CORE PROTOCOL

An international adaptive multi-country randomized, placebo-controlled, double-blinded trial of the safety and efficacy of treatments for patients with monkeypox virus disease

Version 4.0

Disclaimer.
This protocol is the outcome of the deliberations from several individual experts and from various expert groups including: the WHO R&D Blueprint expert group on clinical trials and statistical methods experts, WHO Clinical Expert Group which comprised the monkeypox guidelines development group, regulatory experts consulted by the WHO Access to Medicines and Health Products Division, members of the WHO expert group for the Target Product Profile for monkeypox therapeutics.

Importantly this protocol also benefits from the inputs from over 500 experts who attended the first and second consultations on this topic in June and July 2022 organized by the National Institute for Biological Research (INRB) from the DRC, the ANRS Emerging Infectious Disease, and US NIAID/NIH with the support of WHO.

The protocol writing group would like to thank the INRB and its partners in particular US NIAID/NIH for providing access to their protocol for randomized evaluation of treatments for human monkeypox (the PALM 007 RCT protocol) which served as the initial basis for this protocol.

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1. SUMMARY

Study description: This is a CORE protocol for an adaptive multiregional international global randomized, placebo-controlled trial to evaluate the safety and efficacy of drugs for the treatment of human monkeypox (Phase 3). Each site interested in participating can enroll patients in this international trial and implement the core protocol. This will require commitment to assess the main objectives as defined by the core protocol; enrolling homogenous population (common inclusion criteria); and evaluating the same interventions with the same primary and secondary endpoints. This adaptive design will allow future flexibility in testing several treatments.

Add-on studies Particular countries, or groups of centres may want to collaborate in assessing additional endpoints or to include further measurements or observations and include questions that are locally relevant (add-on trials).

Simplicity of procedures: Within each country or region, the national or reginal Principal Investigators invites selected centres and helps them get ethical and regulatory approval and study drugs, then patient recruitment can begin. To facilitate collaboration, patient enrolment and randomisation are simplified, and core variables are collected using standardized definitions and will be sent in real time to a centralized data base (potentially across countries via a cloud-based GCP-compliant platform). All trial procedures are greatly simplified, and minimal paperwork is required. Once consent has been obtained, electronic entry of anonymised details of a few key characteristics of each patient takes only a few minutes. At the end of patient entry, a random treatment allocation is generated using a national (or by a global randomization center).

Quality requirements: centers sending these data should meet quality requirements (to be defined) that make them eligible to be part of the global analysis.

Eligibility: Adults and children (6 years and older) with laboratory-confirmed (PCR) monkeypox illness of any duration (provided that the patient has at least one active, not yet scabbed, lesion), and, who have no contra-indication to potentially study drug.

Consent: Once the information has been explained to patients, obtaining consent takes only a few minutes. An electronic image of the signature page is kept (or, if national regulations forbid this, a note to file), and the printed information and original consent stays with the patient or legal representative.

Data collected electronically immediately before randomisation. These include:
- Country, geographic region of residence, hospital and randomizing doctor
- Confirmation that informed consent was obtained from the patient (or a surrogate/ representative)
- Age, sex and (yes/no): HIV, TB, malaria, hypertension, diabetes mellitus, asthma, hepatitis, hyperlipidemia, cancer, heart failure, renal disease, liver disease, chronic obstructive pulmonary disease (COPD), COVID-19, neoplasm, obstructive sleep apnea, obesity, immunosuppressive disorder other than HIV, sickle cell anemia, concurrent bacterial infections such as urinary tract, ear nose and/or throat, pulmonary, central nervous system, skin or gastrointestinal infection, bacteremia/sepsis or other.
- Date of onset of symptoms, date of hospitalization, and (yes/no) current/planned use of a few drugs
- Monkeypox lesions status (yes/no): at least one active, not yet scabbed, monkeypox lesion, other.
- Current symptoms (yes/no): nausea, vomiting, abdominal pain, anorexia, cough, lymphadenopathy, dysphagia, fever, headache, ocular lesions, and buccal ulcers.

- Smallpox vaccination status (yes/no) or presence of vaccination scar (yes/no).
- Risk factors for monkeypox infection (yes/no): recent contact with known monkey pox case, type of contact, residing or visiting an area with an active monkey pox outbreak, animal handling.

Trial entry; randomization: A participant will be considered enrolled beginning from when the informed consent form is signed and randomization to an assigned treatment has occurred. Once enrolled, study drug administration will begin according to study group assignment. Participants will be randomized to one of the experimental treatments (k in number) for which they are eligible (no specific exclusion criteria) or to one of the placebos that correspond (in appearance, dosing interval, and route of administration) to each of those treatments. The randomization ratio will ensure that participants have the same chance of receiving a placebo as they have of receiving each individual treatment for which they are eligible. All participants will also receive local SOC that is standardized at each site according to local/site guidance.

Follow up: Participants will either be hospitalized or outpatients and will undergo frequent clinical and laboratory assessments for safety and efficacy. Day 28 is the final required study visit, but participants may return for an optional visit at day 58 for long-term clinical and laboratory evaluations.

Objectives and endpoints: This CORE protocol will include outpatients and hospitalized patients. It is being designed to test one or more targeted interventions across multiple types of disease stages. Sites may choose to enrol outpatients, hospitalized patients or both.

The primary objective is to evaluate the clinical efficacy, as assessed by time to lesion resolution, of treatment plus SOC versus placebo plus SOC for patients with monkeypox.

The primary endpoint is time to resolution of all lesions[1] (including skin and mucosa), up to 28 days after randomization (assessment every 3-5 days).

For secondary and exploratory endpoints please see section 5.

Safety: Any suspected unexpected serious adverse reactions (SUSARs) that are life-threatening must be reported within 24 hours, as must any other possibly related treatment-related serious adverse events (SAEs).

Study Population

Inclusion criteria

- Adults and children (6 years and older) with laboratory-confirmed (PCR) monkeypox illness of any duration (provided that the patient has at least one active, not yet scabbed, lesion), and, who have no contra-indication to potentially study drug.
- Men and non-pregnant women of reproductive potential must agree to use effective means of contraception when engaging in sexual activities that can result in pregnancy, from the time of enrolment through the end of study participation. Acceptable methods of contraception include the following: hormonal contraception, male or female condom, diaphragm or cervical cap with a spermicide and intrauterine device.

Exclusion criteria

- Current or planned use of another investigational drug at any point during study participation.

[1] **Time to lesion resolution:** lesions of skin and mucosa are crusted, scabs have fallen off and a layer of skin has formed underneath

- Patients who, in the judgement of the investigator, will be at significantly increased risk as a result of participation in the study.
- Specific exclusion criteria for each evaluated drug will be considered.

Pregnant women and special populations will be enrolled in this study if the national principal investigator, the national regulatory authorities, and the ethics committee agree that the benefits of receiving the experimental treatment outweigh its risks, and specifically if they consent to participate after the information on risk and benefits is provided.

Study sites: Study sites will be in geographic locations where cases of monkeypox were reported. Sites will be opened one after another to ensure correct workflow of activities within a site and synchronization of activities between sites later on.

Study intervention: Details regarding dose administration for each evaluated treatment will be added here

Study Duration: The day when the subject is randomized to their assigned treatment arm is denoted as Study Day 1. Screening procedures will occur in the 24 hours prior to randomization (Study Day -1 to 1). Note that there is no Study Day 0. Study Day -1 is the 24-hour day prior to the day of randomization. The first day after randomization is Study Day 2. Subsequent days will be numbered chronologically through Day 58 of study.

Statistical considerations

Primary endpoint analysis: A stratified log-rank test will be used to compare arms with respect to time to lesion resolution[2], where stratification is by days from onset of symptoms to randomization (≤7 days vs >7 days) and by baseline severity[3]. Participants with any lesions not scabbed or desquamated at 28 days after randomization will be censored for statistical analysis of this endpoint. Though deaths are expected to be relatively rare, deaths will also be censored at 28 days post-randomization.

Number of participants: The precise rates of clinical and microbiological resolution are uncertain for monkeypox in general, and for the current epidemiological context. The larger the numbers entered the more accurate the results will be. Realistic, appropriate sample sizes may not be estimated at the start of the trial; the numbers that can be entered will depend on the evolution of the outbreak.

Data Monitoring Committee: A global Data Monitoring Committee (DMC) will monitor accumulating efficacy and safety data on an ongoing basis. The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. The DMC will be asked to recommend stopping the study early for efficacy only when there is clear and substantial evidence of a treatment benefit. The PIs and Sponsors will make decisions about trial continuation based on recommendations received from the DMC.

[2] **Time to lesion resolution:** lesions of skin and mucosa are crusted, scabs have fallen off and a layer of skin has formed underneath
[3] The definition of severity is being discussed.

2. Schema

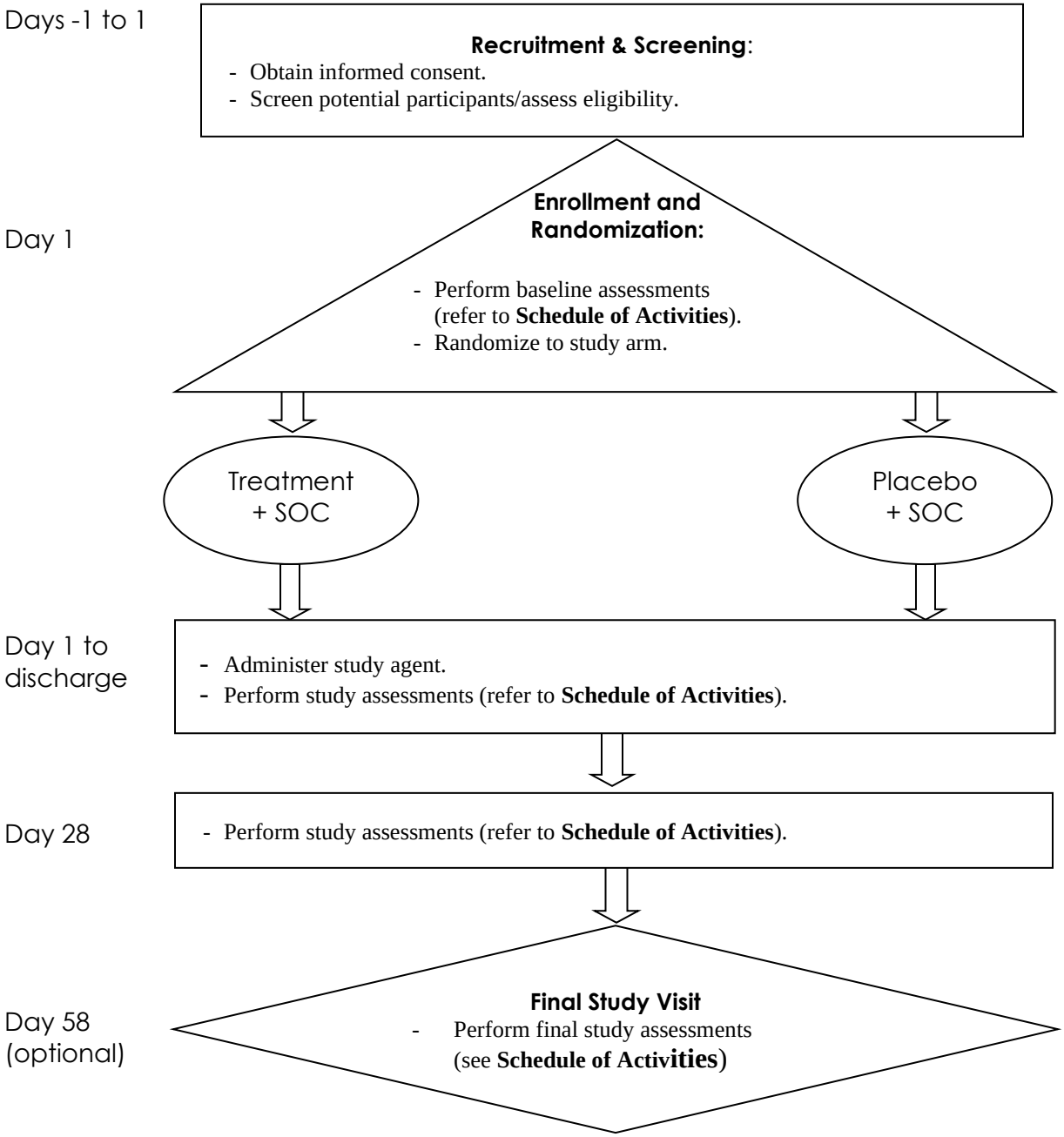

Figure 1. Study Schema.

3. Schedule of Activities

Evaluation/Procedure	Screen	Baseline	Follow-Up		
Day +/- Window	−1 or 1	1	Daily if hospitalized, or every 3 to 5 days for outpatients[d]	28±7[a]	58±7[b]
OPERATIONAL AND CLINICAL ASSESSMENTS					
Informed consent	X				
Eligibility (inclusion/exclusion) assessment	X				
Demographics	X				
Medical history	X				
Randomization		X			
Vital Signs		X	X	X	X
Lesion Assessment[e]		X	X		
Record standard-of-care treatments		X	X		
Current symptoms		X	X	X	X
Assessment of AEs/SAEs		X	X	X	X
STUDY DRUG ADMINISTRATION					
Study drug administration		Treatment or placebo following schedule of administration of the drug			
RESEARCH LABORATORY EVALUATIONS					
Monkeypox PCR (blood) with CT	X[g]		Every other day if hospitalized, or every 3 to 5 days for outpatients if in virological sub-study		
Blood for storage		X	Day 14 for outpatients or earlier upon discharge for hospitalized patients (if feasible consider for outpatients)	X	X
Oropharyngeal and rectal lesions swab		X	For hospitalized patients: every other day until discharge; or every 3 to 5 days for outpatients if in virological sub-study		
Skin lesions swab		X	For hospitalized patients: every other day until discharge; or every 3 to 5 days for outpatients if in virological sub-study		

To be included in some sites if locally relevant and feasible

CLINICAL LABORATORY EVALUATIONS[h]					
Malaria rapid test	X				
Glucose (mg/dl)	X	X	Every other day until discharge	X	X
Hemoglobin (g/dL)	X	X	Every other day until discharge	X	X
Hematocrit (L/L)		X	Every other day until discharge	X	X
Creatinine (mg/dL)		X	Every other day until discharge	X	X
Potassium (mmol/L)		X	Every other day until discharge	X	X
Sodium (mmol/L)		X	Every other day until discharge	X	X
eGFR (mL/min/1.73m^2)		X	Every other day until discharge	X	X
AST (U/L)		X	Every other day until discharge	X	X
ALT (U/L)		X	Every other day until discharge	X	X
BUN (mg/dL)		X	Every other day until discharge	X	X
CBC with differential (c/mm^3)		X	Every other day until discharge	X	X
Calcium (mg/dL)		X	Every other day until discharge	X	X
Total protein (g/dL)		X	Every other day until discharge	X	X
C-reactive protein (ug/mL)		X	Every other day until discharge	X	X
Creatinine kinase (U/L)		X	Every other day until discharge	X	X
Total CO_2 (mEq/L)		X	Every other day until discharge	X	X
Chloride (mEq/L)		X	Every other day until discharge	X	X
Alkaline phosphatase (IU/L)		X	Every other day until discharge	X	X
t-Bilirubin (mg/dL)		X	Every other day until discharge	X	X
Amylase (U/L)		X	Every other day until discharge	X	X

CLINICAL LABORATORY EVALUATIONS[h]					
Albumin (g/dL)		X	Every other day until discharge	X	X
PT (sec)/aPTT (sec)/INR		X	Every other day until discharge	X	X
D-dimer (ng/mL)		X	Every other day until discharge	X	X
Fibrinogen (mg/dL)		X	Every other day until discharge	X	X
Urinalysis, dipstick		X	Every other day until discharge	X	X

Abbreviations: AE, adverse event; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; BUN, blood urea nitrogen; CBC, complete blood count; CO_2, carbon dioxide; CT, cycle threshold; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PCR, polymerase chain reaction; PT, prothrombin time; SAE, serious adverse event.

[a] This study visit will include a +/- 7-day visit window for outpatients and hospitalized participants discharged prior to Day 28. For participants who remain inpatient through Day 28, the visit should take place exactly on Day 28.

[b] The Day 58 visit is optional and may be completed in person or by phone. Failure to complete a Day 58 visit will not result in a protocol deviation. Some procedures may not be able to be performed if the visit takes place over the phone.

[c] Only for participants who weigh <40 kg. For these participants, weight will be taken each morning before breakfast and used to calculate the study drug dose for that day.

[d] Hospitalised participants are eligible for discharge at the discretion of the treating physician; after discharge they will be followed-up every 3 to 5 days. The date of discharge will be documented.

[e] During lesion assessments any unresolved lesions in the target assessment region will be counted. While the participant still has unresolved lesions in the target region, assessment of whether there are unresolved lesions on other areas of the body will be optional but preferred. Once all lesions in the target region are resolved, a simplified full body lesion assessment will be done until all lesions are resolved.

[f] All baseline assessments should be complete before starting study drug. Administration of the evaluated drug or placebo should be continued if the participant meets the criteria for discharge.

[g] Although any positive monkeypox PCR from blood collected up to 48 hours prior to informed consent may be used to establish eligibility, a new specimen must be collected within 24 hours prior to randomization if the prior specimen is more than 24 hours old.

[h] With the exception of screening collection of glucose and hemoglobin (both of which are required for determining eligibility), all labs at all time points, though highly desirable, may be waived if not feasible (e.g., due to blood draw volume concerns related to participant weight or due to site logistics), per investigator discretion. Any laboratory tests obtained within 24 hours from randomization for screening purposes do not need to be repeated on day 1.

4. Introduction

Study Rationale

WHO calls for the use of antivirals for the treatment of monkeypox cases within a framework of collaborative research and randomized clinical trial (RCT) protocols with standardized data collection tools for clinical and outcome data to rapidly increase evidence generation on efficacy and safety[4,5]. This includes a scientific steering committee, common data management, and robust statistical analysis plan to satisfy regulatory requirements. Harmonised data collection for safety and clinical outcome (using WHO Global Clinical Platform for Monkeypox[6]) would represent a desirable minimum in the context of an outbreak such as current one.

A platform trial uses a shared infrastructure, in which various treatments are evaluated using the same 'CORE protocol' and tested against a shared control condition. Moreover, the speed of platform trials might help to accelerate the evaluation of drugs and generate evidence from different subgroups and different geographic locations.

Each site interested in participating can enroll patients in this international trial and implement the core protocol. This will require commitment to assess the main objectives as defined by the core protocol; enrolling homogenous population (common inclusion criteria); and evaluating the same interventions with the same primary and secondary endpoints. There will be an option for countries or regions to complement the core protocol through add-on studies with additional sub-analyses

Ethical and regulatory approvals will be handled by each country's or region's principal investigators. A centralized randomization facility will be available. Data, corresponding to main objectives and core variables will be sent in real time to a centralized data base (using WHO provided platforms); centers sending these data should meet quality requirements (defined a priori) which make them eligible to be part of the global analysis. A statistical analysis plan will be developed. Monitoring of a proportion of data should be possible (by the entity doing the central data collection, or at least overseen by them).

A scientific steering committee and global DSMB will help steer the trial decisions regardless of existence of individual trials ones should be implemented.

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[4] https://cdn.who.int/media/docs/default-source/2021-dha-docs/20220706_monkeypox_external_sitrep_final.pdf?sfvrsn=1b580b3d_4&download=true

[5] https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON396

[6] https://www.who.int/tools/global-clinical-platform/monkeypox#:~:text=Global%20understanding%20of%20the%20natural,patient%2Dlevel%20anonymized%20clinical%20data

5. Objectives and endpoints

5.1 Primary Objective

To evaluate the clinical efficacy, as assessed by time to lesion resolution, of treatment plus SOC versus placebo plus SOC for patients with monkeypox.

Rationale: Lesion resolution is a patient-important clinically meaningful outcome that can be measured. A well-known hallmark that characterizes MPX from all clades is the presence of a rash, and that rash can be located in any area of the body, including the skin and mucosa. Limited published data and clinical experiences have suggested an association with extent of skin lesions and complications and death. Secondarily, lesions are infectious and account for majority of transmission via contact route. Due to the very low case fatality ratios reported with MPX, a mortality outcome is not reasonable primary endpoint.

Definition of primary endpoint
Time for all lesions (skin or mucosal) to heal with a new fresh layer of skin "re-epithelialization= resurfacing of a wound with new epithelium layer. For skin lesions, typically this means the lesion has scabbed, desquamated and new layer of skin formed. For mucosal lesions, the phase of scabbing and desquamation is absent, and healing with new layer of skin ensues. The median time for lesions healing is not well documented in the current outbreak. Emerging information on this would strengthen our estimation of sample size.

5.2 Secondary objectives

1. To evaluate the **clinical efficacy** of treatment plus SOC versus placebo plus SOC in patients with monkeypox as assessed by mortality, clinical severity, and duration of symptoms.

2. To evaluate the **safety** of treatment plus SOC relative to placebo plus SOC in patients with monkeypox.

Definition of secondary end points
1.1 All-cause mortality within the first 28 days (applied to all patients)
Rationale: all -cause mortality more reliably measured than MPX-specific mortality. Easy to measure, reliable.

1.2 All-cause admission to hospital within first 28 days (applies to outpatients)
Rationale: Most patients will be managed at home or in community and this is both an important patient centered and health system outcome. All-cause is easier to measure than MPX specific and will ease data burden.
1.3 Proportion of patients with a complication within first 28 days (applies to all patients)
Complications include genitourinary (ex. urinary retention), lower respiratory tract (ex. pneumonia, need for oxygen), ocular impairment (ex. keratitis), neurologic impairment (ex. encephalitis) or mental health disturbance, confusion), cardiac impairment (ex.

cardiomyopathy, myocarditis), severe dehydration, secondary bacterial skin infection (cellulitis, abscess, necrotizing fasciitis, need for antibiotics), severe pain.
Rationale: Progression to complications is an important patient-centered outcome and important health system outcome to prepare clinical services for MPX cases. Easy to measure, as long as definitions are clear, and staff is trained.
Frequency of data collection: baseline and at day 28

1.4 Time to resolution of symptoms and signs (applies to all patients)
Definitions:
- Symptoms include fatigue, malaise, nausea, vomiting, abdominal pain, anorexia, cough, dysphagia, odynophagia, fever, headache, oral pain, pain with urination, rectal/anal pain.
- Signs include including lymphadenopathy, ocular lesions, pharyngitis, urethritis, and proctitis.

Rationale: collection of symptoms and signs can be useful to understand the clinical characterization, however, requires intensive data collection.
Frequency of data collection: at baseline and every 3-5 days.

1.5 Definition of key supportive end points
Frequency of severe adverse events for specific therapeutics (applies to all patients)
Rationale: very important to collect standardized data for adverse events to increase our understanding of safety.
Frequency of data collection: TBD dependent on study drug

1.6 Viral clearance up to 28 days after randomization (applies to subset of inpatients and possibly outpatients):
Definition: Time to the first negative blood, oropharyngeal (OP), rectal swab PCR, and skin swab result up to 28 days after randomization. For skin lesions sampled, specific protocols for standardization necessary.
Sampling schedule: every other day for inpatients, and 3-5 days for outpatients.

5.3 Exploratory outcomes for add-on studies

Viral trajectories:
- Correlation of skin lesion evolution with CT values;
- Correlation of CT values and infectious virus;
- Environmental sampling for viral PCR and infectious virus;
- Sequential sampling of semen, vaginal fluid and breast milk.

Skin lesion evolution:
- Maximal body regions involved (new, inpatients and outpatients). Maximum lesion count in affected regions (new, inpatients and outpatients)
- Time to maximum lesion count in the affected region up to 28 days after randomization (inpatients)

6. Study design

This is a CORE protocol for a global randomized, placebo-controlled trial to evaluate the safety and efficacy of drugs for the treatment of human monkeypox (Phase 3).

Study sites will be in geographic locations where cases of monkeypox were reported. Sites will be opened one after another as they obtain approvals and are ready to start the trial.

A participant will be considered enrolled beginning from when the informed consent form is signed and randomization to an assigned treatment has occurred. Once enrolled, study drug administration will begin according to study group assignment.

Participants will be randomized to one of the experimental treatments (k in number) for which they are eligible (no specific exclusion criteria) or to one of the placebos that correspond (in appearance, dosing interval, and route of administration) to each of those treatments. The randomization ratio will ensure that participants have the same chance of receiving a placebo as they have of receiving each individual treatment for which they are eligible. All participants will also receive local SOC that is standardized at each site according to local/site guidance.

Participants will either be hospitalized or outpatients and will undergo frequent clinical and laboratory assessments for safety and efficacy. Day 28 is the final required study visit, but participants may return for an optional visit at day 58 for long-term clinical and laboratory evaluations.

Scientific rationale for study design

Randomization will be used to balance the groups with respect to many known and unknown confounding or prognostic variables. The use of a placebo control group will enable a reliable assessment of efficacy and safety of the experimental treatment. To enhance trial integrity, the study was designed to be double blinded.

7. Study population

Inclusion criteria

- Adults and children (6 years and older) with laboratory-confirmed (PCR) monkeypox illness of any duration (provided that the patient has at least one active, not yet scabbed, lesion and, who have no contra-indication to potentially study drug.
- Men and non-pregnant women of reproductive potential must agree to use effective means of contraception when engaging in sexual activities that can result in pregnancy, from the time of enrolment through the end of study participation. Acceptable methods of contraception include the following: hormonal contraception, male or female condom, diaphragm or cervical cap with a spermicide and intrauterine device.

Exclusion criteria

Exclusion criteria

- Current or planned use of another investigational drug at any point during study participation.
- Patients who, in the judgement of the investigator, will be at significantly increased risk as a result of participation in the study.
- Specific exclusion criteria for each evaluated drug will be considered.

Pregnant women and special populations will be enrolled in this study if the national principal investigator, the national regulatory authorities, and the ethics committee agree that the benefits of receiving the experimental treatment outweigh its risks, and specifically if they consent to participate after the information on risk and benefits is provided.

8. Study intervention

The details regarding the study treatments will be included in Appendix 1.

Dosing and administration

The details regarding dosing and administration be included in Appendix 1..

Dose modifications

No dosage adjustment is required for patients with mild, moderate, or severe renal or hepatic impairments at baseline.

Drug administration

Details regarding dose administration will be included in Appendix 1.

Preparation/handling/storage/accountability

Acquisition: Study treatment and placebo will be shipped to the study site where administration will take place, in compliance with all applicable transport guidelines.
Accountability: The study pharmacist will be responsible for maintaining an accurate record of the study arm codes, inventory, and an accountability record of study agent supplies.
Formulation, Appearance, Packaging, and Labelling:
Details regarding the study treatment will be included in Appendix 1
Product Storage and Stability:
Details regarding the study treatment will be included in Appendix 1
Preparation: Details regarding the study treatment will be included in Appendix 1

9. Measures to minimize bias

Randomization

Once eligibility has been confirmed, subjects will be eligible for randomization. Randomization will be performed onsite.

Participants will be randomized to one of the experimental treatments (k in number) for which they are eligible (no specific exclusion criteria) or to one of the placebos that correspond (in appearance, dosing interval, and route of administration) to each of those treatments.

A randomization SOP will be developed prior to study start to provide details on the randomization process and procedures for maintaining the integrity of the randomization. The treatment allocation table and the program used to generate the treatment allocation table will be maintained by the data coordinating center on secure servers. The allocation table will not be revealed to anyone outside the unblinded team responsible for creating the table.

Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

Blinding/Unblinding

Study team members, including the pharmacovigilance team, and participants will be blinded to treatment arm assignment throughout the duration of the study. To preserve blinding, after preparation, the drug or placebo will be placed outside the pharmacy for pick-up. The pharmacist will alert the responsible study team member that the treatment is ready to be picked up. The unblinded pharmacy staff is responsible for maintaining security of the study treatment assignments.

Scheduled unblinding: After all participants have completed the final study visit, the study will be unblinded and participants will be informed about their study treatment assignment by the study team.

Unscheduled unblinding: Intentional: A request for unblinding of treatment assignment may be made by the principal investigator only in the setting where the knowledge of

the blinded treatment assignment is necessary in decisions about proper subsequent treatments of that participant.

If a participant's study agent assignment is unblinded, the information will only be provided to the study principal investigators and team members needing it for treatment decisions; those individuals will keep the information secure and limit its use to a "need-to-know" basis for patient wellbeing, to maintain blinding for the rest of the study team.

Unintentional: If unintentional unblinding of study agent assignment occurs, the site principal investigator will create a plan for ongoing management of the participant(s) involved and for preventing the recurrence of a similar incident, as appropriate.

Intentional and unintentional unscheduled unblinding will be documented in the appropriate source and/or research record and will include the reason for the unscheduled unblinding, the date it occurred, who approved the unblinding, who was unblinded, who was notified of the unblinding, and the plan for the participant. If the unblinding meets the definition of a reportable event, it will be reported to the ERC(s) according to their respective procedures.

Study intervention compliance

The pharmacist will monitor the inventory of investigative products through the distribution log, which will record entries and exits, quarantines, transfers between sites, and the conditions of storage, as well as any comments useful to inform about the quality of the product. During the dispensing of the product, the dispensing log will be completed with participant number, quantity (mg) of product received, day, date, batch of medication, and initials of the pharmacist and the preparer.

The pharmacist will perform the randomization and keep a randomization log to document the link between the participant number and the product assigned. Study drug will be administered to participants under direct observation by a member of the study team.

A quality log will be kept documenting any temperature excursions affecting the study agents (less than 15°C and more than 30°C). Temperature excursions outside of this range will be reported, and the log will be made available to the principal investigator, pharmaceutical company, and study pharmacist to establish whether the affected product can be used. All critical issues/conditions relating to the quality of the product will be documented. A destruction log will be available at the site to document the destruction of all expired or damaged product batches.

Concomitant therapies

All concomitant prescription and nonprescription (including over-the-counter, herbal, or traditional) medications taken during study participation will be recorded. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

10. Drug discontinuation (which does not imply withdrawal from follow-up)

At all times the patient's medical team remains responsible for decisions about that patient's care and safety. Hence, if the medical team decide any deviation from the randomly allocated treatment arm is definitely appropriate then this should be done, although the patient would remain in the trial and should still be followed for outcomes.

1. Study drug administration should be stopped if the team suspects any serious unexpected drug-related adverse reaction that is life-threatening, and this SUSAR should immediately be reported electronically. The patient will still be followed in the usual way at the end of their time in hospital.
2. Study drug administration should be stopped if the treating physician considers this is definitely in the patients' best interest (including but not limited to life threatening events) or if the patient or a legal representative decide it should be stopped. The patient should still be followed in the usual way at the end of their time in hospital, unless it is decided otherwise (see below).

11. Decision by a patient or legal representative to withdraw from follow-up

Patients are informed at study entry of their right to withdraw at any time their consent to participate without any adverse consequence and without giving any reason. Withdrawal from the treatment that was randomly allocated at study entry need not imply withdrawal from information on outcome in hospital being reported to the WHO at the end of the hospital stay. But, if the patient (or a legal representative) decides the patient will withdraw *and* that no further data will be sent to the WHO study office, then only the date of withdrawal will be reported; no further information will be given, unless an adverse drug reaction report is legally required.

12. Study assessments and procedures

Study schedule

See section 3 for a detailed schedule of procedures. The day when the subject is randomized to their assigned treatment arm is denoted as Study Day 1. Screening procedures will occur in the 24 hours prior to randomization (Study Day -1 to 1). Note that there is no Study Day 0. Study Day -1 is the 24-hour day prior to the day of randomization. The first day after randomization is Study Day 2. Subsequent days will be numbered chronologically through Day 58 of study.

Informed consent

The national investigator or a qualified and previously designated member of the study team will review the informed consent documents with the subject. If a subject is incapable of reading the informed consent, the study procedures will be explained in the local language preferred by the subject. Once the information has been explained to patients, obtaining consent takes only a few minutes. An electronic image of the signature page is kept (or, if national regulations forbid this, a note to file), and the printed information and original consent stays with the patient or legal representative. The date that informed consent was obtained will be documented on the informed consent form. The informed consent process will occur on or before Study Day 1. Informed consent will be obtained prior to initiating study procedures.

Data collected electronically immediately before randomisation

- Country, geographic region of residence, hospital and randomizing doctor
- Confirmation that informed consent was obtained from the patient (or a surrogate/ representative)
- Age, sex and (yes/no): HIV, TB, malaria, hypertension, diabetes mellitus, asthma, hepatitis, hyperlipidemia, cancer, heart failure, renal disease, liver disease, chronic obstructive pulmonary disease (COPD), COVID-19, neoplasm, obstructive sleep apnea, obesity, immunosuppressive disorder other than HIV, sickle cell anemia, concurrent bacterial infections such as urinary tract, ear nose and/or throat, pulmonary, central nervous system, skin or gastrointestinal infection, bacteremia/sepsis or other.
- Date of onset of symptoms, date of hospitalization, and (yes/no) current/planned use of a few drugs
- Monkeypox lesions status (yes/no): at least one active, not yet scabbed, monkeypox lesion, XXXX
- Current symptoms (yes/no): nausea, vomiting, abdominal pain, anorexia, cough, lymphadenopathy, dysphagia, fever, headache, ocular lesions, and buccal ulcers.
- Smallpox vaccination status (yes/no) or presence of vaccination scar (yes/no).
- Risk factors for monkeypox infection (yes/no): recent contact with known monkey pox case, type of contact, residing or visiting an area with an active monkey pox outbreak, animal handling.

Determination of eligibility

Once the screening procedures are complete, eligibility will be determined based on the inclusion and exclusion criteria. Subjects that are found to be ineligible will be informed during the screening evaluation, and the reason for their ineligibility will be discussed and documented.

Lesion assessments

Time to lesion resolution is an outcome that may be subject to inter-observer variability and a blinded, placebo control arm is essential to reduce this potential bias. In addition, some body areas it may be easier to count lesions (i.e. arm, legs) whereas others more difficult (i.e. oral, peri-anal). Thus, it is also important to implement trial with

standardized assessment tools (i.e. body areas, counting techniques) and trainings to ensure reliable and accurate measurements.

In addition, independent adjudication for assessments may provide additional verification, as long a stringent privacy and patient confidentiality is maintained.

Frequency of data collection: This may be dependent on study design. For example, for inpatients, assessments can be collected on a daily basis; but for outpatients a frequency of 3-5 days may be more reasonable. At minimum, to recognize meaningful difference, a time frame of 3-5 days was deemed clinically relevant.

Tools:

- Use standard pain scale
- Use standard adverse event scales
- Use standardized scale for body areas
- QOL scales
- Digital technology for skin lesion assessment

Randomization

Eligibility for an experimental treatment will be based on availability of the treatment at the time of randomization and any specific inclusion/exclusion criteria associated with that treatment.

Participants will be randomized to one of the experimental treatments (k in number) for which they are eligible or to one of the placebos that correspond (in appearance, dosing interval, and route of administration) to each of those treatments. The randomization ratio will ensure that participants have the same chance of receiving a placebo (with probability 1/(k+1) for placebo in aggregate, which is the sum of the probabilities 1/k(k+1) for each individual placebo) as they have of receiving each individual treatment (with probability 1/(k+1)) for which they are eligible.

Efforts will be made to harmonize inclusion/exclusion criteria among treatments in order to simplify the randomization and increase trial efficiency.

Outcomes in recipients of each experimental treatment will be compared with outcomes in all placebo recipients who were eligible to be randomized to that treatment. This approach preserves blinding and enables comparison of each treatment's results directly to results from an equal number of controls who received placebo at the same time and place.

	Time Window #1	Time Window #2	Time Window #3
Regimens	A	AA BB	AAA BBB CCC
Placebos	P_A	P_A P_B	P_A P_B P_C
Individual regimen : matched-placebo	1:1	2:1 2:1	3:1 3:1 3:1
Individual regimen : shared-placebo	1:1	1:1	1:1

Figure 2: Randomization scheme. Experimental treatment A and its matched placebo P_A enter the trial in time window #1. In this example, Treatment A utilizes the combined placebo arms (P_A, P_B and P_C) from all three time windows. Treatment B and its matched placebo PB enter in time window #2. In this example, Treatment B utilizes the combined placebo arms from time windows #2 (P_A and P_B) and #3 (P_A, P_B and P_C). Treatment C and its matched placebo P_C enter in time window #3. In this example, Treatment C utilizes only the placebo arms (P_A, P_B and P_C) from time window 3.

This randomization scheme is illustrated in Figure 2, where experimental treatments A, B and C, and their matched placebos, P_A, P_B and P_C, enter the trial at 3 different times. This design is efficient in allowing the assessment of each treatment to use a shared placebo arm with concurrent follow-up. Participants may be able to determine, based on specific characteristics, which treatment they might be receiving, yet will always be blinded to whether they are receiving the active treatment candidate or the corresponding placebo.

Study drug administration

Study drug administration will begin on Day 1 and continue for up to 14 days, as described in section 0.

SOC Received

All current SOC treatments will be recorded.

Current symptoms

Current symptoms and conditions will be recorded, including identification of any new or worsening (S)AEs as well as presence, of any bacterial complications such as urinary

tract, ear nose and/or throat, pulmonary, central nervous system, skin or gastrointestinal infection, bacteremia/sepsis or other.

Research laboratory evaluations (as part of add-on studies if feasible)

Blood will be collected via venipuncture for monkeypox PCR with CT, and blood will be stored for antibody titer measurements and other future research testing. Swabs will be collected from oropharyngeal lesions and open skin lesions for viral load assessments.

Clinical laboratory evaluations (as add on studies if feasible)

Laboratory testing, including urinalysis, will be performed as described in section 3. While every effort should be made to obtain these laboratories as indicated, note that the frequency and volume of blood draws is always subject to the clinical judgment of the site investigator as to safety and logistical considerations. Hence any inability to obtain the minimal laboratory assessments on a given day due to clinical or other extenuating circumstances will not constitute a protocol deviation.

Adverse reaction reporting

Any suspected unexpected serious adverse reactions (SUSARs) that are life-threatening must be reported electronically within 24 hours of diagnosis, without waiting for death or discharge; as must any other potentially treatment-related serious adverse events (SAEs). Other adverse events do not need to be reported. A subset of countries or collaborators will also collect fuller information on adverse events. Where countries collect more extensive adverse reaction data, those datasets are not included in the CORE trial dataset.

In addition to reporting SAEs possibly related to the treatment and SUSARs, doctors will be asked, after patient discharge or death in hospital, what was the probable cause of death, and will be asked about drug use and respiratory support in hospital, including initiation of ventilation. Information on other non-fatal adverse outcomes is not in general required. It is, however, anticipated that some centres will choose to collect more detailed information on adverse events (eg, through linkage to medical databases) or on other aspects of outcome (eg, laboratory or radiological features), but this is not a requirement of the core protocol.

13. Statistical considerations

Design overview

This is a randomized, placebo-controlled, double-blind trial to test superiority of experimental treatments, as described above. **Figure 1** provides a study schema of the trial design. To date there have been no studies of monkeypox therapeutics in humans to inform the design of the present trial.

Populations for analyses

The primary analysis and secondary efficacy analyses will be based on a modified intention-to-treat population consisting of all randomized subjects who have a true positive monkeypox blood PCR result and grouped according to their true number of days since onset of symptoms for the purposes of stratification. Safety analyses including 28-day mortality, incidence of SAEs, incidence of AEs requiring drug discontinuation, and incidence of other AEs will be based a modified intent-to-treat population consisting of all subjects who received at least one dose of experimental treatment or placebo.

Statistical Analyses

This is a randomized, placebo-controlled, double-blind trial testing a superiority hypothesis with a two-sided type I 2.5% false positive error rate of 5%. Secondary endpoints have been ordered according to relative importance. The study will employ a hierarchical testing procedure highlighting the relative importance of the primary and key secondary endpoints. A statistical analysis plan will be developed prior to unblinding of the study and database lock.

Primary endpoint analysis

A stratified log-rank test will be used to compare arms with respect to time to lesion resolution, where stratification is by days from onset of symptoms to randomization (≤7 days vs >7 days) and by baseline severity.

Participants with any lesions not scabbed or desquamated at 28 days after randomization will be censored for statistical analysis of this endpoint. Though deaths are expected to be relatively rare, deaths will also be participants who die before 28 days without prior lesion resolution will have their time to lesion resolution censored at 28 days post-randomization (equivalent to assigning deaths the worst possible time to resolution).

Secondary endpoint analyses

- Time to event endpoints will be summarized using Kaplan Meier curves along with treatment effect rate ratios and accompanying 95% confidence intervals. Statistical significance, where appropriate, will be assessed using the log-rank test.
- Mortality within the first 28 days by study arm will be summarized by proportions with 95% confidence intervals and assessed for statistical significance using the Newcombe method is available in SAS and R via the pairwise CI package on CRAN.
- All-cause hospital admission within the first 28 days by study arm will be summarized by proportions with 95% confidence intervals and assessed for statistical significance using the Newcombe method is available in SAS and R via the pairwise CI package on CRAN.
- Incidence of a complication within the first 28 days by study arm will be summarized by proportions with 95% confidence intervals and assessed for statistical significance using the Newcombe method is available in SAS and R via the pairwise CI package on CRAN.

- Time to resolution of symptoms and signs will be analysed using a stratified log-rank statistic, and will be descriptively summarized using Kaplan Meier curves. Symptoms will include fatigue, malaise, nausea, vomiting, abdominal pain, anorexia, cough, dysphagia, odynophagia, fever, headache, oral pain, pain with urination, rectal pain, and signs will include lymphadenopathy, ocular lesions, urethritis, and proctitis.

Additional analyses of efficacy and safety measures

- Frequency of clinical symptoms by symptom and study arm will be summarized as proportions at baseline and day 3 to 5, 6 to 10, 12 to 15, 15 to 20, 28, and 51 days post-randomization. Duration of clinical symptoms will be summarized according to median days and interquartile range.
- Time to the first negative blood, oropharyngeal (OP), rectal swab PCR result up to 28 days after randomization will be summarized descriptively, using Kaplan-Meier curves.
- Incidence of bacterial infections by study arm will be summarized by proportions and differences in proportions with 95% confidence intervals.
- Each SAE, grade 3 and 4 events, Grade 1-2 hypersensitivity-related and infusion related AEs, and AEs of special interest will be summarized, by System Organ Class and Preferred Term, with the number and percentage of patients with at least one event and the total number of events for each endpoint. Discontinuation of investigational therapeutics (for any reason) will be summarized with the number and percentage of patients by treatment group and overall. Patients with at least one SAE, patients with at least one grade 3 or 4 AE, patients with at least 1-2 hypersensitivity-related and infusion related AEs and patients with at least one AE of special interest will be compared using a Chi squared test (or Fisher exact test if appropriate) test or a stratified Cochran-Mantel-Haenszel test.

Hierarchical testing scheme

The study will employ a hierarchical testing scheme, beginning with the primary endpoint and then testing in the order of the secondary endpoints.

Additional analyses (not as part of core protocol)

Efforts will be made to develop and validate a baseline disease severity metric for use in future studies of human monkeypox. Risk classification models, described in detail in the statistical analysis plan, will be implemented to summarize the strength of the relationships between baseline characteristics (including age, sex, baseline lesion count, type and duration of symptoms, viral load, and selected comorbidities) and the primary and key secondary endpoints.

Baseline descriptive statistics

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category.

Number of participants

The larger the numbers entered the more accurate the results will be. Realistic, appropriate sample sizes may not be estimated at the start of the trial; the numbers that can be entered will depend on the evolution of the outbreak. Sufficient robustness also would be important, given heterogeneity of this clinical setting and interest in having reliability in key subgroups such as by outpatient vs hospitalized patients and by clade. The larger numbers of participants enabled by this international collaboration will provide meaningfully enhanced reliability of results. Sample size calculations will be refined when improved insight would be available about rate of lesion resolution and heterogeneity in the evolution of the outbreak.

As an illustration, if the trial were designed to provide 90% power to detect a 1.4 relative increase in the rate of lesion resolution, using a stratified-log rank statistic with 2.5% false positive error rate, it would be required to have 372 patients having documented lesion resolution by day 28. The sample size needed to achieve that number of events currently is not known since the precise rates of clinical and microbiological resolution are uncertain for monkeypox in general, and for the current epidemiological context.

Data Monitoring Committee

A global Data Monitoring Committee (DMC) will monitor accumulating efficacy and safety data on an ongoing basis. The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. The DMC will be asked to recommend stopping the study early for efficacy only when there is clear and substantial evidence of a treatment benefit. The PIs and Sponsors will make decisions about trial continuation based on recommendations received from the DMC.

Informed consent process

Informed consent will be obtained in person by a study team member authorized to obtain consent. The privacy of the subject will be maintained. The consenting investigator and participant will be located in a private area (e.g., clinic consult room). Discussions about the research will provide essential information about the study and include purpose, duration, experimental procedures, alternatives, risks, and benefits. Coercion and undue influence will be minimized by informing participants that their decision to join the study will not affect any medical care they are currently receiving, or their eligibility to participate in other research studies. Participants will be given as much time as they need to read the consent form and ask questions of the investigators. Participants over 18 years of age will sign the informed consent document (in a language understood by the subject) prior to any procedures being done specifically for the study. The signature of a legally acceptable representative of the potential subject will be obtained for adults who are impaired and unable to provide informed consent. In the case of adults whose ability to consent is uncertain, capacity to consent will be evaluated by the principal or associate investigator(s).

Parental/guardian permission and minor assent for children through 17 years of age will be obtained according to local standards and country-specific requirements.

A copy of the informed consent document will be given to the participants for their records. The consenting investigator will document the signing of the consent form in the participant's study record. The investigator will confirm that written legally effective consent has been obtained prior to initiating any study interventions. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participants may withdraw consent at any time throughout the course of the trial.

14. Study discontinuation and closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principal investigators, pharmacovigilance committee, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the study participants, ERC, pharmacovigilance committee, and relevant regulatory authorities, as applicable, and will provide the reason(s) for the termination or suspension. Study participants will be informed of changes to study visit schedule, if applicable.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination that the effect on the primary endpoint has been reliably established.

In the case of a temporary suspension, the study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the ERC, pharmacovigilance committee, and regulatory authorities, as applicable.

15. Confidentiality and privacy

All records will be kept confidential to the extent provided by federal, state, and local laws in the jurisdictions in which the study is conducted. Study monitors and other authorized individuals may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. Records will be kept locked and data will be coded. Any personally identifiable information maintained for this study will be kept on restricted-access computers and networks. Personally identifiable information will only be shared with individuals authorized to receive it under this protocol. Individuals not authorized to receive personally identifiable information will be provided with coded information only, as needed. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the Ethics review Committee, local regulatory agencies, the pharmaceutical supporter, or other authorized individuals.

Future use of stored data

Coded data and specimens will be stored indefinitely for future research after the study is complete. Plans for future use of data and specimens will be described in the informed consent document. Case report forms will be retained in secure facilities at the study sites. Coded specimens will be stored in secure facilities. The key to the participant codes will be maintained securely at the study sites.

Other investigators may wish to study these data and/or specimens. In that case, the principal investigators and the steering committee will review the request. If the planned research falls within the category of "human subjects research" on the part of the investigators, ERC review(s) and approval(s) will be obtained as appropriate. This includes the investigators sending out coded and linked specimens or data and getting results that they can link back to their subjects.

Safety oversight

Safety oversight for this study is described in section XXXX

Data management responsibilities

The site investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of information) should support the data transferred to the electronic data system and, when possible, should be signed and dated by the person recording and/or reviewing the data. All data should be reviewed by the Investigator and co-signed as required.

Data Capture Methods

Study data collected at the bedside at study sites will later be recorded as paper or electronic CRFs with subsequent transmission to the Data Coordinating Center. Data Coordinating Center personnel shall enter data into an electronic database. Corrections to electronic data systems will be tracked electronically (password protected and through an audit trail) with time, date, individual making the correction, and what was changed.

Types of data

Source documents may include, but are not limited to, the subject's medical records, laboratory reports, ECG tracings, x-rays, radiologist's reports, subject's diaries, biopsy reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study.

Source documents and access to source data/documents

Source documents include all recordings of observations or notations of clinical activities, and all reports and records necessary for the evaluation and reconstruction of the clinical trial.

Record retention

The national protocol team is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects is to be maintained by the investigators in a secure storage facility for a minimum of 3 years or per in-country local or federal regulatory requirements (whichever is longer). These records are also to be maintained in compliance with ERC and local medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent required by applicable laws in the jurisdiction in which they are stored.

Site monitoring plan

As per ICH-GCP 5.18, clinical protocols are required to be adequately monitored by the study sponsor. The objectives of a monitoring visit would be: 1) to verify the existence of signed informed consent documents and documentation of the Informed Consent Form process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare data abstracts with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, medical progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also may inspect the clinical site regulatory files to ensure that regulatory requirements and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel should be available to discuss the study progress and monitoring visit. Monitoring of a proportion of data should be possible (by the entity doing the central data collection, or at least overseen by them)

Human Data Sharing Plan

At the completion of the trial, a comprehensive study report will be prepared by the Data Management Team and host countries researchers and submitted for review to the DMC, study partners, and all other applicable regulatory bodies. The relevant primary and secondary outcome data from this trial will also be entered into a trial registry for access by other researchers. In addition, it is the intention of the extended protocol team that de-identified data from this trial will be made available upon request to outside investigators upon scientific review of the merits of their proposed research plan. This availability will be in accordance with the WHO Joint statement on public disclosure of results from clinical trials.

Collaborative Agreements

Agreements for each participating site will be executed as needed.

ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AR	adverse reaction
AST	aspartate transaminase
BUN	blood urea nitrogen
CAPA	corrective and preventive action plan
CBC	complete blood count
CT	cycle threshold
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CYP	cytochrome P450
DCR	Division of Clinical Research
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug (application)
INR	international normalized ratio
ERC	institutional review board
MOP	manual of procedures
MPXV	monkeypox virus
PCR	polymerase chain reaction
PT	prothrombin time
SAE	serious adverse event
SAR	suspected adverse reaction
MM	medical monitor
SOC	standard of care
SRCP	safety review and communication plan
SUSAR	serious and unexpected suspected adverse reaction
UP	unanticipated problem
UPnonAE	unanticipated problem that is not an adverse event

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Appendix 1. Study intervention

(Information to be included)

Dosing and administration

Dose modifications

Drug administration

Preparation/handling/storage/accountability