CORE PROTOCOL

A randomized, placebo-controlled, double-blinded trial of the safety and efficacy of treatments for patients with monkeypox virus disease

(Adapted from PALM 007 protocol)

Standard Operating Procedures and Appendixes

Version 1.0
July 18, 2022

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SOP-1 Approval of centres to join the trial and access trial drugs

One National Co- Principal investigator will work together to get all necessary approvals rapidly, to select as potential collaborating research centres and/or local hospitals that already have, or are expected soon to have, substantial numbers of outpatient and or inpatient admissions for Monkeypox, and to facilitate local ethical approval on behalf of willing local collaborators. The following steps should ensure the trial can start promptly in each collaborating hospital. They should happen in parallel and not in sequential fashion.

Step	What?	Who?	How?	Remarks
1	Officially confirm interest to participate	To be defined for each country	Communication to trial secretariat	
2	Appoint one National Co-Principal investigator	A leading clinical investigator	Communication to trial secretariat	These National Co- Principal investigator should both be senior
3	Identify which research centres and/or local hospitals will have substantial numbers and will collaborate	One National Co-Principal investigator	Communication to trial Secretariat	Selected centres and hospitals should have basic GCP knowledge
4	Facilitate Approval - or not - by national authority and local ethics committees	National Co- Principal investigator	High-level national decisions, not just local applications by each collaborator	No modification of the protocol is possible, as very large numbers of hospitals are involved. Add on studies can be considererd
5	Establish which study drugs are available in each location	National Co- Principal investigator	Bilateral interactions	Trial secretariat will facilitate study drug provision where this is needed
6	Facilitate import permits for study drugs, as pertinent	National Co- Principal investigator	Depends on national guidelines and regulations	After permits for initial amounts, resupply will depend on entry rate
7	Set up personnel and logistics for study implementation	Appoint small central administrative staff for the Clinical National Representative	Make use of existing p.a. and other staff of known reliability to disseminate study	Local centres will need help on approvals, drug supplies, getting going, and maximising accrual
8	Within research centres and/or local hospitals, move quickly into rapid recruitment	Lead doctor and lead pharmacist motivate and train colleagues	Local leads explain and discuss study with colleagues	Local leads motivates & ensures full compliance, rapid entry & discipline

SOP-2 Access to global enrolment and randomization center

To facilitate collaboration even in overloaded hospitals, patient enrolment and randomisation (via a cloud-based GCP-compliant platform) and all other trial procedures are greatly simplified.
Within each country, the national co-ordinator invites selected hospitals and helps them get ethical and regulatory approval and study drugs then patient entry can begin.
Access is via the study website XXXXXXXXXX.
Each doctor has access to the platform using an individual secured password. A study ID for the patient is then generated and displayed.
Eligibility: Adults and children with laboratory-confirmed (PCR) monkeypox illness of any duration (provided that the patient has at least one active, not yet scabbed, lesion), and, have no contra-indication to potentially study drug.
Consent: The study website XXXXXXXXXXX has printable patient information in some languages. 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 copy of the consent must be kept in the file), and the printed information and original consent stays with the patient or legal representative.
Data collected electronically <u>immediately before</u> 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, 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.

SOP-3 Informed consent form*

*For minors the consent of both parents as well as an information note for children is required.

Principal Investigator	
Study Sponsor	
Name of protocol and version	

A randomized, placebo-controlled, double-blinded trial of the safety and efficacy of treatments for patients with monkeypox virus disease

To the health worker: We are inviting adults and children with laboratory-confirmed (PCR) monkeypox illness of any duration (provided that the patient has at least one active, not yet scabbed, lesion) and, Trial Sponsor have no contra-indication to potentially study drug to participate in this trial. All Trial Sponsor participate will receive the usual care offered in this health facility (health center, clinic or hospital), and in addition some but not all will be given one extra treatment chosen at random from a few untested treatments. The aim is to discover whether any of these treatments slows disease progression or improves survival.

To the patient: You have a disease called monkeypox. Several medicines for it have been proposed. These medicines may have no effect or a moderate effect on the disease. This health facility (health center, clinic or hospital) is collaborating through the XXXXXXXXXX and health facilities in many other countries in a study to help discover whether any of these treatments can help.

Whether or not you choose to join, you will still receive the usual standard of care at this health facility. If you do not join the study, you will receive whatever your doctor thinks is best. If you decide to join, you may receive one treatment being tested chosen by chance, as if on the roll of a dice. This form has two parts:
1. To share information about the treatments being tested.
2. For your signature, if you do decide to take part

PART 1: Information Sheet

Introduction
I am _____, working for the _____.

You have a disease called monkeypox that recently spread across the world. Most people recover fully from monkeypox, but a few experience complications. This hospital is collaborating in an international research study to help discover whether some untested treatments could help treat monkeypox. I am going to tell you about the study, then invite you to join it.

Before you decide, you can talk to anyone about it. If there are any words you don't understand, please ask me to stop and explain. If you have questions later, I'll be available to answer them, and so will the study doctors.

Purpose of the research
Monkeypox is an illness caused by the monkeypox virus. It is a viral zoonotic infection, meaning that it can spread from animals to humans. It can also spread from person to person. Monkeypox can cause a range of signs and symptoms. While some people have mild symptoms, others may develop more serious symptoms and need care in a health facility. Those at higher risk for severe disease or complications include people Trial Sponsor are pregnant, children and persons that are immunocompromised. In most cases, the symptoms of monkeypox go away on their own within a few weeks. However, in some people, an infection can lead to medical complications and even death. Newborn babies, children and people with underlying immune deficiencies may be at risk of more serious symptoms and death from monkeypox. . The study treatments are listed briefly below.

During the study, some treatments may get removed from this list, and others may get added to it. Each patient will receive at most one of the treatments.

Invitation to participate
Adults and children with laboratory-confirmed (PCR) monkeypox illness of any duration (provided that the patient has at least one active, not yet scabbed, lesion) and, Trial Sponsor have no contra-indication to potentially study drug to participate in this trial. If you join, you will be asked to sign that you understand that there are possible risks and benefits and consent to join the study. Your doctor will check whether you are eligible to join, and whether any of the study treatments would definitely be unsuitable for you.

After those checks, brief details identifying you and any other conditions you have are put into the computer, and you are then randomly allocated to receive the care you normally would receive in this hospital alone or with one of the drugs being evaluated in the study. Neither you nor the medical staff can choose which of the study options you will receive, as the computer makes this allocation at random, as if on the roll of a dice.

Any study treatment should start promptly unless you or your doctor decide for any reason that it should stop. In addition, you will still receive what is already being done for monkeypox patients in this health facilities. X additional visits after you leave the clinic/hospital are required. You or our doctor can stop the untested treatment at any time before it has been completed, and you are free at any time to change your mind and stop participating.

Joining is voluntary and will not affect the care you receive at this health facility. You have the right to withdraw consent to participate at any time without reprisal. but could still remain in the study, with the outcome of your disease being reported by the study team. You will not be paid for your participation, and neither will the medical staff. Your identifying details will be shared confidentially with international researchers, along with information about the course of your illness, and we would like to use your identifying details to link your treatment to your future medical records for long enough to know

whether you are properly cured. The findings will be made freely available worldwide to help future patients, but your details will not be identifiable.

I've got a list describing the possible side-effects of each of the study drugs briefly. We could either read it now, or you could join the study, find out immediately whether you'd be taking one of these drugs, and then just learn about that one and decide whether or not you want to take it.

Risks and benefits

Any study treatment you receive may or may not help you personally, but this study could help future patients. This study has been reviewed and approved by _____, a committee (contact details) set up to make sure research participants are protected.

XXXXXXX. *yyyyyyyyy*

Before administering you any of these drugs your doctor will review if any of these drugs is not appropriate for you. There are a few specific contraindications:

XXXXXXXX

PART II: Certificate of consent

Clinic/Hospital : **City/Town:**

Province/Region: **Country:**

Participant: I read the information, or had it read to me. I could ask any questions I wanted and had any questions answered satisfactorily. I consent voluntarily to participate in this study.	**Literate Witness (if the participant is illiterate):** I witnessed the information sheet being read verbatim. The participant could ask any questions and got satisfactory replies. I confirm that they gave their consent freely.
First & last name	**First & last name**
Signature	**Signature**
Date	**Date**
Thumb-print (if illiterate*)	
☐ ***Deferred consent*** Check this if randomization is done at the investigator's discretion according to criteria that have been explicit during national ethical approval of the protocol.	This must be followed by the request for patient's (deferred subject consent) or representative's (deferred proxy consent) informed consent in a later phase, as per national regulations. **If the patient previously declined to consent, then deferred consent is not applicable and will not be pursued.**

**Illiterate participants include their thumbprint, and a literate witness countersigns the form.*

Statement by the researcher/person taking consent/or documenting deferred consent

I read verbatim the information sheet to the participant and made sure they understand what the study entails. The participant could ask questions about the study, and all questions asked were answered correctly to the best of my ability. Consent was given freely and voluntarily, and a copy of this form has been given to the participant.

Person taking the consent:	
First & last name	
Signature	
Date	

This study has been reviewed by ethics experts at the _____ which is co-sponsoring it. The study has been reviewed and approved locally by _____ .

This committee exists to make sure research participants are protected from harm. If you want to contact them about it, now or later, their contact details are _____ .

SOP-4 Pharmacy manual for XXXXXX

1. Drug product

XXXXXXXXX

2. Drug receipt

XXXXXXX

3. Storage and handling

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.

4. Dose preparation

XXXXXX

5. Disposition of unused product

XXXXXX

6. Maintenance of inventory logs

XXXXXX.

7. Emergency contact

XXXXXX.

To facilitate collaboration even in health facilities that have become overloaded, patient enrolment and randomization (via the internet) and all other trial procedures are greatly simplified, and no paperwork at all is required.

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 trial database at the end of the study follow up. But, if the patient (or a legal representative) decides the patient will withdraw *and* that no further data will be sent to the TRIAL SPONSOR 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.

At discharge or death, the study doctor will log into the study website and enter:

When patients die or are discharged, follow-up ceases and it is reported:

- Which study drug was given (and for how long?)
- Which of a few selected other drugs were given (and for how long?)
- What treatment support was given

Patient information will be encrypted and held securely by the at the cloud database.

Those analysing it will use only anonymized data, and no identifiable patient details will be released to any unauthorized third party. Patient confidentiality will be maintained when study results are disseminated.

The principles of ICH E6 (R1) GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol.

Standard Operating Procedure (SOP) outlining the reporting procedure for clinicians will be provided on the reverse of the SAE form. An SOP will also be available as part of the Trial Specific SOPs which will outline the reporting procedure for the Trial Co-ordinating Centre.

Definitions

The definitions of the EU Directive 2001/20/EC Article 2 (and subsequent revised version CT3) based on the principles of ICH E6 (R1) GCP and any local requirements apply to this trial protocol. These definitions are given in Table 1

Table 1: Definitions of Adverse Events

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product
Adverse Reaction (AR)	All untoward and unintended responses to an investigational medicinal product related to any dose administered
Death	Deaths are always SAEs. For fatal cases, the Investigator (and/or the designees) will have to fill-in an "SAE" CRF form, an "SAE" form which will be immediately notified by the Investigator to the sponsor or its designees). In case "death" is the only information available at the time of the SAE notification, it has to be reported as such. Nevertheless, the cause of death should be further investigated since death has to be considered as an outcome and not as an event.
Life threatening	Life threatening refers to an event/reaction in which the subject is at risk of death at the time of the event/reaction; it does not refer to an event/reaction that hypothetically might have caused death if more severe.

Important Medical Event (IME)	Any event that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above.
Serious Adverse Event or Serious Adverse Reaction (SAE or SAR)	Respectively any adverse event, adverse reaction that: ▪ results in death ▪ is life-threatening ▪ requires hospitalisation or prolongation of existing hospitalisation ▪ results in persistent or significant disability or incapacity ▪ is a congenital anomaly or birth defect ▪ other medically important/clinically significant events
Severity (AE grading scale to be defined into the protocol)	Intensity of any adverse event from grade 1 to 5. 1=mild 2=moderate 3=severe 4=life threatening 5=death
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: ▪ in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product ▪ In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)

Exempted Adverse events, Disease-Related Events and others notable events: To be listed and defined according the study drugs safety profile and the disease under the research

Notification Procedure: a specific SOP focusing AE/SAE management will be drafted as SOP Working instructions for sites investigators.

The SAE Form must be completed by an investigator (a clinician named on the Signature List and Delegation of Responsibilities Log who is delegated as responsible for the participant's care), with due care being paid to the grading, causality and expectedness of the event as outlined in the related SOP. The initial report must be followed by detailed, written reports as appropriate.
The relevant concomitant medication should be documented in the SAE form. The term "relevant" refers to any treatment administered before or at the time of the event that could be related to the occurrence of the SAE, that could have a possible drug-drug interaction, that have a relevant toxicity profil for the SAE evaluation or that it is judged as important by the investigator..
The SAE Form must be e-mailed to the concerned sponsor by the applicable modality within 24h after becoming aware of the event.

Expedited reporting procedure:

According to the applicable laws and regulations, the concerned sponsor must report all fatal and life-threatening SUSARs to the competent authorities/Ethics committees within 7 days of becoming aware of the event; other SUSARs must be reported within 15 days. In addition, any safety concern must be reported immediately to competent authorities/Ethics committees with the appropriate safety measures according to local requirements.

The concerned sponsor will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) or in any requested format to Competent Authorities (Regulatory Authority and Ethics Committee).

SOP-9 Reporting of protocol deviations and violations

A protocol deviation is generally considered to be a departure from the study protocol, or other study-related documents, that has not been approved by the Ethics Review Committee.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/ favourable opinion from the Ethics Review Committee of such amendment, except where:

- it is necessary to eliminate an immediate hazard(s) to trial subjects (because the protocol leaves the local doctor fully responsible for all decisions about patient care, including discontinuing study medication if considered appropriate), or
- when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)

A protocol violation is a divergence from the protocol that materially (a) reduces the quality or completeness of the data, (b) makes the Informed Consent Form inaccurate, or (c) impacts a subject's safety, rights, or welfare.

When investigators are aware that a deviation is likely to take place, they may take a prior approval of the sponsor in the form of a waiver for the deviation, but when the deviation is discovered after it has taken place, and then the incident is a deviation and not a waiver.

The local monitor may grant waivers (in writing) for deviations that are not likely to impact either the data quality or safety of the subject. Since waivers are preapproved deviations, no action is necessary to be taken.

Major protocol deviations and protocol violation should be uncommon but must be reported promptly by logging into the study website.

The investigator reporting the event then enters a narrative description of the event and its seriousness that includes the trial identification number patient affected and the corrective actions taken.

Appendix 1. Global Data and Safety Monitoring Committee

Global Data and Safety Monitoring Committee (DSMC): This independent committee will not include representatives of the trial sponsors, trial committees or trial centers, and will not include any doctors Trial Sponsor are directly responsible for the treatment of individual monkeypox patients.

Interim trial analyses will be monitored by the DSMC. Otherwise, the trial sponsor, collaborators, and administrative staff (except those Trial Sponsor produce the confidential analyses) will remain ignorant of the interim results.

The DSMC will, at intervals decided by itself, examine confidential interim analyses of safety and efficacy, reporting them to the executive group only if the DSMC considers them likely to require publication or a change in the conduct of the trial. Otherwise, the trial sponsors, trial committees, and trial centers will remain blind to the interim findings.

The protocol states that the evidence on mortality must be strong enough, and the range of uncertainty around the results must be narrow enough to affect national and global treatment strategies. It also states that realistic, appropriate sample sizes could not be estimated at the start of the trial; that it may be possible to enter several thousand hospitalized patients with the relatively mild disease when admitted and a few thousand with severe disease, yielding results that are separately reliable for each; and that the response to certain treatments may differ substantially between different populations or sub-populations (e.g., patients with particular prior conditions, older adults, patients in one or another large country).

In the light of this, the DSMC will independently evaluate the interim analyses and will inform the Executive Group of the Steering Committee if at any stage the results are, in the judgement of the DSMC, sufficiently robust for general release (ie, strong enough and with a sufficiently narrow range of uncertainty around the findings to affect national and global treatment strategies). The DMSC will decide independently how best to respond to interim analyses of safety and apparent efficacy, and what further such analyses to require.

Although the DSMC will be informed of each such SAE and SUSAR and major protocol violations as the trial office deals with reporting it, the DSMC may chiefly be concerned not with each individual event, but with the confidential analyses of the accumulated evidence on all such events. In light of this, the DMSC will decide independently how best to respond to the evidence on adverse reactions.

Appendix 2. Trial Governance

The trial sponsor will invite the research institutions to join the trial. Within each country, one of the research institution would act as co-chief investigators of the trial.

International Steering Committee: This will govern the conduct of the trial in accordance with the agreed international protocol, amended as necessary during the study. Sites that do decide to join will, in consultation with trial sponsor, appoint one member to the international steering committee. Sponsor would seek the collaboration of appropriate local research sites at various health facilities. These members from each country would be jointly responsible for obtaining rapidly, at national and at the local hospital level, ethical approval and any other relevant permissions, and for encouraging Trial participation by the collaborating sites.

Executive group of the steering committee: For practicality, a smaller executive group of about 5-9 members of this committee will be set up in consultation with trial sponsor. They will confer electronically at frequent intervals with trial sponsor to ensure the study is being conducted appropriately by the team within trial sponsor and to ensure the trial steering committee is appropriately informed and consulted.

TRIAL SPONSOR trial center (XXXXXX): This will be responsible for the conduct of the trial. It will establish and maintain a web-based service for randomization, for receiving electronic reports of any SAEs and SUSARs for entry of follow-up information, and for sending reminders when follow-up is overdue. The trial center will help deal with obtaining all necessary approvals, recruiting and motivating centers, ensuring drug supplies, and reporting SUSARS. It will monitor recruitment rates, follow-up rates, data plausibility, and overdue follow-up, describing and regularly discussing with the executive group all aspects of the progress of the trial, but not conducting interim analyses of trial results.

Global Data and Safety Monitoring Committee (DSMC): This independent committee will examine confidential interim analyses of safety and efficacy, reporting them to the executive group only if the DSMC considers them likely to require publication or a change in the conduct of the trial. Otherwise, the trial sponsors, trial committees, and trial centers will remain blind to the interim findings.

Add-on studies: The trial involves only a simple characterization of patients and outcomes. So, within particular countries, some sites participating in the trial may choose to collaborate with each other in more detailed studies. Such add-on studies should not analyze trial treatment allocation in relation to the main trial outcomes until after the main trial findings have been published in the names of all collaborators. Apart from that, the planning, conduct, and reporting of any such studies are independent of trial governance.

Appendix 3. Protocol amendment history

Version	Date	Description of main amendments
		○
		○
		○
		○