days post dose 2 (visit 10), 28 days post dose 2 (visit 11), 42 days post dose 2 (visit 12), day180 (visit 13) and day 365 (visit 14). Vital Signs will be taken (including heart rate, blood pressure, oral/tympanic/axillary temperature, respiratory rate) at all visits. Non-Serious Adverse Events including solicited and unsolicited adverse events will be monitored at every visit after first dose of vaccine or placebo through Day 42. Non-Serious Adverse Events

				including solicited and unsolicited adverse events will be monitored at every visit after second dose of matching vaccine or placebo through Day 42. Serious Adverse Events will be monitored at every visit through Day 365.
6	2.7	11May17	Dr. Joanne Langley	**Section 7.1.5.2 Vaccination Visit** Added: to participants in Cohort 1-4. Two doses of study vaccine will be administered to Cohort 5 participants at first at visit 1 and second dose at visit 7
6	2.7	11May17	Dr. Joanne Langley	**SECTION 7.2.4.1 SERIOUS ADVERSE EVENTS** Added 'first' to this sentence for clarity: For the time period beginning at treatment allocation/randomization through 365 days following first vaccination
6	2.7	11May17	Dr. Joanne Langley	**Section 7.2.4.2 Events of Clinical Interest** Corrected the time period for reporting ECI from 14 (for non-live virus vaccine) to 42 days (live virus vaccine)
6	2.7	11May17	Dr. Joanne Langley	**Section 8.1 Statistical Analysis Plan Summary** Updated section to include Cohort 5 analysis plan summary
6	2.7	11May17	Dr. Joanne Langley	**Section 8.2.2 Objective(s) and Hypotheses(s)** Primary Hypotheses:

				1) The geometric mean titer (GMT) of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults at Day 28 in Cohorts 1-5 combined. 2) The geometric mean titer (GMT) of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults and adolescents Day 28 after the last dose of vaccine (equivalent to Day 84 from first dose) in Cohort 5
6	2.7	11May17	Dr. Joanne Langley	**Section 8.2.3.1 Immunogenicity Endpoints** Added to include biobank blood draws in Cohort 5: Participants who consent to bio-bank will undergo up to six blood draws in cohort 5: at baseline on the day of vaccination before vaccine or placebo is administered; at D28 post-vaccination; at D56 on the day of second dose of vaccination before vaccine or matching placebo is administered, at 28 days post-dose 2 vaccination, at D180 post dose 1-vaccination; and at D365 post dose 1-vaccination.
6	2.7	11May17	Dr. Joanne Langley	**Section 8.2.5.1 Statistical Methods for Immunogenicity Analyses** Added:'and Geometric Mean Fold Increase from baseline (GMFI)' Updated this section to describe how the immunogenicity and safety for the

				second dose in Cohort 5 will be summarized
6	2.7	11May17	Dr. Joanne Langley	**Section 8.2.7 Sample Size and Power Calculations** Updated with cohort 5 sample size and power calculations
6	2.7	11May17	Dr. Joanne Langley	**Section 8.2.9 Interim Analyses** Changed to reflect 'four safety analyses will be conducted, one for each of the first four cohorts
6	2.7	11May17	Dr. Joanne Langley	**Section 9.1 Investigational Product** Changes made to reflect the dosing for cohort 5
6	2.7	11May17	Dr. Joanne Langley	**Section 9.1 Investigational Product** Treatment Allocation: Changes made to reflect the dosing for cohort 5
7	2.8	Not a valid version		**Draft document**
7	2.9	Not a valid version		**Draft document**
7	3.0	10 January 2018	Dr. Joanne Langley	**Section 5.1.2 Subject Inclusion Criteria** #1 increase inclusion age to 70.
7	2.1.	10 January 2018	Dr. Joanne Langley	Section 2.1. Clarified that participant allotment between the sites may be reassigned based on enrolment between sites in order to ensure the integrity of the study.

7	3.0	10 January 2018	Dr. Joanne Langley	**Section 5.1.3 Subject Exclusion Criteria** #3 deleted. Will now include health care workers.
7	3.0	10 Janaury 2018	Dr. Joanne Langley	**Section 4.1.2 Rationale for the Trial and Selected Subject Population:** Added the rationale for inclusion of HIV positive subjects 66-70 years of age.
7	3.0	10 January 2018	Dr. Joanne Langley	**Section 4.3.1.9 Risks to the Study Personnel and the Environment** Added experience and safety information in Health Care Workers (HCW) to support the inclusion of HCW in the trial
8	4.0	17 September 2019	Dr. J Langley	Title Page. Correction of Investigator degrees.
8	4.0	17 September 2019	Dr. J Langley	Section 5.1.3. Exclusion criteria. Revised to allow enrolment of participants with screening hematologic and chemistry values outside of normal site reference ranges, if deemed not clinically significant by the clinical investigator. In this study local normal reference ranges are used to determine eligibility. FDA Guidance for Industry Toxicity Grading Scales (Appendix 2), which are directed at healthy populations, are not applicable as the target population has HIV infection. The following five screening parameters will have limits set, and other values are assessed by the clinical investigator as clinically significant (and thus exclusionary) or not clinically significant: 1. absolute lymphocyte count ≥1000 cells/mm^3

				2. hemoglobin not greater than 1.5 grams below the lower limit of the normal reference range at the local laboratory 3. ALT, AST not greater than 2 to 2.5 times the upper limit at the local laboratory 4. Platelet count ≥ 125,000 and ≤ 550,000
8	4.0	17 September 2019	Dr. J Langley	Section 6.0. Trial Flow Chart and Section 7.1.3. Cohort 5 laboratory tests , and Section 8.2.3.1. Analysis endpoints, revised to delete HIV RNA reservoir testing and biobank samples, and correct total sample volumes.
8	4.0	17 September 2019	Dr. J Langley	Section 7.1.5.1. Clarified that to exclude transient laboratory abnormalities the investigator may repeat a specific Screening test (E.g. hemoglobin) once during the screening period (E.e. a maximum of two tests) during the screening period. Clarified that a participant who is not eligible for an earlier cohort may be screened for eligibility for a subsequent cohort.
8	4.0	17 September 2019	Dr. J Langley	Section 7.1.3. Laboratory/ procedures/assessments. Removed Urinalysis - specific gravity to align with 5.1.3. Inclusion and exclusion criteria. Removed

No modification of this protocol will be allowed unless discussed and approved by the Coordinating Investigator and a filed and approved change to the protocol is submitted to and approval received from the local REBs. Any administrative changes or amendments to this protocol will be adhered to

by all participating centres and will apply to all participants. Documentation of amendments and REB approvals will be maintained at each centre

1.0 TRIAL SUMMARY

Short Title:	A Phase 2 Study of V920 Ebola Virus Vaccine Candidate in HIV Infected Adults and Adolescents
Manufacturer Product Identifier	V920
Trial Phase	Phase 2
Clinical Indication	Prevention of Ebola Disease
Trial Type	Randomized, multi-center
Type of control	Placebo
Route of administration	IM
Trial Blinding	Double blind
Select Cohorts	HIV-infected individuals within each of the five cohorts will be randomly assigned to receive V920 or placebo: Cohort 1: 50 adults with CD4 ≥ 500 cells/mm^3 Cohort 2: 50 adults CD4 > 350 and < 500 cells/mm^3 Cohort 3: 50 adults CD4 ≥ 200 and ≤ 350 cells/mm^3 Cohort 4: 50 adolescents CD4 ≥ 200 cells/mm^3 Cohort 5: 50 adults and adolescents CD4 ≥ 200 cells/mm^3
Number of trial subjects	Approximately 250 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 30 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 13 months, from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to one month, each subject in Cohorts 1 to 4 will be receiving one dose of assigned vaccine/placebo and each subject in Cohort 5 will be receiving one dose of assigned vaccine/placebo at Day 0, and followed by a second dose of the same vaccine/placebo treatment at Day 56. Each subject will be followed for 365 days from the first vaccination.
Randomization Ratio	200:50 (4:1)

A list of abbreviations used in this document can be found in Section 12.0.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, multi-site, double-blind trial of V920 (rVSVΔG-ZEBOV-GP) Ebola Virus vaccine candidate in subjects with HIV infection to be conducted in conformance with Good Clinical Practices. The study will take place at 2 Canadian sites (Centre Hospitalier de l'Université de Montréal and Ottawa General Hospital) and 2 African sites (Centre MURAZ, Burkina Faso and Institut de Recherche en Santé, de Surveillance Epidemiologique et de Formations (IRESSEF), Dakar, Senegal). The Duration of Study: 365 days for each participant not including screening.

The study will enroll approximately 250 participants, ~100 at 2 sites in Canada and ~150 at 2 sites in Africa. Depending on recruitment rates, participants may be reallotted between sites in order to ensure the integrity of the study. Overall ~200 participants will receive the study vaccine and ~50 will receive placebo. Sequential enrollment of five study Cohorts will occur over time at each study site according to CD4 T-cell counts: Cohort 1 will include adult subjects with CD4 $\geq$ 500 cells/mm^3, Cohort 2 CD4 > 350 and < 500 cells/mm^3, Cohort 3 CD4 $\geq$ 200 and $\leq$ 350 cells/mm^3, Cohort 4 adolescents CD4 $\geq$ 200 cells/mm^3, and Cohort 5 adults and adolescents with CD4 $\geq$ 200 cells/mm^3 receiving two doses 56 days apart. Enrollment and vaccine administration will begin with the cohort with the highest CD4 count. When the D42 post-vaccination period is completed for all subjects in Cohort 1, and the Data Safety Monitoring Board (DSMB) has reviewed the safety data and determined that there are no concerns, enrollment and vaccination of the next CD4 cohort may begin. Similarly, when the D42 safety data for Cohort 2 has been reviewed/approved by the DSMB, enrollment and vaccination of participants in Cohort 3 may begin. Cohort 4 with adolescents 13-17 years of age (inclusive) with CD4 $\geq$ 200 will be enrolled after D42 safety is reviewed in adults with CD4 $\geq$ 200. Within each Cohort 1-4, participants will be randomly assigned to receive one dose of $\geq 2 \times 10^7$ pfu of the study vaccine or the placebo in a ratio of 4 to 1. In Cohort 5, participants will be randomly assigned to receive one dose of $\geq 2 \times 10^7$ pfu of the study vaccine or the placebo in a ratio of 4 to 1, and followed by a matching vaccine or placebo dose at Day 56. All participants will complete memory aids for 42 days following each vaccination.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

This trial will use an adaptive design based on pre-specified criteria, using an independent, external DSMB to monitor safety. There will be 4 formal safety analyses performed by the DSMB. Data for at least 75% of participants must be available for each analysis. The first safety analysis will be conducted when the first Cohort (CD4 $\geq$ 500 cells/mm^3) will have completed 42 days of follow-up post vaccination. The second safety analysis will be conducted when the second Cohort (CD4 > 350 and < 500 cells/mm^3) will have completed 42 days of follow-up post vaccination. The third safety analysis will be conducted when the third Cohort (Adults CD4 $\geq$ 200 and $\leq$ 350 cells/mm^3) will have completed 42 days of follow-up post vaccination. The fourth safety analysis will be conducted when

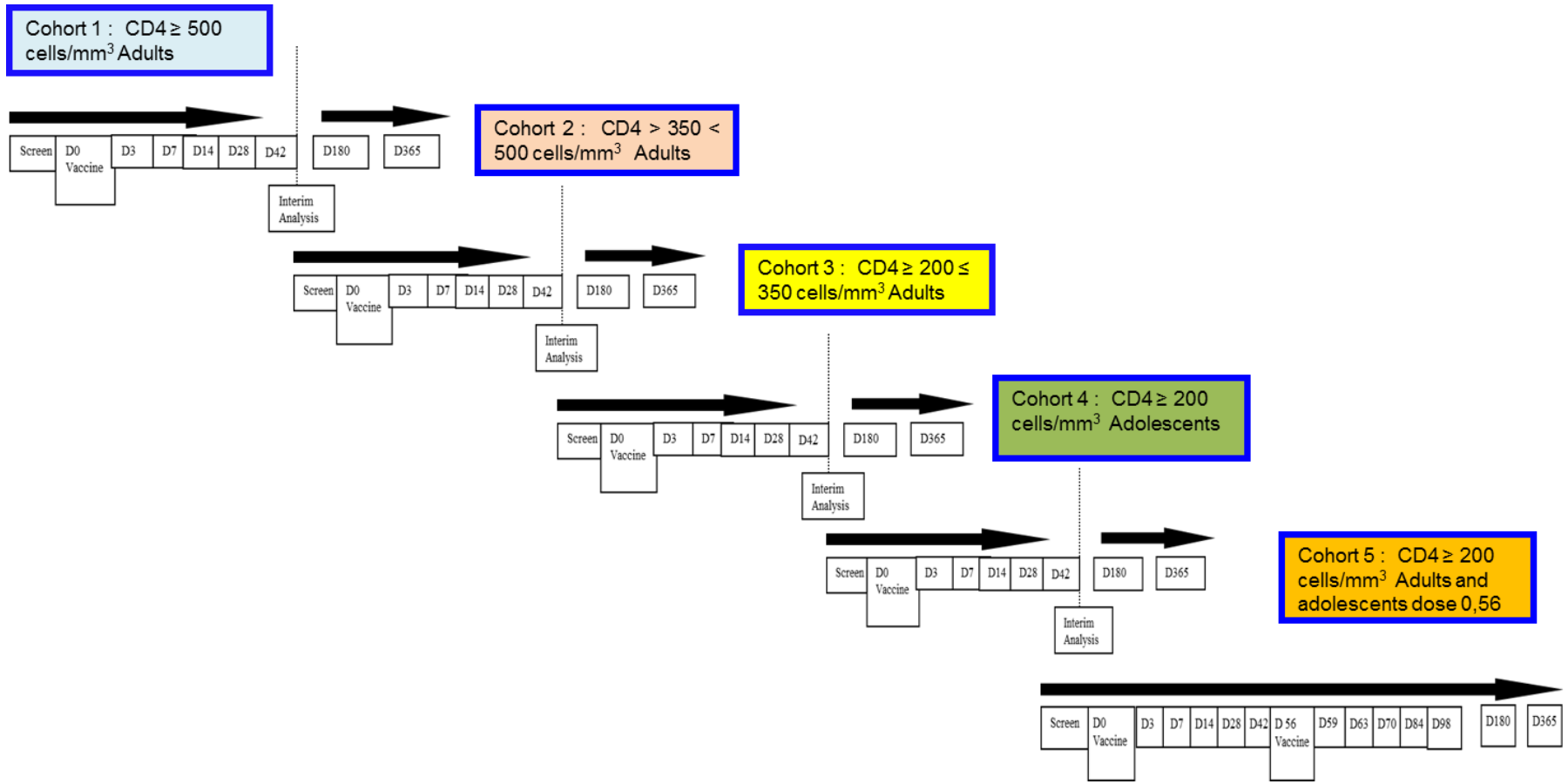
the fourth Cohort (Adolescents CD4 ≥ 200 cells/mm^3) will have completed 42 days of follow-up post vaccination.

Results of the safety analysis will be reviewed by the DSMB, which will make recommendations to the Sponsor to continue, modify or end the trial according to the plan described briefly in Section 2.2 - Trial Diagram and in detail in Section 8.0 - Statistical Analysis Plan. In case of an outbreak of Ebola Zaire the DSMB may recommend to vaccinate subjects randomized to receive placebo with V920 provided at least 84 days of SAE follow-up is conducted.

2.2 Trial Diagram

The trial diagram is depicted in Figure 1.

Figure 1: Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESES

3.1 Primary Objective(s) & Hypotheses

(1) **Objective:** Evaluate the safety and tolerability of V920 in HIV-infected adults and adolescents.

(2) **Objective:** Evaluate the immunogenicity of V920 via ZEBOV- specific antibody responses induced by V920 in HIV-infected adults and adolescents.

Primary Hypotheses:

1) The geometric mean titer (GMT) of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults at Day 28 in Cohorts 1-5 combined.

2) The geometric mean titer (GMT) of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults and adolescents Day 28 after the last dose of vaccine (equivalent to Day 84 from first dose) in Cohort 5

3.2 Secondary Objective(s)

(1) **Objective**: Evaluate VSV viremia and shedding after administration of V920.

(2) **Objective**: Evaluate ZEBOV-specific antibody responses induced by V920 through D180 and D365.

(3) **Objective**: Evaluate the impact of V920 on HIV viral load, CD4 counts, and CD4/CD8 ratio.

(4) **Objective**: Evaluate the safety and tolerability of two doses of V920 in HIV-infected adults and adolescents administered 56 days apart.

(5) **Objective**: Evaluate the immunogenicity of two doses of V920 administered 56 days apart via ZEBOV-specific antibody responses induced by V920 at D28 post-dose 2 in HIV-infected adults and adolescents.

3.3 Tertiary Objective(s)

(1) **Objective:** Evaluate Ebola-specific CD8 T cell responses

(2) **Objective:** Evaluate B-cell repertoire

(3) **Objective**: Evaluate the impact of V920 on HIV viral reservoir

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on V920.

Ebolaviruses (EBOV) are members of the Filoviridae and are known primarily as the underlying cause of severe viral hemorrhagic fevers with disturbingly high case fatality rates. Between 1994 and the present, there have been many EBOV outbreaks (refer Table 1) affecting mostly central Africa, with two large outbreaks in 1995 in Kikwit, DRC and in Gulu, Uganda in 2000-2001.

The West African outbreak significantly exceeds all previous outbreaks in geographic range, number of patients affected and in disruption of typical activities of civil society [1]. The West African Ebola outbreak was first recognized in Guinea, and then spread to Liberia and Sierra Leone, with a few imported cases resulting in some spreading in Nigeria, Mali, Senegal, U.S., UK and Spain. The vast majority of cases are from Guinea, Liberia and Sierra Leone. The epidemic peaked from Aug-2014 to Oct-2014, and as of 25-Nov-2015, it has caused over 28,000 reported cases and 11,000 deaths reported by the WHO (Figure 2).

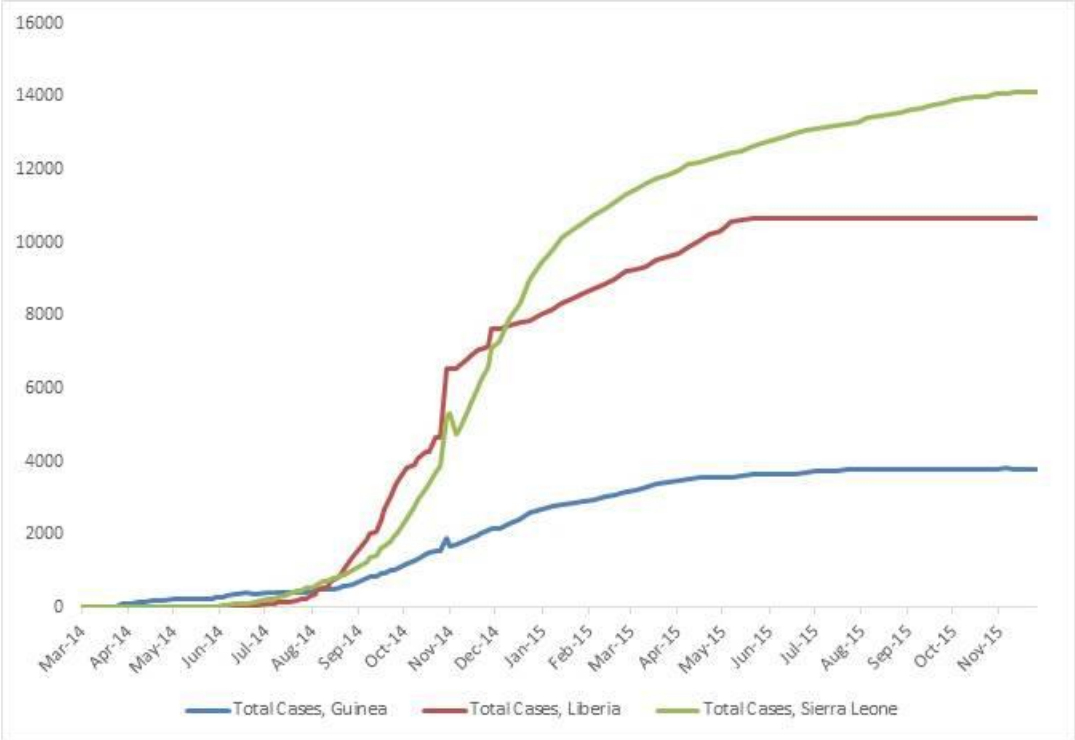
The disease affects both adults and children, although most cases are aged 20 to 50 years. The incubation period ranges from 2 to 21 days, with an average of 10 days in patients aged 16 to 44 years, 11 days in patients aged 45 years or older, and a shorter average in children (7 days in children younger than 1 year and 10 days in children aged 10 to 15 years)[2].

Table 1: Ebolavirus Outbreaks

Viral species	Year	Outbreak location	# of human cases (% fatality)
Zaire Ebolavirus	1976	Yambuku, Zaire (DRC)	318 (88%)
	1977	Tandala, Zaire (DRC)	1 (100%)
	1994	Ogooue-Invindo province, Gabon	51 (60%)
	1995	Kikwit, Democratic Republic of Congo	315 (79%)
	1996	Mayibout, Gabon	37 (57%)
	1996	Booue, Gabon and Johannesburg, South Africa	61 (74%)
	2001-02	Ogooue-Invindo province, Republic of Congo	124 (79%)

	2002-03	Cuvette region, RC and Ogooue-Invindo province, Gabon	143 (90%)
	2003	Mboma and Mbandza, Republic of Congo	35 (83%)
	2005	Etoumbi and Mbomo, Republic of Congo	12 (75%)
	2007	Kasai Occidental province, Democratic Republic of Congo	249 (73%))
	2008/2009	Democratic Republic of the Congo	32 (47%)
	2014	Democratic Republic of the Congo	66 (72%)
	2014-2016	West Africa including Guinea, Sierra Leone, Liberia	28,652 (40%)
	2017	Democratic Republic of the Congo	17 (23%)
Sudan Ebolavirus	1976	Nzara, Maridi, Tembura, Juba, Sudan	284 (53%)
	1979	Nzara, Yambio, Sudan	34 (65%)
	2000-01	Gulu, Masindi, Uganda	425 (53%)
	2004	Yambio, Sudan	17 (41%)
	2011	Uganda (Luwero District)	1 (100%)
Taï Forest	1994	Tai forest, Ivory Coast	1 (0%)
	1995	Liberia, Liberia	1 (0%)
Reston Ebolavirus	1989	Reston, USA	4 (0%)
	1992	Siena, Italy	0
	1996	Alice, Texas	0
	2008	Phillipines	0
Bundibugyo Ebolavirus	2007/2008	Uganda	131 (37%)

Figure 2: Total suspected, probable, and confirmed cases of Ebola virus disease in Guinea, Liberia, and Sierra Leone, March 25, 2014-February 14, 2016, by date of WHO Situation Report, n=28603.



By WHO Situation Report
Source: http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/cumulative-cases-graphs.html

Therapies for Filovirus infections

Treatment of Ebola hemorrhagic fever is mainly supportive, involving fluid and electrolyte replenishment and pain reduction. Specific treatments are under development. Convalescent plasma was used in a limited number of patients during the Kikwit 1995 ZEBOV outbreak, but its success was disputable[3]. Passive immunization with hyperimmune horse serum delayed but did not prevent death in cynomolgus macaques[4,5]. Monoclonal antibody treatment was successful in rodent models, but failed in preliminary NHP studies, indicating a possible evasion of antibody neutralization[6-9]. All of the abovementioned studies used single monoclonal antibody clones, which may not be sufficient to control infection.

During the recent outbreak, experimental therapies including a cocktail of 3 monoclonal antibodies (ZMapp, Mapp Biopharmaceutical), lipid encapsulated siRNA (small interfering RNA, TKM-Ebola, Tekmira Pharmaceuticals Corp), and two antiviral drugs (brincidofovir and favipiravir) have been employed in individual patients. Although the efficacy of these treatments in these patients is not clear, they have been shown to be successful in animal

studies. Treatment with the optimized ZMapp cocktail rescued 100% of rhesus macaques when treatment was initiated up to 5 days after lethal EBOV challenge[10]. The Tekmira siRNA product similarly showed high-grade protection against lethal filovirus infection when NHP were treated up to 3 days after challenge[11]. The rVSVΔG-ZEBOV-GP vaccine may also play an important role in preventing the onset of the Ebola virus disease (EVD) in situations where the precise time of exposure were known, and the vaccine could be applied early after exposure.
A preventive vaccine, in contrast, could be used to protect individuals at high risk in advance of exposure, such as persons traveling to or residing in endemic or epidemic settings, and could be used for outbreak control at a population level to interrupt transmission. Since the rVSVΔG-EBOV-GP vaccine elicits rapid and likely durable immunity after a single dose, it has important potential for use in this context, as well as for the indication of post-exposure prophylaxis after recognized, high-risk exposure.

Vesicular stomatitis virus as a vaccine vector

VSV belongs to the family Rhabdoviridae, genus Vesiculovirus. These are bullet-shaped, single-stranded, negative-sense RNA viruses containing five genes, one of which is the viral GP. In the U.S., the two most common serotypes are VSV-New Jersey and VSV-Indiana. VSV cause significant disease in pigs, cattle, and horses, primarily manifesting as crusting and vesiculation of the mucous membranes and skin, and lameness due to involvement of the coronary bands of the hoof. The virus is maintained in nature in a cycle involving sandflies and rodent reservoirs. It is also transmitted between livestock by direct contact, likely including droplet spread and fomites, as well as mechanically by non-biting houseflies and face flies. Pre-existing immunity to VSV is not prevalent in humans in the U.S., and VSV does not circulate outside the Western Hemisphere; therefore it is not expected to be a significant factor in a potential vaccination campaign in the U.S. or in parts of Africa with VSV-based vaccines. Moreover, in VSV vaccines where the viral GP is replaced with GPs of other viruses, the impact of pre-existing anti-VSV neutralizing antibodies is theoretically minimized.

VSV virus can be transmitted to humans who come in close contact with infected animals. The incubation period is most commonly 3 to 4 days. The most common clinical manifestation is a limited, 3- to 5-day flu-like illness. In rare cases, humans can manifest vesicles on the oropharyngeal, nasal mucosa or skin. Human deaths secondary to infection have not been reported; however, encephalitis was reported in a single case of a 3-year old child secondary to VSV-Indiana infection[12] . As there is only one case report in the literature, the risk of central nervous system infection following VSV infection is undoubtedly rare. In some areas of tropical America, a high seroprevalence to VSV has been reported without recognized disease[13] . Thus, it is likely that the ratio of infection to illness with VSV is high.

The V920 construct used in the clinical trials was derived from the VSV-Indiana serotype. As described above, the rVSV-based vector used in this vaccine lacks the VSV GP, the viral determinant for neurotropism and pathogenicity[14-16], rVSVΔG-ZEBOV-GP has approximately 33% slower growth kinetics than wild-type VSV in Vero cell cultures, contributing to

attenuation[17]. The rVSVΔG-ZEBOV-GP virus is apathogenic for hamsters, whereas wild-type VSV is lethal in hamsters after peripheral inoculation (Feldmann H., unpublished data, 2014).

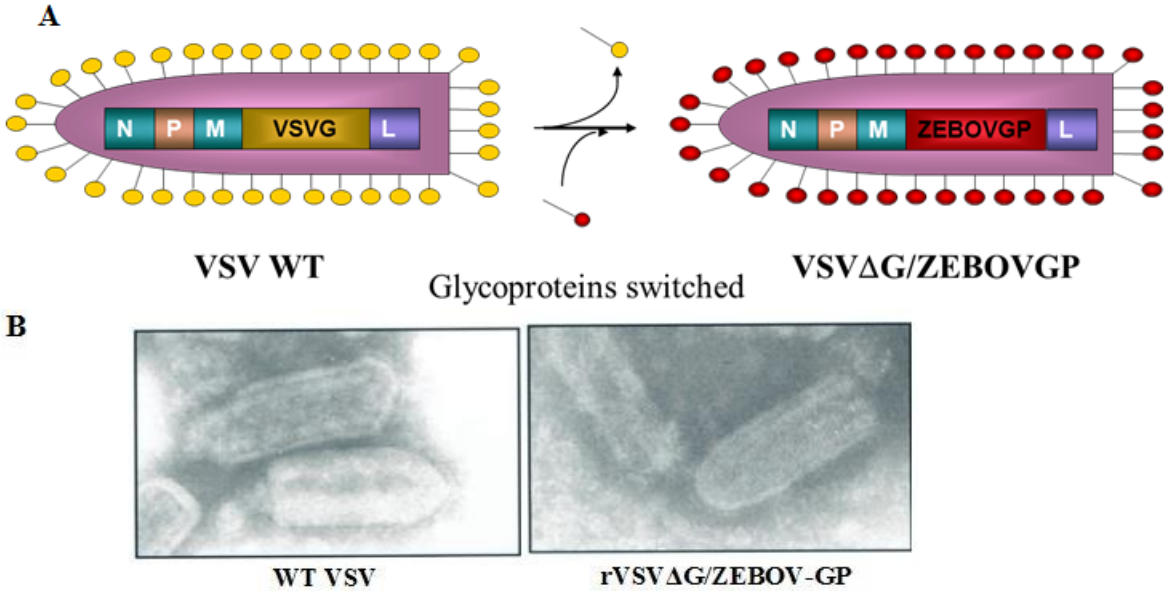
4.1.1 Pharmaceutical and therapeutic background

rVSVΔG-ZEBOV-GP AS A CANDIDATE VACCINE FOR EBOLA ZAIRE DISEASE

The rVSVΔG-ZEBOV-GP vaccine is a live attenuated recombinant virus consisting of a single recombinant VSV isolate (11481 nt, strain Indiana) with the gene for the *Zaire ebolavirus* GP (ZEBOV GP), Kikwit strain replacing the gene for the VSV GP, which has been deleted. This results in a VSV backbone with the ZEBOV GP constituting the envelope of the virus. As for similar chimeric vaccines, the substitution of the native virus GP genes with a heterologous GP leads to significant attenuation of a virus[18]. The ZEBOV GP on the surface of the virus may narrow the cell tropism of the recombinant virus. The substitution of the heterologous Ebolavirus GP does not perturb the proper assembly of the virus particle, and the recombinant vaccine resembles the native VSV bullet structure in electron micrographs (Figure 3). Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on V920.

Figure 3: (A) A single-stranded, negative-sense RNA encoding 5 transcriptional units: N (nucleoprotein), P (phosphoprotein), M (matrix), G (glycoprotein), and L (polymerase).

rVSVΔG-ZEBOV-GP was generated by deleting the VSV G gene and inserting the ZEBOV GP gene in the new transcriptional unit after the VSV M gene. (B) Electron micrograph of the WT VSV and rVSVΔG-ZEBOV-GP.



4.1.2 Pre-clinical Trials

Immunogenicity as well as pre- and post-exposure prophylactic efficacy of VSVΔGZEBOV-GP, has been demonstrated following a single IM injection in multiple nonclinical studies in rodent species and nonhuman primates (NHP). Briefly, vaccination of mice with a single intraperitoneal (IP) injection of as few as 200 plaque-forming units (pfu) of VSVΔGZEBOV-GP provided 100% protection against lethal mouse-adapted ZEBOV challenge 28 days after immunization[19]. Similarly, a single intramuscular (IM) vaccination of cynomolgus macaques with rVSVΔG-ZEBOV-GP induced strong and long-lasting humoral and cellular immune responses[20] and 100% protection against a lethal IM challenge of homologous ZEBOV given by the IM route 28 days later[16] or by aerosol[21]. Protection from aerosol challenge has not been replicated in more recent studies and vaccinated animals experienced pulmonary inflammation with significant lung pathology; the reasons for this are being studied further. Additionally, a single IM injection of rVSVΔG-ZEBOV-GP protected macaques against lethal IM challenge with the West African EBOV-Makona strain, with complete protection achieved against challenge 7 days post vaccination and partial protection at 3 days post vaccination[22]. In a post-exposure prophylaxis model, 50% of NHP vaccinated within 30 minutes after a severe (1000 median lethal dose [LD50]) aerosol EBOV challenge survived[23].

Various studies in animal models have shown no toxicities in rodent or NHP models, including in immunocompromised NHP[24]; particularly noteworthy was the absence of neurovirulence in NHP following intrathalamic inoculation[15]. Current Good Laboratory Practice (cGLP) repeated dose toxicology studies are ongoing to evaluate the toxicity and local tolerance of V920 in mice and monkeys. In these studies V920 was administered via IM injection on Study Days 1 and 14 followed by a 30-day observation period. BALB/c mice and cynomolgus monkeys received V920 at up to 2.0×10^7 pfu/animal and 1.0×10^8 pfu/animal, respectively. To date, there has been no evidence of systemic toxicity based on preliminary clinical pathology and necropsy data.

4.1.3 Ongoing Clinical Trials

Eight Phase 1 and four Phase 2/3 clinical trials are ongoing. The Phase 1 studies have been undertaken in North America (U.S. and Canada), Europe (Switzerland and Germany), and non-epidemic regions of Africa (Gabon and Kenya) to evaluate the immunogenicity and safety of V920 administered as pre-exposure prophylaxis. The four late phase studies include (1) a Phase 2 placebo-controlled trial in Liberia[25], (2) a Phase 3 trial in Sierra Leone with early and delayed vaccination arms, (3) a Phase 3 ring vaccination trial in Guinea, and (4) a Phase 3 immunogenicity, safety, and consistency lots trial in North America and Europe. Robust antibody responses to the ZEBOV-GP (with 100% of subjects seroconverting by 28 days) have been noted both by the enzyme-linked immunosorbent assay (ELISA) and virus neutralization assays in the Phase 1 program. After qualification and validation, these assays will be used to assess the antibody responses from subjects in the Phase 2/3 studies. If one assay is found to be sufficient to characterize the immune response, use of the assay that does not add value may be discontinued.

Preliminary efficacy and effectiveness data have been assessed in an interim analysis of ring vaccination trial in Guinea [26]. Per the publication, 7,651 subjects were included in the planned interim analysis which included 48 clusters (4,123 subjects) randomly assigned to immediate vaccination with V920 ($2x10^7$ pfu), and 42 clusters (3,528 subjects) randomly assigned to delayed vaccination with V920 ($2x10^7$ pfu). In the immediate vaccination group, there were no cases of EVD with symptom onset at least 10 days after randomization, whereas in the delayed vaccination group there were 16 cases of EVD from seven clusters reported, demonstrating a vaccine efficacy of 100% (95% CI: 74.7, 100.0; p=0.0036). At the cluster level, with the inclusion of all eligible adults, vaccine effectiveness was 75.1% (95% CI: 7.1, 94.2; p=0.1791). No new cases of EVD were diagnosed in vaccines from the immediate or delayed groups from 6 days post vaccination.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Future Ebola outbreaks are likely to occur in countries where HIV infection is endemic or present in large segments of the population. It is important to know whether V920 will be safe and effective in this patient population as efforts to roll out vaccination during an epidemic need to be quick and HIV testing may not be possible. Twenty two known HIV-infected individuals have received V920 in the Phase 2 placebo-controlled trial in Liberia, and the preliminary safety profile in this small number of subjects appeared to be generally similar to the overall vaccinated population. However, safety and immunogenicity of V920 has not been formally evaluated in HIV-infected individuals in a randomized controlled manner to date. This is what is intended with this study.

Persons 65 to 70 years were initially excluded and subsequently included as there are a number of potential participants in this age group who are interested in participating. The risk of including this age group is the risk that poor immunogenicity could be attributed to vaccine rather than to immunosenescence in this age group and that older HIV positive subjects may have a different safety profile. However, it is unlikely that immune and safety responses will be remarkably different in 60 to 65 year old subjects (who are currently eligible) compared to 66 to 70 year old subjects who will become eligible. To date over 400 non-HIV infected subjects over 65 years of age have been enrolled in clinical trials and safety concerns in this age group have not been identified to date. Detailed analyses of age strata >65 years of age are ongoing.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for the Use of Placebo Control

The use of placebo control will allow for comparison of safety and immunogenicity against an inert substance (normal saline). It is ethical to use normal saline in this study as Ebola is not circulating in areas where the study will be conducted. If an Ebola outbreak were to occur and local public health authorities recommended Ebola vaccination then placebo participants could

choose to receive an Ebola vaccine. Local public health guidance in each study site would be followed.

4.2.2.2 Vaccine Dose for This Trial

One dose of ≥2 x 10^7 pfu of the study vaccine or placebo will be administered at D0 in all Cohorts. In Cohort 5, a second dose of matching vaccine (≥2 x 10^7 pfu/ml) or placebo will be administered at Day 56. The rationale for assessing a second dose in HIV positive subjects is to access whether a second dose will provide a greater immune response or a response in a greater proportion of subjects in case one dose is less immunogenic in HIV positive subjects than in non-HIV positive subjects assessed in other studies. The 56 day interval is based on the interval utilized in other studies that include non-HIV positive adults and children.

4.2.3 Rationale for Endpoints

4.2.3.1 Immunogenicity Endpoints

1. Primary endpoints:
    a. ZEBOV-specific antibody responses measured by ELISA and neutralization on Day 28 in Cohorts 1-5 combined.
    b. ZEBOV-specific antibody responses measured by ELISA and neutralization on Day 28 after the last dose of vaccine (equivalent to Day 84 from first dose) in Cohort 5.
2. Secondary endpoints:
    a. ZEBOV-specific antibody responses measured by ELISA and neutralization on Day 28 in Cohort 5.
    b. ZEBOV-specific antibody responses measured by ELISA and neutralization on Days 180 and 365 after the first dose of vaccine.

The V920 vaccine candidate is a live recombinant vesicular stomatitis virus (VSV) expressing the glycoprotein (GP) of Zaire Ebola virus (ZEBOV). Two independent assays are currently being utilized in the clinical development program to clinically evaluate the immunogenicity of V920:

- GP-ELISA measures the total IgG antibody response and can also be correlated to the plaque reduction neutralization assay (PRNT) titer result.
- Plaque reduction neutralization assay (PRNT) is a functional assay and a gold standard platform in the field for quantitating the neutralizing antibody response elicited by the vaccine.

If in the clinical development program one assay is found to be sufficient to characterize the immune response, use of the assay that does not add value may be discontinued.

4.2.3.2 Safety Endpoints

1. Primary endpoints:
    a. The occurrence of adverse events, in all participants, in all cohorts:
        i. The occurrence of each solicited local and systemic AE, during a 14-day follow-up period following each vaccination, and fever, arthritis, arthralgia, rash and blisters/vesicular lesions during a 42-day follow – up period following vaccination.
        ii. The occurrence of any hematological (hemoglobin level, WBC, lymphocyte, neutrophil, eosinophil and platelet count) and biochemical (ALT, AST and creatinine) laboratory abnormality at days 0, 3, 7, 14, and 28 after each vaccination.
        iii. The occurrence of any unsolicited AE, during a 42-day follow-up period after each vaccination.
    b. The occurrence of vaccine related SAE through to Day 365.

2. Secondary endpoints:
    a. Detection of rVSV by PCR in blood, urine, and saliva in all subjects (D3, 7, 14, 28, 42 following each vaccination)
    b. Detection of rVSV by PCR in through 42 days from skin vesicles, joint fluid, or skin biopsies if specimens are obtained
    c. The occurrence of any SAE through to Day 365
    d. Decrease in CD4 T cell-count (i.e., CD4< 200 mm^3)
    e. Increase in HIV viral load (i.e., VL > 50 c/ml over two consecutive measurements)

Adverse events are collected 42 days post-vaccination for live-attenuated vaccines because of the time required for viral replication and manifestation of adverse events. The Memory Aid will prompt the subject to record his/her temperature for 42 days following vaccination starting with the day of vaccination (D0-D42). Injection site and systemic reactions will be monitored on the day of vaccination (D0) and for 14-days post-vaccination (D1-D14). In addition subjects will be prompted for joint pain, joint swelling, rashes, and blisters or vesicular lesions during the 42-day post-vaccination period as these events have been reported in the development program. Subjects who demonstrate these symptoms may be asked to return to the study site for additional evaluation and work-up. All other unsolicited systemic and/or injection-site adverse events will be recorded during the 42-day post-vaccination period. Following the 42-day detailed safety reporting period, any serious adverse events (SAEs) that occur through 12 months after first vaccination are to be reported in order to provide long-term safety data. Safety laboratory data is obtained through Day 42, as in Phase 1 studies transient decreases in white blood cells and platelets have been assessed for 28 days in HIV- subjects.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Potential risks may include those common to other vaccine products, and include local injection site reactions, as well as systemic reactions. The following sections discuss these potential risks in more detail and include brief descriptions for possible procedures to ameliorate risks and symptoms. All known risks and precautions described are explained in detail in the informed consent document. For live-attenuated vaccines such as V920 it is expected that the second dose of vaccine will have fewer safety concerns than the first dose of vaccine as the immune response from the first dose decreases viral replication.

4.3.1 Risks

4.3.1.1 Local Reactions

Local reactions, with either V920 or placebo, may include pain, swelling, and/or redness at the injection site. Although highly unlikely, IM injections, independent of investigational product, can result in acute muscle damage, bruising, and/or injection site infection.

Vaccine will be administered by experienced and trained staff, using aseptic technique, in order to minimize or avoid these risks.

4.3.1.2 Systemic Reactions

Systemic reactions include a predictable period of early reactogenicity which is common after receipt of other live-virus vaccines, and resolves spontaneously. On occasion, individuals may feel light-headed or faint after the act of injection or blood draw (vasovagal reaction).

Monitoring for these and other systemic symptoms commonly seen in investigational vaccine studies will be performed throughout the study, and addressed as required in order to maximize subject safety.

There is a theoretical risk of viral encephalitis or neurological impairment following vaccination with rVSV. As described previously, the vaccine vector has been specifically attenuated to eliminate neurovirulence, and the aforementioned NHP neurovirulence study supports the efficacy of this approach. Subjects will be closely monitored for vaccine neurological impact during the study.

Wild type VSV may also cause mild oral ulceration or stomatitis in humans. Volunteers will be closely monitored for such a manifestation and oral swabs will be performed to monitor for viral shedding in association with such a manifestation.

4.3.1.3 Reactions to V920

Detailed safety data collected in the Phase 2 and 3 studies to date have demonstrated V920 to be generally well-tolerated when administered to healthy, non-pregnant, adults. Injection site reactions following vaccination are generally mild to moderate and self-limited. Thereafter, there is a predictable period of early reactogenicity, including fever and a flu-like syndrome and resolves with 7 days. During this time, transient decreases in white blood cells and platelets

have also been observed but bleeding or increased risk of infection has not been reported. The early reactogenicity is likely to be a result of viremia with the vaccine virus which resolves within 2 weeks. Vaccine virus has been found in saliva, urine, and skin-vesicles in vaccines. Person-to-person transmission has not been documented, however transmission through shedding and close personal contact is accepted as a theoretical possibility. Joint pain (arthralgia) is part of the early flu-like syndrome in the first week after vaccination in up to 44% of vaccines. In a small proportion of subjects (<5%), joint swelling (arthritis) may develop in the 2nd to 3rd week after vaccination. The arthritis is thought to be virally-mediated, and while the majority of arthralgia and arthritis events resolved spontaneously, recurrent or persistent arthralgia and arthritis have also been reported. The safety profile reported from the Ebola-epidemic region has been similar to that observed outside the region.

4.3.1.4 Pregnancy

Risks from the study vaccines to human fetuses are unknown at this time. As such, pregnant females will be excluded from participation. All female subjects of childbearing potential must be abstinent from intercourse with a male partner or utilize effective contraceptive precautions, as defined in the inclusion criteria (section 8.4), from 30 days prior to the date of vaccination through 2 months after the last vaccination. Non-childbearing potential is defined as either surgically sterilized or one year post-menopausal (defined as 12 consecutive months without menses).

Given the theoretical risk of transmission to a female partner of child bearing potential, male subjects will also be required to utilize effective contraception precautions for the same period of time.

4.3.1.5 Lactation

Risks from the study vaccines to nursing infants are unknown at this time. As such, breastfeeding females will be excluded from participation, and female subjects will be required to avoid breastfeeding during the study to minimize any potential risk.

4.3.1.6 Venipuncture

Some discomfort from the needle stick for the blood draw is possible, including swelling or bruising, and there is a very small risk of infection at the site of the needle stick. A few subjects may feel light-headed and may develop a rapid heartbeat during blood collection. These symptoms can be stopped by having the subject lie down and/or by stopping the procedure.

4.3.1.7 Allergic Reaction

As with any product, there is the potential risk of a serious, or even life-threatening, allergic reaction to one or more components of the investigational products to be used in this study. To mitigate this risk, potential subjects with a history of severe allergic reaction of any kind,

or significant allergic reaction to a known component of the experimental products, will be excluded from participation.

In the event of a severe allergic reaction, each study site is staffed with trained medical personnel and stocked with appropriate medical emergency equipment to provide acute care for conditions such as anaphylaxis. Further, a formal emergency medical response service at each study site, capable of treating and transferring any life-threatening injuries to a higher level of medical care, will be available.

4.3.1.8 Unknown Risks

Furthermore, as with all research there is the remote possibility of risks that are unknown or that cannot be foreseen based on available information. This would include late effects that have been seen with some vaccines.

At the time of writing the protocol, the V920 study vaccine has been given to >20,000 participants in clinical trials in Africa. Serious adverse event reporting is monitored in real time in a blinded fashion. Un-blinded interim analyses have been performed in several trials.

4.3.1.9 Risks to the Study Personnel and the Environment

The principal risk for study personnel is exposure in the clinical setting to infectious pathogens from study subjects through various contact mechanisms (eg, needle stick exposure to blood borne pathogens and exposure to respiratory pathogens). There is also the theoretical risk of transmission of vaccine vector (rVSV) through exposure to shed vaccine in blood or body fluids. Adherence to routine practices and additional precautions and standard operating procedures (SOPs) for working with infectious agents will reduce the risk of exposure.

There are no known risks to the environment other than those associated with the generation of biohazardous waste attendant to vaccination of humans. All biohazardous waste will be disposed of as stipulated by local, state, and federal regulations and in accordance with study site SOPs.

Health Care Workers (HCW) were initially excluded and subsequently included in order to increase recruitment. During the original design of the trial HCWs were excluded because of the theoretical possibility that HIV infected persons would be more likely to shed vaccine vector following immunization due to their immune-compromise. Since that time accumulated evidence does show transient vector viremia but no evidence of transmission of the VSV vector. All study participants are given guidance about use of infection prevention and control measures and use of personal protective equipment to prevent sharing of secretions. It is anticipated therefore that the risk of a participant's VSV vector being transmitted to the persons they care for is very low. Health care workers are enrolled in other V920 studies and given guidance about infection prevention and control measures.

4.3.2 INTENDED BENEFIT FOR SUBJECTS

There is no intended direct benefit for study subjects. Subjects will receive a general health care screening as part of their participation in the study, and these results may be shared with their health care provider for their medical care, if permission of the participant is given. It is possible that vaccination with V920 may result in an immune response to Ebola virus. The protective efficacy of such a response is unknown.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with HIV-infection at least 13 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

To be eligible for the study, each participant must satisfy ALL of the following criteria:

1) HIV-infected adult or adolescent male or non-pregnant, non-breastfeeding female, ages 13 to 70 (inclusive) at the time of screening;
2) On antiretroviral therapy with an undetectable viral load (< 40 c/ml);
3) CD4 T cell counts ≥ 200 cells/mm^3;
4) Written informed consent (subject or parent) and assent (adolescent), after reading the consent form and having adequate opportunity to discuss the study with an investigator or a qualified designee
5) Free of clinically significant health problems that could affect the safety of the participant, as determined by the Investigator by pertinent medical history and clinical examination prior to entry into the study;
6) Available, able, and willing to participate for all study visits and procedures;
7) Males and females who are willing to practice abstinence from sexual intercourse, or are willing to use effective methods of contraception, from at least 30 days prior to vaccination until 2 months after vaccination.
    a. If the partner is NOT of childbearing potential, the couple will only be required to use condoms, without other adjunctive contraception.
    b. For this study, a woman is considered of childbearing potential unless postmenopausal (≥ 1 year without menses) or surgically sterilized (tubal ligation, bilateral oophorectomy, or hysterectomy)
    c. Effective contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:
        i. Male condoms PLUS:

ii. Oral contraceptives, either combined or progestogen alone
iii. injectable progestogen
iv. implants of etenogestrel or levonorgestrel
v. oestrogenic vaginal ring
vi. percutaneous contraceptive patches
vii. intrauterine device or intrauterine system

8) Be willing to minimize blood and body fluid exposure of others for 8 weeks after vaccination
   a. Avoiding the sharing of needles, razors, or toothbrushes
   b. Avoiding open-mouth kissing

5.1.3 Subject Exclusion Criteria

Participants with any of the following criteria will be excluded:

1. History of prior infection with a filovirus or prior participation in a filovirus vaccine trial;
2. History of prior infection with VSV or receipt of a VSV-vectored vaccine;
3. Presence of any febrile illness or any known or suspected acute illness on the day of any first immunization (subject may be rescheduled);
4. Clinical manifestations of systemic diseases considered by the investigator to impact safety or immunogenicity
5. Receipt of systemic glucocorticoids (a dose ≥ 20 mg/day prednisone or equivalent) within one month, or any other cytotoxic or immunosuppressive drug within 12 months;
6. Receipt of any investigational drug within 12 months of vaccination;
7. Receipt of any live virus vaccine within 42 days prior to study entry or any other (non-live virus) vaccine within 14 days prior to study entry.
8. History of sensitivity to any component of study vaccines per investigator brochure or package insert;

Any baseline laboratory screening tests which is outside of acceptable range as defined in the protocol (local site reference ranges): ALT, AST, creatinine, hemoglobin, platelet count, total white blood cell count, urine protein, urine occult blood, urine glucose AND considered clinically significant by the clinical investigator. The following five screening parameters have limits set:

a. absolute lymphocyte count ≥1000 cells/mm^3
b. hemoglobin not greater than 1.5 grams below the lower limit of the normal reference range at the local laboratory
c. ALT, AST not greater than 2 to 2.5 times the upper limit at the local laboratory

d. Platelet count ≥ 125,000 and ≤ 550,000

9. To exclude transient laboratory abnormalities, the investigator may repeat a specific test (E.g. hemoglobin) once during the screening period (I.e. a maximum of two tests), , and if the repeat test is normal, subject may be enrolled;
10. Have an active malignancy or history of metastatic or hematologic malignancy except non-melanoma skin cancers;
11. Suspected or known alcohol and/or illicit drug abuse within the past 5 years;
12. Moderate or severe illness and/or fever >101°F (38.3ºC) orally or > 100°F (37.8ºC) axillary within one week prior to vaccination;
13. Pregnant or breastfeeding female, or female who intends to become pregnant during the study period;
14. Administration of immunoglobulins and/or any blood products within the 120 days preceding study entry or planned administration during the study period;
15. Any other significant finding that in the opinion of the investigator would increase the risk of the individual having an adverse outcome from participating in this study.

5.2 Trial Vaccination

The vaccines to be used in this trial are outlined below in Table 2:

Table 2: Trial Treatment/Vaccination

Vaccine	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use
V920	≥2x10^7 PFU in 1mL	Once in cohorts 1-4/Twice in Cohort 5	IM	Visit 1, D0 and Visit 7 (Day 56), where applicable	Experimental
Normal saline (0.9%)	1 ml	Once in cohorts 1-4/Twice in Cohort 5	IM	Visit 1, D0 and Visit 7 (Day 56), where applicable	Placebo-control
Subjects in Cohort 5 will receive two doses of V920 ≥2x10^7 PFU or two doses of normal saline placebo (0.9%) on D0 and D56.					

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

The vaccine dose will be administered at the trial site at Visit 1 (and Visit 7 for Cohort 5). Participants will be observed 30 minutes after vaccination to monitor for immediate hypersensitivity reactions.

All products indicated in Table above will be provided centrally by the Manufacturer or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

5.2.1 Formulation, Packaging, and Labeling of V920

The rVSVΔG-ZEBOV-GP vaccine (V920) consists of a single recombinant VSV isolate modified to replace the gene encoding the G envelope glycoprotein with the gene encoding the envelope glycoprotein from Ebola virus-Zaire.

The vaccine product is supplied in a sterile 1.0-mL vials. Each vial contains vaccine virus frozen in a mixture of 10mM Tris, pH 7.2 and recombinant human serum albumin 2.5 mg/mL. After thawing, the content of the vials is a clear liquid. The vaccine concentration in the vial is titered to at least $2x10^7$pfu/mL (stock).

5.2.2 Storage and Stability

rVSVΔG-ZEBOV-GP vaccine product (V920) is to be stored at or below -60°C for long-term storage. Storage temperature will be continuously monitored and recorded. Vaccine product will be stored in a locked room with access restricted to only necessary study site personnel. Vaccine should be stored and transported at temperatures at or below -60°C.

Normal saline (0.9%) should be stored according to its labeling.

5.2.3 Preparation, Administration, and Dosage of V920

rVSVΔG-ZEBOV-GP vaccine (V920) will be administered as an IM injection. V920 should be removed from the freezer and thawed at room temperature (not 2-8°C) for approximately 10-15 minutes. The thawed vial should then be gently inverted several times prior to withdrawal with the syringe. The study vaccine is considered to be thawed when there is no visible ice on the outside of the vial. The study vaccine should appear as a colorless liquid with no particulates visible. If the study vaccine appears cloudy or has particulates, a replacement vial should be assigned and administered. Once thawed in the clinic, a total cumulative of 15 minutes at 25°C and/or 27 days at 2-8°C is permitted. Refreezing is not permitted by the end user. The formulation and/or image of the study vaccine and placebo control may appear

different. Therefore, an unblinded pharmacist (or other designated unblinded person) at the site will be required to prepare the study vaccine/placebo in order to maintain the blinding. The unblinded personnel will not participate in post-vaccination assessments. Both study vaccine and placebo are clear, and indistinguishable from one another once in the syringe. Once the syringe is prepared, the blinded personnel will administer the study vaccine/placebo to the subject. If V920 is administered, a dose of $2x10^7$ pfu/mL will be given in a 1mL volume. Prior to injection, the area to be injected will be cleaned with an alcohol swab. 1.0 mL of study vaccine/placebo should be administered intramuscularly (IM) in the deltoid muscle of the non-dominant arm at a 90º angle into the muscle tissue, using a needle long enough to ensure IM deposition of the study vaccine/placebo. A 1-inch #23-gauge needle is recommended. The vaccination arm must be recorded on the appropriate case report form for future reference in the event of potential injection-site reaction(s). Emergency medical supplies including epinephrine and advanced airway support will be available in case of serious allergic reaction.

5.2.4 Dose Selection/Modification

5.2.4.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.5 Timing of Dose Administration

All subjects will receive on D0 either the V920 (rVSVΔG-ZEBOV-GP) vaccine at a dose of $\geq 2x10^7$ PFU in 1mL IM, or normal saline (0.9%) placebo control in 1mL volume. Subjects in Cohort 5 will also receive on D56 a matching dose of either the V920 at a dose of $\geq 2x10^7$ PFU in 1mL IM, or normal saline (0.9%) placebo control in 1mL volume.

5.2.6 Trial Blinding

This is a double-blind trial; therefore, the Sponsor, investigator, and subject will not know the vaccine administered until unblinding.

5.3 Randomization or Treatment Allocation or Vaccine Allocation

Subjects will be assigned randomly according to a computer-generated allocation schedule. Participants will be randomized 4:1 (study vaccine: placebo control) using centralized randomization, with a total of approximately -200 study vaccine recipients and 50 placebo control recipients. Treatments will be stratified as described below.

5.4 Stratification

To satisfy the requirement that each site enrolls at least one placebo subject in each cohort, enrollment will proceed until treatments have been randomized to at least one complete block of subjects (consisting of four subjects receiving treatment and one receiving placebo) at each site.

Treatment allocation/randomization will be stratified by the 5 cohort groups:

Cohort 1: Screening CD4 cell counts for adults: CD4 cells/mm3 ≥ 500

Cohort 2: Screening CD4 cell counts for adults: CD4 cells/mm3 >350 and < 500

Cohort 3: Screening CD4 cell counts for adults: CD4 cells/mm3 ≥ 200 and ≤ 350

Cohort 4: Screening CD4 cell counts for adolescents, age 13 to 17: CD4 cells/mm3 ≥ 200

Cohort 5: Screening CD4 cell counts for adults and adolescents, age 13 to 17: CD4 cells/mm3 ≥ 200 with 2 doses.

All sites are stratified by site (two sites per cohort).
Cohort 5 is stratified by site, and by age group (adolescent vs. adult). Once three blocks of five adolescents have been enrolled, with at least one block at each site, the requirement to enroll at least 12 adolescents in Cohort 5 will be met.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. The investigator should discuss any questions regarding this with the Medical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

Listed below are specific restrictions for concomitant therapy or vaccination following each vaccination:

1. Systemic glucocorticoids (a dose ≥ 20 mg/day prednisone or equivalent) within one month, or any other cytotoxic or immunosuppressive drug within twelve months;
2. Any investigational drug within twelve months;
3. Any live virus concomitant vaccinations within 42 days
4. Any other (non-live) concomitant vaccinations within 14 days

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw from the trial at any time for any reason or the subject may be withdrawn from the trial at the discretion of the investigator should any untoward effect occur. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

1. The subject or legal representative (such as parent or legal representative) withdraws consent from the trial.
2. The subject is lost to follow-up

5.8 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.9 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The subject participation portion of the overall trial ends when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall trial ends when the Sponsor receives the last serology assay result or subject data from the last study-related phone call or visit and the database has been cleaned and locked.

5.10 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early. The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

(COHORTS 1- TO 4)

Trial Period:	Screening	Vaccination	Follow-up						
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
Administrative Procedures									
Informed Consent	x								
Inclusion/Exclusion Criteria	x	x							
Subject Identification Card	x	x							
Medical History	x	x							
Concomitant Medication Review	x	x	x	x	x	x	x	x	x
Randomisation/Vaccine Administration		x							
Clinical Procedures/Assessments									
Full Physical Examination	x								
Height	x								
Weight	x								
Vital Signs (heart rate, blood pressure, respiratory rate, oral/tympanic/axillary temperature)	x	x	x	x	x	x	x	x	x
Post vaccination Monitoring for Hypersensitivity Reactions (30 Minutes)		x							
Non-Serious Adverse Events Monitoring		x	x	x	x	x	x		
Serious Adverse Events Monitoring	x	x	x	x	x	x	x	x	x

Trial Period:	**Screening**	**Vaccination**	**Follow-up**						
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
Distribute Patient Memory Aid and Review Procedures with Subject		x							
Review Arthralgia/Arthritis, Rash and/or Vesicular Lesion Reporting Requirements with Subject[a]	x	x	x	x	x	x	x		
Review Memory Aid with Subject			x	x	x	x	x		
Collect Memory Aid from Subject							x		
Laboratory Procedures/Assessments									
Hematology (~4mls)	x	x	x	x	x	x	x		
Urinalysis	x								
Chemistry (~8mls)	x	x	x	x	x	x	x		
Urine Pregnancy Test (if applicable based on subject's age/gender)	x	x							
HIV serology (if not previously documented) (~8mls)	x								
HBsAg (~8mls)	x								
Hepatitis B & C serology (combined with HBsAg)	x								
ZEBOV-specific Serum Antibodies (~20mls-combined with ZEBOV-specific Neutralizing antibodies)		x[b]				x		x	x
ZEBOV-specific Neutralizing antibodies (see volume above)		x[b]				x		x	x

Trial Period:	**Screening**	**Vaccination**	**Follow-up**						
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
VSV (Blood, Urine and Saliva Sample) (~5mls blood)			x	x	x	x	x		
HIV viral load (~8mls)	x	x	x	x	x	x	x	x	x
CD4/CD8 T Lymphocytes count (~4mls)	x	x	x	x	x	x	x	x	x
HIV RNA (reservoirs) (~20 mls combined with HIV DNA and HIV TILDA below)		x				x		x	x
HIV DNA (reservoirs) (see volume above)		x				x		x	x
HIV TILDA (reservoirs) (see volume above)		x				x		x	x
*Biobank samples-optional (~35mls)		x[b]				x		x	x
Total Blood volumes (*including optional Biobank sample)	~ 40mls	~64mls (*~89mls)	~29mls	~29mls	~29mls	~69mls (*~94mls)	~29mls	~52mls (*~87mls)	~52mls (*~87mls)

a. Specimens should be obtained for rVSV detection by PCR in through 42 days from skin vesicles, joint fluid, or skin biopsies

b. Specimens should be obtained before vaccination

(COHORT 5)

Trial Period:	**Screening**	**Vaccination**	**Follow-up**												
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**56**	**3 days post dose 2**	**7 days post dose 2**	**14 days post dose 2**	**28 days post dose 2**	**42 days post dose 2**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±3**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
Administrative Procedures															
Informed Consent	x														
Inclusion/Exclusion Criteria	x	x						x							
Subject Identification Card	x	x													
Medical History	x	x													
Concomitant Medication Review	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomisation/		x													
Vaccine Administration		x						x							
Clinical Procedures/Assessments															
Full Physical Examination	x			c.											

Trial Period:	**Screening**	**Vaccination**	**Follow-up**												
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**56**	**3 days post dose 2**	**7 days post dose 2**	**14 days post dose 2**	**28 days post dose 2**	**42 days post dose 2**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±3**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
Height	x														
Weight	x														
Vital Signs (heart rate, blood pressure, respiratory rate, oral/tympanic/axillary temperature)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Post vaccination Monitoring for Hypersensitivity Reactions (30 Minutes)		x						x							
Non-Serious Adverse Events Monitoring		x	x	x	x	x	x	x	x	x	x	x	x		
Serious Adverse Events Monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Distribute Patient Memory Aid and Review Procedures with Subject		x						x							
Review Arthralgia/Arthritis, Rash and/or Vesicular Lesion Reporting Requirements with Subject[a]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Review Memory Aid with Subject			x	x	x	x	x	x	x	x	x	x	x		

Trial Period:	**Screening**	**Vaccination**	**Follow-up**												
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**56**	**3 days post dose 2**	**7 days post dose 2**	**14 days post dose 2**	**28 days post dose 2**	**42 days post dose 2**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±3**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
Collect Memory Aid from Subject							x						x		
Laboratory Procedures/Assessments															
Hematology (~4mls)	x	x	x	x	x	x	x	x	x	x	x	x	x		
Urinalysis	x														
Chemistry (~8mls)	x	x	x	x	x	x	x	x	x	x	x	x	x		
Urine Pregnancy Test (if applicable based on subject's age/gender)	x	x						x							
HIV serology (if not previously documented) (~8mls)	x														
HBsAg (~8mls)	x														
Hepatitis B & C serology (combined with HBsAg)	x														

Trial Period:	**Screening**	**Vaccination**	**Follow-up**												
Visit Number/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Day:	**-30 to 0**	**0**	**3**	**7**	**14**	**28**	**42**	**56**	**3 days post dose 2**	**7 days post dose 2**	**14 days post dose 2**	**28 days post dose 2**	**42 days post dose 2**	**180**	**365**
Scheduling Window (Days):	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±7**	**±3**	**±1**	**±1**	**±3**	**±3**	**±7**	**±14**	**±28**
ZEBOV-specific Serum Antibodies (~20mls-combined with ZEBOV-specific Neutralizing antibodies)		x[b]				x		x[b]				x		x	x
ZEBOV-specific Neutralizing antibodies (see volume above)		x[b]				x		x[b]				x		x	x
VSV (Blood, Urine and Saliva Sample) (~5mls blood)			x	x	x	x	x	x	x	x	x	x	x		
HIV viral load (~8mls)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CD4/CD8 T Lymphocytes count (~4mls)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Total Blood volumes	~ 40mls	~44mls	~29 mls	~29 mls	~29 mls	~49 mls	~29 mls	~49 mls	~29 mls	~29 mls	~29 mls	~49 mls	~29 mls	~32 mls	~32 mls

a **Specimens should be obtained for rVSV detection by PCR in through 42 days from skin vesicles, joint fluid, or skin biopsies**

b Specimens should be obtained <u>before</u> <u>vaccination</u>

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

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

The subject identification card also contains contact information for the emergency unblinding so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Record any pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 6 months before dose of trial vaccination.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

7.1.1.8 Trial Compliance

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

Administration of trial vaccination will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

Cohorts 1 to 5:

At the screening visit after the Informed consent will be signed a full medical evaluation will be performed, including physical examination, vital signs (heart rate, blood pressure, oral/tympanic/axillary temperature, respiratory rate), height and weight.

Cohorts 1 to 4:

At visit 1 (Randomization /vaccination), the inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject still qualifies for the trial. Vital Signs will be taken (including heart rate, blood pressure, oral/tympanic/axillary temperature, respiratory rate). Participant will be coming to the center at day 3 (visit 2), day 7 (visit 3), day 14 (visit 4), day 28 (visit 5), day 42 (visit 6), day180 (visit 7) and day 365 (visit 8). Vital Signs will be taken (including heart rate, blood pressure, oral/tympanic/axillary temperature, respiratory rate) at all visits. Non-Serious Adverse Events including solicited and unsolicited adverse events will be monitored at every visit through Day 42. Serious Adverse Events will be monitored at every visit through Day 365.

Cohort 5:

At visit 1 (Randomization /vaccination), the inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject still qualifies for the trial. At visit 1 (first dose of vaccine or placebo) and visit 7 (second dose of matching vaccine or placebo), vital signs will be taken (including heart rate, blood pressure, oral/tympanic/axillary temperature, respiratory rate)

Participant will be coming to the study site at Screening (day -30 to 0), day 0 (visit 1), day 3 (visit 2), day 7 (visit 3), day 14 (visit 4), day 28 (visit 5), day 42 (visit 6), day 56 (visit 7), 3 days post dose 2 (visit 8), 7 days post dose 2 (visit 9), 14 days post dose 2 (visit 10), 28 days post dose 2 (visit 11), 42 days post dose 2 (visit 12), day180 (visit 13) and day 365 (visit 14). Vital Signs will be taken (including heart rate, blood pressure, oral/tympanic/axillary

temperature, respiratory rate) at all visits. Non-Serious Adverse Events including solicited and unsolicited adverse events will be monitored at every visit after first dose of vaccine or placebo through Day 42. Non-Serious Adverse Events including solicited and unsolicited adverse events will be monitored at every visit after second dose of matching vaccine or placebo through Day 42. Serious Adverse Events will be monitored at every visit through Day 365.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn/collected over the course of the trial including approximate blood volumes drawn/collected by visit and by sample type per subject will not exceed 10.5mls/kg or 550mls, whichever is less, in an 8 week period as per NIH recommendations (https://irb.research.chop.edu/sites/default/files/documents/g_ nih_blood draws. pdf). In addition to anti-Ebola immune assessments blood samples, optional blood samples will be drawn at visits 1, 5, 7, & 8 (cohorts 1-4) if subjects sign a separate consent form. These samples will be conserved in a biobank for future research studies. These studies will serve to add in depth knowledge on the Ebola-specific and HIV-specific immune responses as it relates to cytotoxic T cells activation, innate immunity and virological studies. All study samples will be managed by the Canadian Center for Vaccinology (CCfV), Halifax, NS, under the custody of Dalhousie University on behalf of the Canadian Immunization Research Network (CIRN). Testing of samples will be conducted by Focus Diagnostics Clinical Trials, a Q2 Solutions Quintiles Quest Joint Venture Company, located at 33608 Ortega Highway, San Juan Capistrano, CA 92675 and at the lab of Dr. Cecile Tremblay, the Laboratory of Retrovirology, CRCHUM at 900 St- Denis street Tour Viger, Montreal.

7.1.3.1 Laboratory Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 3.

Table 3: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Blood Urea Nitrogen	Blood	Urine pregnancy test
WBC (total and differential)	Creatinine	Glucose	Hepatitis B and C Serology
Platelets	Alanine aminotransferase (ALT)	Protein	HbsAg
RBC	Aspartate aminotransferase (AST)		HIV ELISA
Hematocrit	Glucose	Microscopic exam, if abnormal results are noted	HIV viral load

Hematology	Chemistry	Urinalysis	Other
MCV (mean corpuscular volume)			CD4/CD8+ Lymphocytes
MCH (mean corpuscular hemoglobin)			Serum antibodies against ZEBROV and Neutralizing antibodies (GMT) (sent to Focus Laboratory)
MCHC (mean corpuscular hemoglobin concentration)			VSV-urine, saliva, plasma and any AE samples (sent to Focus Laboratory)
RDW (RBC Distribution Width)			HIV RNA, HIV DNA, HIV TILDA and optional Biobank Samples-sent to CRCHUM laboratory (Cohort 1 – 4 only)
			C-Reactive Protein

7.1.4 Other Procedures

7.1.4.1 HIV Viral Load

HIV viral load will be monitored throughout the study. Standard of care treatment appropriate for the viral load, clinical presentation, and other clinical laboratory evaluation will be provided.

7.1.4.2 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from completion of all study related procedures should be encouraged to continue to be followed for safety assessment at all remaining study visits.

7.1.4.3 Blinding/Unblinding

This is a double blind trial; unblinding will be performed after the database is locked.

A participant may be unblinded during the course of the study if the PI deems that, for health purposes, the blind must be broken. Only in the case of an emergency, when knowledge of whether the participant has received the investigational product is essential for the clinical management or welfare of the participant, the investigator may authorize the unblinding of a participant's treatment assignment. If time permits, the investigator or qualified study staff

designee is encouraged to contact the Sponsor coordinating PI, Dr. Joanne Langley, prior to breaking the blind.

7.1.4.4 Calibration of Critical Equipment

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

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 30 days prior to treatment allocation/randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. To exclude transient laboratory abnormalities, the investigator may repeat a test once during the screening period (ie a maximum of two tests), and if the repeat test is normal, subject may be enrolled. If the screening period for a particular study cohort has elapsed, a participant who was not eligible for an earlier cohort may be screened for eligibility for a later cohort.

7.1.5.2 Vaccination Visit

One dose of study vaccine will be administered at Visit 1 to participants in Cohort 1-4. Two doses of study vaccine will be administered to Cohort 5 participants: first at visit 1 and second dose at visit 7.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a preexisting condition that is temporally associated with the use of the Study product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time.

Study product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including active control medication) or marketed (including normal saline placebo), provided by or distributed by the Sponsor for human use in this study.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to study procedures. From the time of allocation/randomization through 42 days following each vaccination, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Pre-existing conditions or signs and/or symptoms present in a participant prior to the first study injection are not considered to be adverse events. These events will be recorded in the participants' medical history.

7.2.1 Definition of an Overdose and Reporting Overdose to the Sponsor

In this trial, an overdose is defined as greater than one dose of the investigational V920 vaccine/placebo.

7.2.2 Events Specific to Post Vaccination

Study subjects who develop joint pain, swelling or stiffness (arthralgia/arthritis) symptoms, a rash and/or small vesicles from day of vaccination until day 42 following each vaccination are instructed to notify the study site. They will be assessed by the investigator, and it will be determined if they require any additional samples collected, and/or a referral for specialist care, if needed. Specific instructions are provided to the sites in a guidance document for the assessment and work-up of these specific post vaccination events.

7.2.3 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 42 days following any vaccination must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Immediate Reporting of Adverse Events to the Sponsor

7.2.4.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Study product that:

- results in death;
- is life threatening;
- results in persistent or significant disability/incapacity;
- results in or prolongs an existing inpatient hospitalization;
- is a congenital anomaly/birth defect;
- is another important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 4 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention or procedure.

For the time period beginning at treatment allocation/randomization through 365 days following first vaccination, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Study product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting

procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event brought to the attention of an investigator who is a qualified physician at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the subject completing the trial, but outside the time period specified in the previous paragraph.

or

2. A serious adverse event that is considered by an investigator who is a qualified physician to be vaccine related.

All subjects with serious adverse events must be followed up for outcome.

7.2.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 42 days following vaccination, any ECI, or follow up to an ECI, whether or not related to the Study product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. An overdose of Study product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

7.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 4. The investigator's assessment of causality is required for each adverse event. Refer to Table 4 for instructions in evaluating adverse events.

Table4: Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination (D0) through Day 14 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose that:	
	†**Results in death; or**	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of study product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements; **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test vaccine and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose vaccine trial.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**	
Yes, there is a reasonable possibility of vaccine relationship.	There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.	
No, there is not a reasonable possibility of vaccine relationship	Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR the AE is more likely explained by another cause than the Study product. (Also entered for a subject with overdose without an associated AE.)	

7.2.6 Sponsor Responsibility for Reporting Adverse Events

All Serious Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Stakeholder Group

This trial was developed in collaboration with a group of stakeholders comprised of Dalhousie University, CIRN, IDRC, Merck and the trial P.I.

7.3.2 Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee comprises:

- Sponsor Representatives
- Investigators participating in the trial
- Manufacturer Representative

The Trial Steering Committee will provide guidance on the operational aspects of the trial, and will receive and implement recommendations from the DSMB.

7.3.3 Data Safety and Monitoring Board

To supplement the routine trial monitoring outlined in this protocol, an external DSMB will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DSMB must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DSMB will make recommendations to the Trial Steering Committee regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DSMB will review interim safety results, consider the overall risk and benefit to trial participants and recommend to the Trial Steering Committee if the trial should continue in accordance with the protocol. Specific stopping rules can be found in Section 14. Appendix 3.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DSMB reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DSMB. The DSMB will monitor the trial at an appropriate frequency, as described in the detailed DSMB charter. The DSMB will also make recommendations to the TSC regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DSMB recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2.

Study Design Overview	V920 (rVSVΔG-ZEBOV-GP) Ebola Virus Vaccine Candidate in HIV-Infected Adults and Adolescents
Treatment Assignment	Participants in Cohort 1-4, will be randomly assigned to receive one dose of ≥2 x 10^7 pfu of the study vaccine or the placebo control in a ratio of 4 to 1 (200:50). Participants in Cohort 5 will be randomly assigned to receive one dose of ≥2 x 10^7 pfu of the study vaccine or the placebo control in a ratio of 4 to 1 (40:10) on Day 0, followed by booster vaccination at Day 56.
Primary Endpoint(s)	Safety, and ZEBOV-specific antibody responses.
Analysis Populations	The Per-Protocol population (PP) will serve as the primary population for the analysis of immunogenicity data in this study. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary immunogenicity endpoint(s). For example, subjects who are seropositive at baseline will be excluded from the Per-Protocol population. All subjects who meet the inclusion criteria, were seronegative at baseline, and do not have a major protocol deviation will be included in the per-protocol analysis. The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study vaccination. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who received incorrect study vaccine will be included in the treatment group corresponding to the study vaccine actually received.
Statistical Methods for Immunogenicity Analyses	Immunogenicity summaries will include: means and 95% CIs of the Geometric Mean Titers (GMT) and Geometric Mean Fold Increase from baseline (GMFI) of ZEBOV-specific antibody responses at baseline and Day 28, Day 84 (Cohort 5 only), Day 180, and Day 365. Immunogenicity summaries will include: counts, percentages, and 95% CIs of subjects who achieve seroconversion (e.g. 4-fold increase) for

	ZEBOV-specific antibody responses at baseline and Day 28, Day 84 (Cohort 5 only), Day 180, and Day 365. Immunogenicity summaries will include: counts, percentages, and 95% CIs of subjects who achieve seroprotection for ZEBOV-specific antibody responses at baseline and Day 28, Day 84 (Cohort 5 only), Day 180, and Day 365 based on correlate of protection thresholds, if found. Fisher's exact (primary) or Chi-square test (secondary if sample size warrants) will be used to compare the frequency of ZEBOV-specific antibody responses and Student's t (primary) or Wilcoxon rank-sum test (secondary if not normally distributed) will be used to compare ZEBOV-specific GMT ZEBOV-specific antibody between treatment groups. All hypotheses will be evaluated using two-sided tests at $\alpha = 0.05$. Superiority of immune response will be defined as a statistically significant difference.
Statistical Methods for Safety Analyses	Counts and percentages of solicited local and systemic reaction frequency and severity among study cohorts (various CD4 counts and ages) will be summarized. Fisher's exact or Chi-square test will be used to compare the frequency of local and systemic reactions between treatment groups as specified in the SAP.
Multiplicity	Adjustment for multiplicity will not be performed.
Sample Size and Power	For immunogenicity assessment, there is 80% power to detect a Geometric Mean Ratio (GMR) of 1.6 (V920 GP-ELISA GMT of 58 EU/mL vs. Placebo GP-ELISA GMT of 36 EU/mL, the lower limit of quantification [LLOQ]) and 90% power to detect a GMR of 1.7 (V920 GP-ELISA GMT of 62 EU/mL) if comparing all five cohorts (N=200 V920 vs. N=50 Placebo) combined. This power analysis assumes a 10% dropout, a standard deviation of 1 on the log scale, and a 2-sided 5%. There is 80% power to detect a GMR of 2.9 (V920 GP-ELISA GMT of 105 EU/mL) and 90% power to detect a GMR of 3.4 (V920 GP-ELISA GMT of 124 EU/mL) if comparing each cohort independently (N=40 V920 vs. N=10 Placebo). This power analysis assumes a 10% dropout, a standard deviation of 1 on the log scale, and a 2-sided 5%. For safety assessment, there is 80% power to detect a 12% difference in event rates that occur with a frequency of 1% in the control group if comparing all four cohorts (N=200 V920 vs. N=50 Placebo) combined and a 46% difference if comparing each cohort independently (N=40 V920 vs. N=10 Placebo).
Subgroup Analyses and Effect of Baseline Factors	Safety, immunogenicity, seroprotection, and seroconversion will be summarized for these pre-specified subgroups: CD4 cell count ($\geq$ 500 cells/mm3, $>$ 350 and $<$ 500 cells/mm3, CD4 $\geq$ 200 and $\leq$ 350 cells/mm3), and age (adults, adolescents).
Interim Analyses	Four safety analyses will be conducted, one for each of the first four cohorts, when each cohort will have completed 42 days of follow-up post-vaccination

8.2 Statistical Analysis Plan Detailed Description

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the CIRN Biostatistics department.

8.2.2 Objectives/Hypotheses

(1) Objective: Evaluate the safety and tolerability of V920 in HIV-infected adults and adolescents.

(2) Objective: Evaluate the immunogenicity of V920 via ZEBOV-specific antibody responses induced by V920 at D28 in HIV-infected adults and adolescents.

Primary Hypotheses:

1) The geometric mean titer (GMT) of GP-ELISA in V920 vaccinated HIV-infected adults and adolescents will be superior to the GMT of the GP-ELISA in placebo vaccinated HIV-infected adults at Day 28 in Cohorts 1-5 combined.

8.2.3 Analysis Endpoints

8.2.3.1 Immunogenicity Endpoints

The V920 vaccine candidate is a live recombinant vesicular stomatitis virus (VSV) expressing the glycoprotein (GP) of Zaire Ebola virus (ZEBOV). Two independent serological and molecular assays are currently being developed to clinically evaluate the immunogenicity of V920:

- GP-ELISA measures the total IgG antibody response and can also be correlated to the plaque reduction neutralization assay (PRNT) titer result.
- Plaque reduction neutralization assay (PRNT) is a functional assay for quantitating the neutralizing antibody response elicited by the vaccine.

Participants who consent to bio-bank will undergo up to four blood draws in cohorts 1-4: at baseline on the day of vaccination before vaccine or placebo is administered; at D28 post-vaccination; at D180 post-vaccination; and at D365 post-vaccination.

8.2.4 Analysis Populations

8.2.4.1 Immunogenicity Analysis Populations

The Per-Protocol population (PP) will serve as the primary population for the analysis of immunogenicity data in this study. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary

immunogenicity endpoint(s). For example, subjects who are seropositive at baseline will be excluded from the Per-Protocol population. All subjects who meet the inclusion criteria, were seronegative at baseline, and do not have a major protocol deviation will be included in the per-protocol analysis.

The final determination of subjects with major protocol deviations, and thereby the composition of the Per- Protocol population, will be made prior to the unblinding of the database for the primary CSR (see Section 8.2.1) and will be documented in a separate memo.

A supportive analysis using the Full Analysis Set (FAS) population may be performed. The FAS population consists of all randomized subjects with serology data.

8.2.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study vaccination. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who received incorrect study vaccine will be included in the treatment group corresponding to the study vaccine actually received.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Immunogenicity Analyses

Immunogenicity summaries will include: means and 95% CIs of the Geometric Mean Titers (GMT) and Geometric Mean Fold Increase from baseline (GMFI) of ZEBOV-specific antibody responses at baseline and Day 28, Day 84 (Cohort 5 only), Day 180, and Day 365.

Immunogenicity summaries will include: counts, percentages, and 95% CIs of subjects who achieve seroconversion (e.g. 4-fold increase) for ZEBOV-specific antibody responses at baseline and Day 28, Day 84 (Cohort 5 only), Day 180, and Day 365.

Immunogenicity summaries will include: counts, percentages, and 95% CIs of subjects who achieve seroprotection for ZEBOV-specific antibody responses at baseline and Day 28, Day 84 (Cohort 5 only), Day 180, and Day 365 based on correlate of protection thresholds, if found.

Fisher's exact (primary) or Chi-square test (secondary if proportion size warrants) will be used to compare the frequency of ZEBOV-specific antibody responses and Student's t (primary) or Wilcoxon rank-sum test (secondary if not normally distributed) will be used to compare ZEBOV-specific GMT ZEBOV-specific antibody between treatment groups. All hypotheses will be evaluated using two-sided tests at $\alpha = 0.05$. Superiority of immune response will be defined as a statistically significant difference.

8.2.5.2 Statistical Methods for Safety Analyses

Safety parameters will be compared between V920 and placebo control. Fisher's exact or Chi-square test will be used to compare the frequency of local and systemic reactions between treatment groups as specified in the SAP.

Vaccine reactogenicity

Counts and percentages of solicited local and systemic reaction frequency and severity among study cohorts (various CD4 counts and ages) will be summarized.

Adverse events will be classified by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term, severity, seriousness, investigator causality assessment, and time since vaccination.

Safety listings will display all safety events, including a separate display of solicited post-treatment reactions, and all other AEs.

Vital signs & clinical laboratory measures

Mean values for each measure, including ± one standard deviation, will be summarized for each treatment group. Shift tables may also be generated if a significant frequency of abnormalities is noted. Extreme values will be discussed individually.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Continuous variables, such as age and weight, will be characterized by descriptive statistics. Categorical variables, such as ethnicity, will be displayed by percentage frequencies.

8.2.6 Multiplicity

Adjustment for multiplicity will not be performed.

8.2.7 Sample Size and Power Calculations

For immunogenicity assessment, there is 80% power to detect a Geometric Mean Ratio (GMR) of 1.6 (V920 GP-ELISA GMT of 58 EU/mL vs. Placebo GP-ELISA GMT of 36 EU/mL, the lower limit of quantification [LLOQ]) and 90% power to detect a GMR of 1.7 (V920 GP-ELISA GMT of 62 EU/mL) if comparing all five cohorts (N=200 V920 vs. N=50 Placebo) combined. This power analysis assumes a 10% dropout, a standard deviation of 1 on the log scale, and a 2-sided 5%.

There is 80% power to detect a GMR of 2.9 (V920 GP-ELISA GMT of 105 EU/mL) and 90% power to detect a GMR of 3.4 (V920 GP-ELISA GMT of 124 EU/mL) if comparing each cohort independently (N=40 V920 vs. N=10 Placebo). This power analysis assumes a 10% dropout, a standard deviation of 1 on the log scale, and a 2-sided 5%.

For safety assessment, there is 80% power to detect a 12% difference in event rates that occur with a frequency of 1% in the control group if comparing four cohorts (N=200 V920 vs. N=50 Placebo) combined and a 46% difference if comparing each cohort independently (N=40 V920 vs. N=10 Placebo).

8.2.8 Subgroup Analyses and Effect of Baseline Factors

Safety, immunogenicity, seroprotection, and seroconversion will be summarized for these pre-specified subgroups: CD4 cell count ($\geq$500 cells/mm^3, >350 and <500 cells/mm^3, CD4 $\geq$200 and $\leq$350 cells/mm^3), and age (adults, adolescents).

8.2.9 Interim Analysis

Four safety analyses will be conducted, one for each of the first four cohorts, when each cohort will have completed 42 days of follow-up post-vaccination.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

V920 vaccine supplies will be provided by the Manufacturer as summarized in Table 5 .

Clinical supplies will be packaged to support enrollment as required.

All subjects in Cohorts 1 to 4 will receive on D0 either the V920 (rVSVΔG-ZEBOV-GP) vaccine at a dose of $\geq 2x10^7$ PFU in 1mL, or normal saline (0.9%) placebo control in 1mL. Subjects in Cohort 5 will also receive on D56 a matching dose of V920 at a dose of $\geq 2x10^7$ PFU in 1mL, or normal saline (0.9%) placebo control in 1mL.

Placebo Control

Normal saline (0.9%) has been chosen as an inert substance to serve as placebo control.

Mode of Administration:

The vaccine product is supplied as a single 1.0 mL dose in a sterile vial. Each vial contains vaccine virus frozen in a mixture of water for injection, 2.5 g/L recombinant human serum albumin, and 10 mM Tris. After thawing, the content of the vial is a clear liquid. The V920 vaccine candidate will be administered via intramuscular injection into the deltoid region of the upper extremity, using a 3-mL syringe with a 1-inch #23-gauge sterile needle (suggested).

Treatment allocation

Participants will be randomized 4:1 (study vaccine: placebo control), with a total of approximately 200 study vaccine recipients and 50 placebo control recipients.

Table 5: Product Descriptions

Treatment Group	Product Name and Dosage Form	Dose/Potency	Dose Frequency	Total Dosage Forms	Additional Information
A	V920	$\geq 2x10^7$ PFU in 1mL	Once (Cohorts 1-4) Twice (Cohort 5)	IM	Experimental
B	Normal saline (0.9%)	1 mL	Once (Cohorts 1-4) Twice (Cohort 5)	IM	Placebo control

V920 vaccine supplies will be provided by Manufacturer and shipped by Fisher Clinical Services.

Any commercially available product not included in Table will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to prepare the vaccine. Both study vaccine and placebo are clear, and indistinguishable from one another once in the syringe. Once the syringe is prepared, blinded personnel will administer the 1.0 ml study vaccine or placebo control to the subject.

Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.
In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Medical Monitor notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

After unblinding, a letter is to be sent by the investigator to those subjects who received placebo control to provide the following:

"You have participated in a trial of the Merck Ebola vaccine. This is to advise you that you were among those who received a placebo control."

A letter sent to subjects who received study vaccine should provide the following:

"You have participated in a trial of the Merck Ebola vaccine. This is to advise you that you were among those who received the Ebola vaccine."

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11.0 APPENDIX 1: LIST OF ABBREVIATIONS:

Abbreviation/Acronym	Definition
AE	Adverse Event
AR	Adverse Reactions
CD	Cluster Designation
CDC	Centers for Disease Control and Prevention
CIRN	Canadian Immunization Research Network
cDNA	Complementary Deoxyribonucleic Acid
cGLP	Current Good Laboratory Practices
D	Day
CMH	Cochran-Mantel-Haenszel
CVA	Cerebrovascular Accident
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
EBOV	Ebola virus
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
EVD	Ebola Virus Disease
FLW	Front Line Workers
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMO	Genetically Modified Organism
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GP	Glycoprotein
HIV	Human Immunodeficiency Virus
HSA	Human Serum Albumin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
LLOQ	Lower Limit of Quantification
MARV	*Marburg Virus*
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
MSF	Médecins Sans Frontières
NIH	National Institutes of Health

Abbreviation/Acronym	Definition
NHP	Non-Human Primates
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OD	Optical Density
PCR	Polymerase Chain Reaction
PFU	Plaque Forming Units
PHAC	Public Health Agency of Canada
PRNT	Plaque Reduction Neutralization Assay
PsVNA	Pseudovirion Neutralizing Assay
qRT-PCR	Quantitative Reverse-Transcriptase Polymerase Chain Reaction
RNA	Ribonucleic Acid
RT-PCR	Reverse-Transcriptase Polymerase Chain Reaction
rVSVΔG-ZEBOV-GP	Recombinant Vesicular Stomatitis Virus with Envelope Glycoprotein replaced by *Zaire ebolavirus* (Kikwit Strain) Glycoprotein (V920)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sSAP	Supplemental Statistical Analysis Plan
SEBOV	*Sudan ebolavirus*
SHIV	Simian Immunodeficiency Virus
siRNA	Small Interfering Ribonucleic Acid
SMC	Safety Monitoring Committee
TCID	Tissue Culture Infective Dose
TILDA	Tat/rev Induced Limiting Dilution Assay
TSC	Trial Steering Committee
USAMRIID	United States Army Medical Research Institute for Infectious Diseases
USP	United States Pharmacopeia
VSV	Vesicular Stomatitis Virus
WBC	White Blood Cell
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research
V920	rVSVΔG-ZEBOV-GP
ZEBOV	*Zaire ebolavirus*

12.0 APPENDIX 2: LABORATORY ABNORMALITIES*

Grade	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Serum *				
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23-26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN

Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Hematology *				
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	ï€ 1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)
Urine *				
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization forhyperglycemia

Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

13.0 APPENDIX 3: STOPPING RULES

The DSMB will be provided with the following stopping rules as guidance for temporarily halting or terminating the study:

If any of the following events occurs, administration of study vaccine will be temporarily on hold until a thorough review of accumulated safety data is undertaken by the DSMB, the investigator, and /or the SPONSOR's representative.

- Death in any subject if considered related to administration of the test vaccine;
- Unexpected life-threatening event in any subject if considered related to administration of the test vaccine, unless already reported for V920;
- Serious adverse event in any subject if considered related to administration of the test vaccine, unless already reported for V920;
- Event which in the opinion of the investigator and/or safety monitoring committee contraindicates further dosing of additional subjects.