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

Current proposed endpoints for CORE protocol

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Classification of endpoints

• Primary endpoint
• Secondary endpoints
• Exploratory endpoints
### Proposed Primary endpoint

<table>
<thead>
<tr>
<th>PRIMARY OBJECTIVE</th>
<th>PRIMARY ENDPOINT</th>
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<tbody>
<tr>
<td>To evaluate the clinical efficacy, as assessed by time to lesion resolution, of</td>
<td>Time to resolution* of all lesions (including skin and mucosa), up to 28 days after randomization (assessment every 3-5 days)</td>
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<tr>
<td>treatment plus SOC versus placebo plus SOC for patients with monkeypox</td>
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*Time to lesion resolution: lesions of skin and mucosa are crusted; scabs have fallen off and a layer of skin has formed underneath*

**Comments**

1. Feasibility of follow up of all lesions in some patients
2. Impact of ulcers on overall time to resolution - evolution of ulcers different from skin rash?
3. Consider an alternate clinically reasonable endpoint if no resolution on day 28 (e.g., partial resolution)
4. Consider classification resolutions - complete/partial/no --- resolution of rash/resolution of mucosa lesions/resolution of ulcer
5. Potential to miss exact date of resolution with a 5 day follow up
6. Consider variable follow up days - more frequent (2-3 days) after ? 1st 7-10 days since first symptom
7. Feasibility and thoroughness of OPD follow up
8. Impact of new lesions on time to resolution of all lesions
9. Role of other comorbidities (e.g., Diabetes, HIV) in delaying lesion healing
10. Role of prior smallpox vaccination
## Proposed secondary endpoints

### 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.

### SECONDARY ENDPOINTS (OUTCOME MEASURES)

1. **All-cause mortality within the first 28 days**
2. **Admission to hospital (outpatients only) within the first 28 days**
3. **Proportion of patients with at least one complication within the first 28 days**
   - Complications include genitourinary (urinary retention), lower respiratory tract (pneumonia, need for oxygen), ocular impairment, neurologic impairment, antibiotics for secondary bacterial skin infection)
4. **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 including lymphadenopathy, ocular lesions, urethritis, and proctitis.

### Comments

1. Specify clinical indication (e.g., no improvement/worsening features) for admission
2. Diagnostic criteria for complications, including defining the word ‘impairment’
3. Feasibility of evaluation and follow up of all signs and symptoms ........ (To also consider pruritus, mood).
4. Focus on sign and symptoms with high sensitivity for clinical detection and less variable clinical course/interpretation
5. Define the severe adverse events (clinical and laboratory)
# Proposed exploratory endpoints

<table>
<thead>
<tr>
<th>EXPLORATORY OBJECTIVES</th>
<th>EXPLORATORY ENDPOINTS (OUTCOME MEASURES)</th>
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</table>
| 1. To explore viral trajectories | • Proportion of viral load negative from blood, oropharyngeal and rectal swabs assessed at day set time points (day 5, 10, 15, 20 etc. –final schedule to be determined)  
• Optional:  
  o correlation of CT values and infectious virus;  
  o environmental sampling for viral PCR and infectious virus;  
  o sampling from semen, vaginal fluid and breast milk. |
| 2. 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 |

Comments
1. Viral load assessment of skin lesions- standardized protocol
2. Yield of non-skin sites, Rectal and OP sites related to symptoms/signs?
3. Sensitivity of 5 day time points
4. Working definition of body regions
5. Cut off time for determination of maximum lesion count
6. Other measures to consider- time from macule to papules to pustules to vesicles/nodules to crusting/scabbing to normal skin/scare
7. Sequelae and time to sequelae
Thank you for listening