A Global core protocol
Overview of current design

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July 10, 2022
June 2-3, WHO R&D Blueprint consultation (10,500 participants)

June 26, 1st OPEN Meeting with PALM 7 team (INRB, INSERM, NIAID) plus researchers and clinicians from numerous countries (about 120)

June 28, Adaptation of INRB/NIAID PALM 7 protocol as a CORE protocol (version 0.0)

Deliberations from several individual experts and expert groups were held to develop Draft version 1.0

1st week July, WHO Clinical Expert Group which comprised the hMPXV GDG

1st week July, regulatory experts consulted by the WHO Access to Medicines and Health Products Division

July 6, Clinical trials and Statistical methods experts from various countries

July 6, members of the WHO expert group for the Target Product Profile for hMPXV therapeutics

Draft Synopsis version 1.0 of the CORE protocol

(this version is being posted online for comments and will serve as the basis for the deliberations during today's meeting)
**CORE Protocol for hMPXV Therapeutics (2)**

**July 10-11, Hybrid OPEN meeting organized by INRB, ARNS/EID with support from WHO including experts from numerous countries**

- Consensus on the design of the CORE protocol.
- Outline plans for study conducted under a global Consortium approach

**Revised version of CORE protocol developed**
(including inputs received during this meeting and from expert groups)

- Clinical trials and Statistical methods experts from various countries outline the Statistical Analysis Plan
- Trial Steering group and structure of global collaboration outlined
- Initial list of collaborators developed (several countries have already indicated their interest)

**Draft version 2.0 for CORE protocol prepared**

(this version will be posted online and researchers worldwide encouraged to use and adapt it by including add-on studies. Researchers from around the world invited to join the CORE protocol trial)
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).

(Adapted from PALM 007 protocol)
Simplicity of procedures

• Within each country, the national 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 (potentially across countries via a cloud-based GCP-compliant platform).

• All trial procedures are greatly simplified, and no 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).
Eligibility

Adults (and children) with monkeypox illness (laboratory confirmed) of any duration (provided that the patient has at least one active, not yet scabbed, lesion), and, who have no contra-indication to potential study drugs.

Informed 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.
Trial entry and 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.
### PRIMARY objective and endpoint

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoint</th>
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<tbody>
<tr>
<td>To evaluate the <strong>clinical efficacy</strong>, as assessed by time to lesion</td>
<td>Time to resolution of all lesions* (including skin and mucosa), up to</td>
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<tr>
<td>resolution, of treatment plus SOC versus placebo plus SOC</td>
<td>28 days after randomization (assessment every 3-5 days)</td>
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</table>

*Time to lesion resolution*: lesions of skin and mucosa are crusted, scabs have fallen off and a layer of skin has formed underneath
SECONDARY objective and endpoints

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoints</th>
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<tbody>
<tr>
<td>To evaluate the <strong>clinical efficacy</strong> of treatment plus SOC versus</td>
<td>o <strong>All-cause mortality</strong> within the first 28 day</td>
</tr>
<tr>
<td>placebo plus SOC in patients with monkeypox as assessed by mortality,</td>
<td>o <strong>Admission to hospital</strong> (outpatients only) within the first 28 days</td>
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<tr>
<td>clinical severity, and duration of symptoms</td>
<td>o <strong>Proportion of patients with a least one complication</strong> within the</td>
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<tr>
<td></td>
<td>within the first 28 days</td>
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<td></td>
<td>Complications include genitourinary impairment (urinary retention),</td>
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<td>lower respiratory tract impairment (pneumonia, need for oxygen),</td>
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<td></td>
<td>ocular impairment, neurologic impairment, antibiotics use for</td>
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<td>secondary bacterial skin infection)</td>
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<td>o <strong>Frequency and duration of symptoms and signs</strong> within the first 28</td>
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<tr>
<td></td>
<td>days</td>
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<td>Symptoms include nausea, vomiting, abdominal pain, anorexia, cough,</td>
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<td></td>
<td>dysphagia, odynophagia, fever, headache, oral pain, pain with</td>
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<tr>
<td></td>
<td>urination, rectal pain.</td>
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<td>Signs include lymphadenopathy, ocular lesions, urethritis, and proctitis</td>
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# EXPLORATORY objectives and endpoints

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
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<tbody>
<tr>
<td>To explore <strong>viral trajectories</strong> in a subgroup of patients</td>
<td><strong>Endpoints</strong></td>
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<tr>
<td></td>
<td>o <strong>Proportion of viral load</strong> negative from blood, OP and rectal swabs assessed at day set time points (day 5, 10, 15, 20 etc. –final schedule to be determined)</td>
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<td></td>
<td>o <strong>Optional:</strong></td>
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<td></td>
<td>• correlation of CT values and infectious virus;</td>
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<td></td>
<td>• environmental sampling for viral PCR and infectious virus;</td>
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<tr>
<td></td>
<td>• sampling from semen, vaginal fluid and breast milk.</td>
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<td>To understand <strong>lesion characteristics</strong></td>
<td>o Maximal body regions involved</td>
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<td>o Maximum lesion count in affected regions</td>
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<td>o Time to maximum lesion count in the affected region up to 28 days after randomization</td>
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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).
Add-on studies

Particular countries, or particular 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.
Study population

Inclusion criteria

- 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, 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.
- 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 later on.

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, 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 censored at 28 days post-randomization.

Number of participants
The 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.