CEPI

Standardized Phase 1 Clinical Trial Protocol Outline for Multi-Developer Implementation of BDBV Vaccine Candidates

Intended for	Multi-Developer Vaccine Manufacturers, Regulatory Authorities
Rationale	BDBV-vaccine development during the current outbreak demands standardized Phase 1 protocol elements. A unified set of elements as depicted in this framework accelerates and streamlines regulatory review and decision-making, enables transparent comparison of immunogenicity and safety data across multiple vaccine candidates, enhances participant protection through harmonized safety assessments and pre-specified stopping rules, and supports rational dose selection. For candidates evaluated in Phase 1, interim analyses at early timepoints facilitate rapid progression to Phase 2b/3 efficacy evaluation in the affected population, without the need to await complete Phase 1 follow-up data.
ICH-GCP Compliance Statement	This clinical trial must be conducted in full compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH-GCP E6(R3)). The conduct of this study, including all aspects of study design, implementation, data collection, safety monitoring, risk-based quality management , and reporting, shall adhere to the principles and requirements outlined in ICH-GCP. All study personnel, including investigators, sub-investigators, and study coordinators, must receive appropriate training on ICH-GCP principles and requirements prior to study initiation.
Disclaimer	This protocol outline is intended as recommendation for multi-developer implementation. Individual manufacturers must obtain independent regulatory approval before initiating clinical trials. Note that this document represents a minimum framework and should not be regarded as a synopsis, complete protocol, or template. Developers are responsible for building upon this foundation using their own platform-specific data and experience. Developers are encouraged to maintain at least the key elements included in this document to enable a basic level of consistency to allow for meaningfully comparable assessments.
Document status	Version 1; final

TABLE OF CONTENTS

KEY ELEMENTS OF PHASE 1 TRIAL

Table 1: *Key Design Elements*

Key Element	Considerations	Rationale	Reference
Interim Analysis	Interim analysis to be conducted at **14 days post-(first) vaccination**	Standardized timing across all developers enables consistent data collection, comparison, and evidence-based decision-making for progression to Phase 2b/3.	Section 4.4

	when all enrolled participants have completed the study visit at this timepoint	Allows rapid evaluation of accumulated safety and immunogenicity data without awaiting extended Phase 1 follow-up. Immunogenicity assessment after the first vaccination is critical, as such a vaccine may be used in the context of post exposure prophylaxis.	(Interim Analyses)
Number of Dose Levels	Primarily 1 dose level ("lead dose") particular with available platform data; dose levels, including more than two if needed, may be included to characterize the dose–response relationship and provide contingency.	Limiting the number of dose levels to one is preferred to maintain trial timelines; however, additional dose levels may be included, as appropriate, to enable dose–response characterization. The staggered dose escalation design (sentinel followed by main cohort) adds sequential timepoints; multiple dose levels would compound this, add more datapoints and increase immunogenicity samples, thus extending trial duration.	Section 2.1.1
Safety Elements	Disease-specific AESIs: [Protocol-specified AESIs from SPEAC]; Solicited AEs: local (injection site pain, tenderness, erythema, induration) and systemic (fever, headache, fatigue, myalgia, nausea, chills, arthralgia); Grading Scale: FDA toxicity grading scale; Pause Rules: based on SAEs (≥1), Grade 3/4 AEs (≥2), Grade 3 solicited AEs (≥4 participants)	To systematically monitor and assess safety throughout the trial; disease-specific AESIs defined by Safety Platform for Emergency Vaccines (SPEAC) ensure pathogen-relevant safety monitoring; FDA toxicity grading scale provides consistent, objective severity assessment; pause rules enable rapid and consistent response to safety concerns. Standardized safety elements across all developers enable meaningful comparison of safety profiles and reactogenicity patterns between different vaccine candidates, supporting evidence-based regulatory and development decisions.	Sections 2.3, 2.4, 2.5
Trial Location	Trials should preferably be conducted in sub-Saharan African countries whenever feasible; however, parallel conduct in other countries may also be appropriate.	Conducting Phase 1 vaccine trials in African countries is scientifically, ethically, and operationally relevant, as it enables early safety and immunogenicity data to be generated in African populations more broadly, thereby improving the relevance and generalisability of findings. Importantly, this approach recognises that the target populations currently affected by the outbreak may present with confounding factors, including prior exposure to the disease, risk for disease manifestations, baseline disease prevalence, or immunological variability. Therefore Phase 1 trial should preferentially be conducted in African countries outside of active endemic outbreak areas. Expanding early-phase research in African settings also helps address longstanding inequities in clinical research participation and strengthens local research capacity, as emphasised by WHO and Africa CDC.	N/A

CLINICAL TRIAL OUTLINE

1 OBJECTIVES AND ENDPOINTS

1.1 PRIMARY OBJECTIVE

Vaccine developers may refine the specified objectives and endpoints based on the characteristics of their vaccine candidate and platform, as appropriate, while maintaining alignment with core standardized elements.

Table 1: *Primary Objective and Endpoint(s)*

Primary Objective	Primary Endpoint(s)
To assess the reactogenicity and safety after one {and two, if applicable} dose(s) of BDBV {vaccine candidate}	Proportion (%) of immediate AEs occurring within 30 minutes following each study vaccination. Proportion (%) of participants reporting any solicited local AEs up to 7 days following each study vaccination. Proportion (%) of participants reporting any solicited systemic AEs up to 7 days following each study vaccination. Proportion (%) of participants experiencing any unsolicited AEs during the 28 days following each study vaccination. Proportion (%) of participants with any MAAEs until 6 months following the last study vaccination. Proportion (%) of participants experiencing any protocol-specified AESIs, AEs leading to study withdrawal, and SAEs during the entire study period.

1.2 SECONDARY OBJECTIVES

Table 1: *Secondary Objective(s) and Endpoint(s)*

Secondary Objective(s)	Secondary Endpoint(s)
To evaluate the binding antibody response to BDBV {vaccine candidate} after one dose of BDBV {vaccine candidate} across timepoints	GMCs of Bundibugyo-GP binding IgG antibodies 14 days post first vaccination. GMCs of Bundibugyo-GP binding IgG antibodies at baseline, 7 and 28 days after first, 90 days and 180 days post-first vaccination. Percentage of participants (and 95%CI) with seroconversion* across timepoints.

If applicable: To evaluate the binding antibody response to BDBV {vaccine candidate} after two dose(s) of BDBV {vaccine candidate} across timepoints	GMCs of Bundibugyo-GP binding IgG antibodies at baseline, 7, 14, and 28 days after second vaccination.
*Seroconversion is defined as ≥ four-fold increase of the antibody titer compared to the baseline titer for participants with a pre-existing antibody titer, or 4x LLOQ for participants who were seronegative (<LLOQ) at baseline.	

1.3 EXPLORATORY OBJECTIVE(S)

Table 3: *Exploratory Objective(s) and Endpoint(s)*

Exploratory Objective(s)	**Exploratory Endpoint(s)** *
To evaluate the neutralizing antibody response to BDBV *{vaccine candidate}* after one *{and two, if applicable}* dose(s) of BDBV *{vaccine candidate}* across timepoints	GMTs of anti-Bundibugyo neutralizing antibodies 14 days post first vaccination. GMTs of Bundibugyo neutralizing antibodies at baseline, 7 days after first (and second vaccination, if applicable), 14 days after second vaccination (if applicable), 28 days after first (and second vaccination, if applicable), 90 days and 180 days post-first vaccination. Percentage of participants (and 95%CI) with seroconversion* across timepoints.
To evaluate cellular immune responses by measuring antigen-specific T-cell responses to BDBV GP	Enumeration of Bundibugyo GP specific T-cell responses at baseline and key timepoints post vaccination (14 and 28 days after each vaccination, and 90 days post-first vaccination)
To further characterize the humoral immune response	Frequency, specificities, function or other endpoints to be determined for the further characterization of humoral immune responses
*Exploratory Endpoints will be evaluated in a subset of timepoints.	

2 METHODOLOGY

2.1 STUDY DESIGN

Prospective observer-blind, placebo-controlled, randomized, staggered dose-escalation Phase 1 clinical trial.

2.1.1 Dose Selection Decision

The vaccine dose level(s) to be taken forward will be selected on a deep understanding of dose selection informed by available immunogenicity, safety, and tolerability data accumulated from prior studies within the developer's platform technology. The selection will aim to identify a single optimal dose level that best balances immunogenic responses with an acceptable reactogenicity and safety profile. Where prior platform data are not sufficiently informative, limiting the number of dose levels to two is preferred, however, additional dose levels may be included, as appropriate, to enable dose–response characterization.

Dose selection will draw upon a synthesis of relevant prior platform data, including antigen-specific immune responses, local and systemic reactogenicity findings, and any available indicators of protective efficacy. These data will be interpreted in the context of the target population and the intended vaccination schedule.

In the presence of residual uncertainty, the dose level(s) considered most likely to elicit a high immune response while maintaining an acceptable safety and tolerability profile will be prioritised, based on the totality of available evidence.

***Table 3**: Overview of treatment allocation*

Group	Cohort	Population (yrs.)	Dosing-route	No. of participants*	Blinding
1 ("lead dose")	1a sentinels	18-55	I.M.	5	open-label
	1b			15	blinded
Optional: 2	2a sentinels	18-55	I.M.	5	open-label
	2b			15	blinded
Control		18-55	I.M.	5	blinded
Total participants				**45**	

** Number of participants are deemed minimum requirements and depend on manufacturers prior platform evidence. Control group should be multiples of 5, depending on how many (dose-)groups are included in the trial.*

2.1.2 Staggered Dose-Escalation

Sentinel Cohort Dosing

The "lead"-dose level will be initiated with five sentinels. Sentinel participants will be vaccinated sequentially, with a minimum of 1 hour between administrations. Each sentinel participant will be observed on-site for a minimum of 30 minutes post-vaccination *{observation time may be extended based on manufacturers prior platform evidence}*.

Safety Monitoring and Escalation Criteria

Following vaccination of the fifth sentinel subject, an observation period ≥48 hours {may be shortened subject to regulatory acceptability] will be implemented. During this observation window, safety data will be reviewed by the investigator and sponsor medical representative to identify any adverse events or safety concerns of clinical significance.

Data Review and Escalation Decision

Provided that no group pausing rules are met and no safety findings are judged to be of clinical concern during the post-sentinel observation period, the Data Safety Monitoring Board (DSMB) will review the accumulated safety and tolerability data. Upon DSMB recommendation:

- The remaining 15 participants at the current dose level will be vaccinated and randomized with the placebo recipients;
- If applicable, five sentinel subjects will be enrolled and vaccinated at the next selected dose-level, following the same sequential and observational procedures

2.1.3 Study Duration

Minimum of 6 months post-first vaccination to a maximum of 12 months post-first vaccination.

2.2 POPULATION

Healthy adult volunteers aged ≥18 to ≤55 years of age are invited to participate in the trial.

2.2.1 Eligibility Criteria

2.2.1.1 Inclusion Criteria

Each participant must meet ALL of the following criteria to be enrolled in this trial:

1. Aged ≥18 to ≤55 years at the time of informed consent.
2. Willing to complete and provide written informed consent prior to any trial-related procedure.
3. Capable of understanding and agrees to comply with planned study procedures and to be available for all clinical follow-up for all planned study visits.
4. Has a means to be contacted and to contact the investigator during the trial.
5. Able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process.
6. Agree not to donate bone marrow, blood, or blood products until 3 months after the trial vaccination.
7. In good general health without clinically significant medical conditions, based on participant-reported medical history, physical examination, vital signs, and clinical laboratory test results as deemed acceptable by the principal investigator.
8. Negative HIV-1 and HIV-2 antigen/antibody blood test result at the screening visit.
9. Negative Hepatitis B surface antigen test result and negative anti-Hepatitis C virus antibodies (anti-HCV), or negative Hepatitis C virus (HCV) polymerase chain reaction (PCR) test result if the anti-HCV is positive at the screening visit.

Women of Childbearing potential specific criteria:

Female participants who are considered to be women of childbearing potential (WOCBP) have been defined in Appendix 9.1.

1. Negative urine pregnancy test before vaccination, if of reproductive potential.
2. Agrees to use a highly effective (see 9.2) means of birth control from at least *x days {Number of days should be edited based on manufacturer instructions for the IMP}* prior to enrollment through *x days {Number of days should be edited based on manufacturer instructions for the IMP}* post vaccination if assessed to be woman of childbearing potential (WOCBP).

2.2.1.2 Exclusion Criteria

Participants meeting ANY of the following criteria are not eligible to be included in the trial:

1. Known prior laboratory-confirmed diagnosis of EBOV, SUDV or BDBV disease, or history of prior EBOV or SUDV investigational or licensed vaccines determined from the participant's reported medical history.
2. Pregnant or lactating females or those intending to become pregnant or breastfeeding for a total of 3 months from *{"last" if applicable}* study vaccination.
3. History of known or suspected severe adverse reaction including allergic reaction (e.g., anaphylaxis) to vaccines or to vaccine components *{include excipients for the IMP}*
4. Has any medical disease or condition that, in the opinion of the investigator, precludes study participation. This includes clinically significant chronic illness (cardiac, respiratory, gastro-intestinal, hepatic, renal, neurological, musculoskeletal, haematological, oncological, endocrine/metabolic psychiatric) as determined by medical history and physical examination. *{include specific medical conditions as determined for the IMP}*
5. Receipt of any of the following substances:
    a. An investigational vaccine or drug 28 days prior to vaccination or plans to receive a vaccine within 28 days of vaccination. *{Durations may be edited as appropriate}*
    b. Blood products within 3 months prior to enrollment or plans to receive blood products within 90 days of vaccination. *{Durations may be edited as appropriate}*
    c. Another investigational product within the context of another intervention trial. This includes co-enrolment in an interventional vaccine or drug trial.
6. Has a clinically significant acute febrile illness (defined as oral temperature of ≥38.0°Celsius or clinically significant illness within 48 hours prior to vaccination (if present at Visit 1, temporary deferral is permitted).
7. Intends to donate bone marrow, blood, or blood products within 3 months of the study vaccination.

3 STUDY PROCEDURES AND ASSESSMENTS

3.1 SCREENING/BASELINE ASSESSMENTS

3.1.1 Demographic Data

Demographic data (including age, sex, race/ethnicity, and other relevant characteristics) will be collected by the investigator or qualified trial personnel designated by the investigator (e.g., trial

nurse) during the baseline/screening visit. Data will be obtained through participant interview and review of identification documents, as appropriate, and recorded in the respective case report form (CRF).

3.1.2 Medical History

A comprehensive medical history will be collected by the investigator or qualified trial personnel designated by the investigator (e.g., trial physician or nurse) at the baseline visit. Information will be obtained through participant interview and review of available medical records, focusing on prior and current medical conditions, relevant surgical history, allergies, and prior vaccinations. All medical history data will be documented in the respective CRF.

3.1.3 Physical Examinations

Physical examinations may be performed by a qualified delegate within the local scope of practice with the investigator(s) providing oversight and review of participants with abnormal physical findings.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. If a participant reports additional symptoms, a symptom-directed physical examination will be performed at the visit during which these symptoms were reported and at subsequent visits.

3.1.4 Vital signs

Vital signs to be collected include temperature (measured orally), pulse rate, respiratory rate, and blood pressure. Blood pressure and pulse measurements will be assessed after the participant has been sitting upright for approximately 5 minutes in a quiet setting without distractions (e.g., television, cell phones), with an adequately calibrated, completely automated device. Manual techniques will be used only if an automated device is not available. Oral temperature will be used for temperature measurements. Respiratory and pulse rates will be measured after the participant has been resting for at least 5 minutes and will be reported as rates/minute.

3.2 BLINDING

The sentinel dosing will be conducted open-label.

The is an observer-blinded trial, such that only site personnel receiving, storing, dispensing, preparing, and administering the trial IMP will be unblinded. All other site personnel, including the investigator(s), investigator staff, as well as the participants themselves will be blinded to participants' assigned trial IMP. In particular, the individuals who perform participants' assessments and/or evaluate trial participant safety will be blinded.

3.3 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will be done for all participants. During sampling visits, a blood sample will be collected at baseline, 1 week, 2 weeks, and 4 weeks post-vaccination(s), as applicable, as well as 3 and 6 months post-first vaccination.

A subset of samples/aliquots collected at baseline and all post-vaccination timepoints will be made available for analysis at the CEPI Central Laboratory Network (CLN) to harmonize and standardize immunogenicity data assessments.

3.4 SAFETY ASSESSMENTS

Safety assessments will be conducted from the point of signing informed consent to the end of study for all participants.

Solicited and unsolicited AEs will be assessed via in-person visits on Days 8, 15 and Day 29 at which point the study diaries will be dispensed, collected and reviewed. Participants will be asked to contact the study team in case of new AEs occurring outside of scheduled visits. Unsolicited AEs will be assessed until Day 29. MAAEs will be assessed until Month 6, and SAEs and AESIs will be assessed until the end of the trial with in-person visits at Month 6 and Month 12, if applicable.

4 SAFETY MONITORING AND REPORTING

4.1 SAFETY DEFINITIONS

4.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. This may include new symptoms, worsening of pre-existing conditions, abnormal laboratory findings, or diagnoses that are temporally associated with the use of an investigational product, whether or not the event is considered causally related to the use of the product.

4.1.1.1 Solicited Adverse Events

Solicited local/systemic AEs will be assessed by site teams after vaccination for at least 30 minutes (but no more than 60 minutes). The following specific solicited AEs will be monitored for this trial:

- **Local reactions at injection site** - injection site pain, tenderness, erythema/redness and induration/swelling
- **Systemic reactions** - fever, headache, fatigue, myalgia, nausea/vomiting, chills, diarrhea, and arthralgia

Solicited AEs will be assessed and graded based on the FDA toxicity grading scale.

4.1.1.2 Unsolicited Adverse Events

Unsolicited AEs occurring from the time of enrollment through to 28 days post-vaccination will be I recorded in the respective CRF.

4.1.1.3 Adverse Event of Special Interest

An Adverse Event of Special Interest (AESI) (serious or non-serious) is defined as an AE or SAE of scientific and medical concern specific to the Sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the Sponsor is appropriate regardless of seriousness.

Protocol-specified AESIs will be defined prior to study initiation, taking into account:

- Known and potential risks associated with the vaccine platform

- Prior clinical and non-clinical experience with related vaccines

- Relevant regulatory guidance and external expert recommendations, including the Safety Platform for Emergency Vaccines (SPEAC)

For each protocol-specified AESI, a minimum diagnostic dataset will be defined, including required clinical assessments, laboratory investigations, and imaging, as applicable, to support standardized case evaluation and classification.

In addition to investigator-identified AESIs, enhanced case identification will be implemented using pre-defined clinical and laboratory trigger criteria (e.g. abnormal laboratory values or symptom clusters). Such triggers will prompt further clinical evaluation to determine whether events meet AESI case definitions.

Events identified by investigators as AESIs, as well as those meeting AESI trigger criteria, will be evaluated using available case definitions provided by the SPEAC project.

Events fulfilling AESI case definitions at any level of diagnostic certainty (LOC 1–3) will undergo enhanced review and will be reviewed by the Data Safety Monitoring Board (DSMB) in accordance with predefined review processes and escalation criteria.

AESIs will be captured using the AE eCRF and, where applicable, dedicated AESI-specific eCRF modules. All events will be coded using MedDRA. Standardized MedDRA queries may be applied to support consistent identification, monitoring, and analysis.

Reporting of AESIs will be conducted for the entirety of the study period. A list of protocol-specified AESIs relevant for BDBV vaccines can be accessed at Ebola - SPEAC and have been summarised in Appendix 9.3.

4.1.1.4 Medically Attended Adverse Event

A medically attended adverse events (MAAE) is an AE that leads to an unscheduled visit to a healthcare practitioner. This would include visits to a study site for unscheduled assessments (e.g., severe headache follow-up) and visits to healthcare practitioners external to the study site (e.g., urgent care, primary care physician). All MAAEs must be fully reported on the AE page of the eCRF. MAAEs will be reported until 6 months following the first study vaccination.

4.1.1.5 Suspected Unexpected Serious Adverse Reaction

The Sponsor is responsible for making the determination of which SAEs are suspected unexpected adverse events (SUSARs) that meet criteria for expedited reporting as defined by the relevant regulatory authority.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

Unexpected AE means an AE that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed.

The Sponsor will submit written safety reports of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible after determining that the information qualifies for reporting. Local reporting requirements of the same event will be stipulated in the respective country/site-specific addendums.

4.1.2 Serious Adverse Event

In addition to assigning a severity grade, each AE will be classified by the Investigator as either "serious" or "not serious." The determination of seriousness will follow applicable regulatory definitions and is generally based on the event's outcome.

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening i.e., in the view of the healthcare provider, places the participant at immediate risk of death. However, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be a medically significant/important event that, in the opinion of the healthcare provider, may jeopardize the participant or may require intervention to prevent one of the preceding SAE quantifiers

4.2 SAFETY ASSESSMENT PROCEDURES

4.2.1 Eliciting Adverse Events

At every study visit, participants will be asked a standard nonleading question to elicit any medically related changes in their well-being. In addition to participant observations, AEs identified from any study data (e.g., physical examination, vital signs) or identified from review of other documents (e.g., participant memory aid or medical records) that are relevant to participant safety will be documented on the AE page in the eCRF. All AEs, SAEs, AESIs and MAAEs reported will be recorded in their respective eCRFs on the EDC.

4.2.2 Assessment of Severity

Solicited AEs will be graded in intensity by the study team based on descriptions and diary cards provided by participants. The investigator will assess the intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs- where applicable) recorded during the study. Changes in the severity of an AE shall be documented to allow an assessment of the duration of the

event at each level of intensity. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.
Grading scales for the severity of AEs and SAE will be based on the FDA Guidance for Industry (September 2007): "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials").

Note: An AE that is assessed as Grade 3 (severe) must not be confused with a SAE. Grade 3 is a category used for rating the severity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as "serious" when it meets one of the predefined outcomes.

4.2.3 Assessment of Relatedness

All solicited injection site reactions are considered related to the IP.

The investigator's assessment of the relationship of solicited systemic AEs and unsolicited AEs to the IP is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event shall be reported.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial IMP administration will be considered and investigated.

The relationship or association of the IP in causing or contributing to the unsolicited AE will be characterised using the following classification and criteria:

- **Unrelated:** The AE is clearly not related to the IP
- **Unlikely:** The AE is doubtfully related to the IP
- **Possible:** The AE may be related to the IP
- **Probable:** The AE is likely related to the IP
- **Definite:** The AE is clearly related to the IP

For the purpose of safety decision-making (e.g. pausing rules, discontinuation), events for which a causal relationship to the IMP cannot be reasonably excluded include those assessed as possible, probable, or definite.

4.3 SAFETY MONITORING

4.3.1 Data Safety Monitoring Board

An independent, external, unblinded DSMB will monitor participant safety throughout the course of the study. A detailed charter will outline DSMB activities (including but not limited to, the composition of the DSMB, DSMB responsibilities, frequency of meetings, pausing rule, etc.). The DSMB will convene at a preplanned frequency throughout the study duration especially during the staggered dose-escalation phase of the trial to review participant data and provide recommendations to the sponsor.

A pool of potential DSMB members with varying expertise may be provided for consideration.

4.3.2 Study Pausing Rules

4.3.2.1 Group Pausing Rules

Trial pausing rules will be applicable during the entire trial as presented in the Table below. If the rules are met, enrollment and vaccination will be suspended within 24 hours of awareness by the trial team. An ad-hoc DSMB meeting will be held to review all safety data as per the DSMB charter. Depending on the DSMB assessment, including the relationship of the AE to the IMP, enrollment and vaccination might be temporarily paused and only be restarted upon approval by the Sponsor upon recommendation of the DSMB.

Table 4: *Trial Pausing Rules Based on Safety Assessments*

Pausing Rules	**Number of Participants**
1) SAE assessed as related to IMP (at any dose level), or for which there is no alternative, plausible, attributable cause	≥1 participant
2) Any similar or same unsolicited Grade 3 or 4 AEs (including laboratory abnormalities, if applicable) considered related to the IMP and/or for which there is no alternative, plausible, attributable cause.	≥2 participants in the same group
3) Any Grade 3 or higher local or systemic solicited AEs lasting for >24 hours	≥4 participants in the same group, (ie., ≥20% of total participants within the group)
<u>AESI-specific pausing rules (delineated from #1):</u> *Any event meeting criteria for a protocol-specified AESI at Level 1 (highest level of diagnostic certainty), where the event is assessed as related to the IMP or cannot be reasonably excluded as related.*	*≥1 participant*
Any clustering of events meeting criteria for protocol-specified AESIs at Level 2 or 3 of diagnostic certainty, where a causal relationship to the IMP is considered possible.	*≥2 participants*
Any event meeting AESI trigger criteria that is clinically severe and concerning for a potential serious AESI (pending full evaluation), particularly for platform-specific risks (e.g. thrombotic, cardiac, or neurological syndromes).	*≥1 participant (pending DSMB review)*

Abbreviations: AE, adverse event; IMP, investigational medicinal product; SAE, serious adverse event; SUSAR, suspected unexpected serious adverse reaction.

{The number of participants to be monitored for group pausing rules may be increased for IMPs depending on prior data.}

4.3.2.2 Discontinuation of single trial participants from trial treatment

It may be necessary to permanently discontinue a participant from further vaccination, applicable for IMP with 2 dose-regimen.

The trial treatment of a single trial participant must be discontinued in the following cases:

- If participant becomes pregnant.
- Any Grade 3 or 4 solicited local reaction or systemic event or unsolicited AE that lasts longer than 3 days with no likely alternative cause than the study vaccine (i.e. possibly or probably related.
- Any Grade 3 unsolicited AE assessed as related to IMP.
- Severe allergic AE (hypersensitivity or anaphylaxis) assessed as related to IMP.
- Any SAE assessed as related to IMP.
- AESI-specific dicsontinuation:
    - Any event fulfilling criteria for a protocol-specified AESI at Level 1 (highest level of diagnostic certainty), where the event is assessed as related to the IMP or a causal relationship cannot be reasonably excluded
    - Any event fulfilling criteria for a protocol-specified AESI at Level 2 or 3, where the event is clinically significant and a causal relationship to the IMP is considered possible, as determined by the investigator and/or Sponsor.
    - Any event meeting AESI trigger criteria that are clinically severe or concerning for a potential serious AESI (e.g. thrombotic, cardiac, or neurological syndromes), pending full evaluation.

Trial participants permanently discontinued from trial treatment will remain in the trial and will complete all assessments as listed in the Schedule of Events.

5 STATISTICAL CONSIDERATIONS

5.1 SAMPLE SIZE

No formal hypothesis testing will be performed. The sample size for each group is mainly driven by typical Phase I designs for the early detection of potential safety and reactogenicity events, and is considered adequate to support the trial objectives, while minimizing the number of trial participants exposed to an IMP.

5.2 STATISTICAL ANALYSIS

{Mention that analysis plans will be defined in a statistical analysis plan to be finalized before any data analysis, preferably prior to the first study enrollment considering the early interim analysis at Day 15. Summarize the overall analysis and reporting principles to be used in the study. Describe the reporting of continuous vs. categorical data, level of significance, reporting of confidence intervals, and whether analyses will be one-sided or two-sided. The use of the estimands in describing the analyses is highly recommended.}

5.2.1 Analysis Populations

{Define all analysis sets e.g., the Immunogenicity Intent-to-Treat (ITT) population, the Immunogenicity Per-Protocol (PP) population, the safety population and any other relevant analysis populations.}

5.2.2 Analysis Methods

5.2.2.1 Analysis Methods for Primary Objective

{Describe the statistical methods for analysis of data relating to the primary objective.}

Any protocol-specified AESIs will be analysed separately from overall adverse event summaries. Events will be evaluated and summarised using predefined case definitions and, where applicable, classified according to levels of diagnostic certainty (LOC 1–3).

For protocol-specified AESIs, descriptive analyses will include incidence, severity, relatedness, time to onset, duration, and clinical characteristics. Particular attention will be given to patterns, clustering, and temporal relationships to vaccination, including across dose groups.

Analyses of protocol-specified AESIs will support ongoing safety review and DSMB evaluations.

5.2.2.2 Analysis Methods for Secondary Objective(s)

{Describe the statistical methods for analysis of data relating to the secondary objective(s), including method of calculating GMCs and GMTs and associated confidence intervals, and method of calculating seroconversion and associated CIs. No multiplicity adjustment is expected.}

5.2.3 Interim Analyses

An interim analysis will be conducted by the sponsor once all enrolled participants have completed the study visit at 2 weeks post-(first) vaccination (ie. Day 15). This analysis will evaluate accumulated safety and immunogenicity data from all participants across all timepoints and dose-levels collected up to and including the Day 15 visit.

This interim analysis serves as the critical gateway enabling rapid, evidence-based progression to a Phase 2/3 efficacy trial without awaiting extended Phase 1 follow-up data.

6 DATA MANAGEMENT – PROPOSED MINIMAL LANGUAGE TO SUPPORT PROTOCOL DEVELOPMENT, AS APPLICABLE

6.1 DATA COLLECTION AND QUALITY ASSURANCE

This trial will be conducted according to the ICH E6(R3) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this trial will be documented and will comply with the current ICH guidance on quality and risk management. The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

A data management plan will be developed before data collection begins and will describe all the processes to be followed during data collection, cleaning and analysis. High-quality standards for the management of data collected during this trial to ensure accuracy in analysis and reporting of results. The investigator will be responsible for maintaining adequate case histories, including CRFs and source documentation, for participants treated as part of this trial. Clinical data management will be performed in accordance with the Sponsor's applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using WHO Drug Dictionary (WHODRUG).

All data collected from the trial, essential documents, and other trial records in accordance with all local, national, and regulatory laws will be retained for a minimum period of one year after completion of the trial. Additional data collection and validation procedures will be detailed in appropriate operational documents.

6.2 Data Storage and Protection

Participant data will be pseudonymised to protect their privacy. Only the principal investigator or designee will have access to fully identified participants' clinical data held in source documents and will maintain the linkage of participant identity to the allocated participant number (i.e., key code).

All trial records with personally identifiable information will be maintained under double lock in an access-restricted room. Access to these data may be granted to other stakeholders, including monitors, representatives of applicable regulatory, and ethical bodies, who may request access to participant identity to perform their specific function. This access will be regulated by the investigator and logs of all who access identifiable participant data will be recorded.

Systems, applications, and technologies to be used in this trial will be regulatory compliant. Parties involved in this trial, including clinical trial sites, Sponsors, CROs, and vendors, will be required to have policies and procedures in place to respond to data breaches. These procedures may include the education of staff on existing measures, immediate steps to take to control and investigate breaches, and the arrangement for any legally mandated notification to participants or regulatory authorities, as guided by local and international data protection and privacy laws.

6.3 Data Sharing

Individual-level anonymised data will be shared with the sponsor. Summary-level statistics will be shared with the wider scientific community and trial stakeholders.

Anonymised individual or aggregate data collected or generated during this trial may be shared for use to support new research. Any future research using information from this trial must first be approved by the Sponsor who will ensure appropriate data sharing agreement(s) are in place and that measures to protect the interests of participants and their communities have been setup.

6.4 DATA RETENTION AND ARCHIVING

Essential documents must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product; or as per local country-specific regulatory requirements - whichever is longer. These documents must be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the Sponsor.

7 QUALITY ASSURANCE – PROPOSED MINIMAL LANGUAGE TO SUPPORT PROTOCOL DEVELOPMENT, AS APPLICABLE

7.1 MONITORING PLAN

This trial will be monitored according to an approved monitoring plan based on the objectives, purpose, design, and complexity of the trial.

The investigator will allocate adequate time for monitoring visits to facilitate the requirements of the trial and trial timelines. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given direct access to all trial related documents and trial related facilities.

The monitor will evaluate the trial processes based on the contract research organisation (CRO) standards, ICH E6, and all applicable, regulatory guidelines.

7.2 PROTOCOL DEVIATIONS

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy and/or reliability of the trial data or that may significantly affect a participant's rights, safety or well being.

Protocol deviations will be identified as soon as possible by the site, the on-site clinical monitor, the data management team, and any additional roles involved in reviewing trial data. While every effort should be made to avoid protocol deviations, all protocol deviations must be reported and will be reviewed in a blinded manner by the sponsor. The investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard/safety risk to trial participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed

protocol amendments must be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, where required.

In order to keep deviations from the protocol to a minimum, the investigator and relevant site personnel will be trained in all aspects of trial conduct by the sponsor/sponsor representative. This training will occur either as part of the investigator meeting or site initiation. Ongoing training and retraining may also be performed throughout the trial during routine site monitoring activities.

The site-investigators will comply with all applicable, country-specific requirements related to reporting of deviations to the regulatory authority, IRB/IEC, as per local regulation/ guidelines.

8 Dissemination and Data Sharing – proposed minimal language to support protocol development, as applicable

8.1 Clinical Study Report

The sponsor will ensure that the final trial data are summarised and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s) regardless of the trial outcome. The Sponsor will also ensure that the clinical trial report in marketing applications (as applicable) meet the standards of the ICH harmonised guideline E3: Structure and content of clinical study reports (CSRs).

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the trial's final report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete trial results.

Upon completion of the final report, the sponsor will provide the investigator with the summary of the trial results. The investigator is encouraged to share a summary of the results with the trial participants, as appropriate. The trial results will be posted on publicly available clinical trial registers.

9 APPENDICES

9.1 DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL

A woman is considered fertile i.e., of childbearing potential, following menarche and until becoming post-menopausal unless permanently sterile.

Premenopausal women who have a documented hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy are considered sterile.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required. Women on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed, additional evaluation may be conducted at the discretion of the investigator.

For women with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion will be applied to determine entry into the trial.

Confirmation of a participant's childbearing status may be done through a review of the participant's medical records, medical examination, or medical history interview.

9.2 HIGHLY EFFECTIVE CONTRACEPTION

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion

- vasectomised partner
- sexual abstinence

9.3 AESI DEFINITIONS (SPEAC)

Prioritized Protocol-specified AESIs

Vaccine Platform	Recommended protocol-specified AESIs
rVSV	Acute aseptic arthritis, Single organ cutaneous vasculitis (SOCV)
ChAdOx1	Thrombosis with thrombocytopenia syndrome and Vaccine-associated immune thrombotic thrombocytopenia (TTS-VITT)
mRNA	Myocarditis, Pericarditis