Statistical Analysis Plan group

CORE Protocol for a global therapeutics trial on Monkeypox

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Study design

• This is a randomized, placebo-controlled, double-blind platform trial to test the addition of experimental treatments to local SOC in adults and children with laboratory-confirmed monkeypox virus disease at participating 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.

• 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.

• All participants will also receive SOC that is standardized at each site according to local/site practice.
Randomisation

• Once eligibility has been confirmed, subjects will be eligible for randomization.

• Randomization will be performed onsite by the site pharmacist.

• 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.

• 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
Randomisation (ctd)

- 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.

<table>
<thead>
<tr>
<th></th>
<th>Time Window #1</th>
<th>Time Window #2</th>
<th>Time Window #3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimens</strong></td>
<td>A</td>
<td>AA</td>
<td>AAA</td>
</tr>
<tr>
<td><strong>Placebos</strong></td>
<td>P_A</td>
<td>P_A</td>
<td>P_A</td>
</tr>
<tr>
<td>Individual regimen: matched-placebo</td>
<td>1:1</td>
<td>2:1</td>
<td>3:1</td>
</tr>
<tr>
<td>Individual regimen: shared-placebo</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
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</tbody>
</table>
Screen failure

• 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.

• 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.
  • 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;
Drug Discontinuation

• 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.

• 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.

• 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).
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.
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 and baseline severity 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 on a modified intent-to-treat population consisting of all subjects who received at least one dose of experimental treatment or placebo.
Hierarchical testing

• This is a randomized, placebo-controlled, double-blind trial testing a superiority hypothesis with a two-sided type I 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 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 (equivalent to assigning deaths the worst possible time to resolution).
Secondary endpoint analysis

• 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.

• Incidence of complications until day 28 by study arm will be summarized by proportions and differences in proportions with 95% confidence intervals.

• Frequency of clinical symptoms by symptom and study arm will be summarized as proportions at baseline and 5, 10, 15, 20, 28, and 51 days post-randomization. Duration of clinical symptoms will be summarized according to median days and interquartile range.
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 will 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.
Discussion
## OBJECTIVES

### Primary

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

### Secondary

- 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.

## ENDPOINTS (OUTCOME MEASURES)

<table>
<thead>
<tr>
<th>Primary</th>
<th>Time to resolution of all lesions (including skin and mucosa), up to 28 days after randomization (assessment every 3-5 days)</th>
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</table>
| Secondary | All-cause mortality within the first 28 days  
Admission to hospital (outpatients only) within the first 28 days  
Proportion of patients with a least one complication within the first 28 days  
  Complications include genitourinary impairment (urinary retention), lower respiratory tract impairment (pneumonia, need for oxygen), ocular impairment, neurologic impairment, antibiotics use for secondary bacterial skin infection  
Frequency and duration of symptoms and signs within the first 28 days  
  Symptoms include nausea, vomiting, abdominal pain, anorexia, cough, dysphagia, odynophagia, fever, headache, oral pain, pain with urination, rectal pain.  
  Signs include lymphadenopathy, ocular lesions, urethritis, and proctitis. |
## OBJECTIVES

### Secondary
- To evaluate the safety of treatment plus SOC relative to placebo plus SOC in patients with monkeypox.

### Exploratory
- To explore viral trajectories in a subgroup of participants
  - Proportion of viral load negative from blood, OP and rectal swabs assessed at day set time points (day 5, 10, 15, 20 etc. – final schedule to be determined)
  - Optional:
    - correlation of CT values and infectious virus;
    - environmental sampling for viral PCR and infectious virus;
    - sampling from semen, vaginal fluid and breast milk.
- To understand lesion characteristics
  - Maximal body regions involved
  - Maximum lesion count in affected regions
  - Time to maximum lesion count in the affected region up to 28 days after randomization

### ENDPOINTS (OUTCOME MEASURES)
- Frequency of severe adverse events for specific therapeutics