Statistical considerations for the PALM007 design

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A primary endpoint

-should capture a central aspect of the disease that characterizes how a patient feels, functions or survives.

-should be expected to be modified by the investigational intervention such that an improvement in the primary endpoint translates to an improvement in how a patient feels, functions or survives

PALM007 primary endpoint

-time too all lesions being scabbed or desquamated: “lesion resolution”
Why time to lesion resolution?

Monkeypox lesions present significant morbidity to patients:
- lesions are painful
- more lesions associated with more severe disease
- lesions present an infection risk to others

An improvement in the lesion resolution time represents a shortened disease course, less suffering, and a decreased risk of infectivity.
Other primary endpoint considerations

Potential modifiers of treatment efficacy:
-- early vs late treatment
-- severe vs mild disease

Key subgroups of interest:
≤ 7 days and
>7 days from onset of illness

Secondary analyses will consider WHO severity scores and baseline “viral load.”
Goal: To find a sample size that gives adequate statistical power for a meaningful improvement in the primary endpoint.

But what is a meaningful improvement in the primary endpoint?

Finding the “just right” effect size:
  - too small of an effect → improvement isn’t clinically meaningful
  - too large of an effect → may miss smaller, clinically meaningful effect sizes
One day shorter time to resolution?
   \textit{too short}

Two days?
   \textit{too short}

In discussions with study physicians, \textit{three days} was agreed to be the \textit{minimal improvement} in time to resolution that would represent a \textit{meaningful improvement}.

An improvement of 3-days in the median time to lesion resolution corresponds to a “resolution rate ratio\textsuperscript{*}” of \textasciitilde1.4\textsuperscript{†}.

\textsuperscript{*}like a hazard ratio but for a good outcome
\textsuperscript{†}based on data from USAMRIID/INRB observational study 2007-2011 in Kole, DRC
Sample size calculations

318 lesion resolution events are required in order to achieve 85% power to detect a rate ratio of 1.40.

Assuming a 77% event rate (the rate observed in a 2007-2011 observational study in Kole, DRC), we would need to enroll 413 patients.

Accounting for loss to follow-up, we target a sample size of 450 participants (225 per arm).

<table>
<thead>
<tr>
<th>Resolution Rate Ratio (θ)</th>
<th>Scenario for 80% Power (β=0.20)</th>
<th>Scenario for 85% Power (β=0.15)</th>
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Sample Size Re-Estimation

- Trial is event-driven: plan to continue until 318 events are observed
- Sample size of 450 (225 per arm) is based on 318 events needed to power trial and an *estimated* 77% event rate (from the USAMRIID/INRB observational study)
- Blinded sample size re-estimation performed at 50% information (159 events) using the overall event rate
- Updating the planned sample size does not impact timing of interim analyses, since these are based on information time (number of events/318)
Procedures to stop a trial early are included in PALM007 for:

1) Early evidence of efficacy:
   If treatment is clearly superior to placebo, unethical to continue

2) Early safety results:
   If a drug causes harm, unethical to continue

3) Futility:
   At some point during the trial, it may be clear that there is no real chance of showing benefit after full enrollment.
Interim monitoring for efficacy and futility

- Interim data (particularly early & small sample size) are unreliable
  - Early trends may reverse
  - Group sequential monitoring provides a framework for the stopping criteria

- Prespecify when interim data will be analyzed
  - At approximately 33%, 67% and 100% of events

- Formally: the Lan-DeMets spending function analog of the O’Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05.

- Conditional power will be presented as an additional guide to the DSMB at interim efficacy analyses. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.
Data collection/data integrity related to lesion assessment

Primary endpoint records day on which all lesions are scabbed or desquamated

- could be accomplished by daily visual full-body assessment

Lesion counts track with severity of disease

- secondary analyses will evaluate changes in counts

Question: can we track an assessment region to obtain counts?
Data collection/data integrity related to lesion assessment

Data from USAMRIID/INRB daily lesion counts by region of (arms, legs, trunk, throat, head, hands, feet) revealed high correlation of counts by region show:

- High correlation (>0.9) for full body counts and
  - One arm, one hand, one leg, and one foot.
  - One arm, one hand, one leg, one foot, and head

To reduce burden associated with lesion counts, a target region of right arm, right hand, right leg and right foot will be utilized for counting.

*Full body assessment will be utilized for time of resolution.*
Data collection/data integrity related to lesion assessment

After all lesions have resolved in the assessment region, the rest of the body will be evaluated until any remaining lesions have resolved.
Why use a placebo?

- Reduces potential for knowledge of treatment assignment to influence endpoints
- For example,
  - Could knowledge of receiving tecovirimat influence lesion assessment and determination of day of lesion resolution?
  - Could knowledge of receiving placebo predispose clinicians to offer alternative treatments (that would otherwise not be offered to tecovirimat recipients)

Primary endpoint: lesion resolution (scabbing or desquamation stage) up to 28 days after randomization.

Primary hypothesis: treatment with tecovirimat will decrease the time to resolution of monkeypox lesions relative to placebo.
Acknowledgments

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Acknowledgements
Other slides
Key Secondary Objectives

1) To evaluate whether tecovirimat (+SC) improves time to lesion resolution compared placebo (+SC) for patients who present with Monkeypox disease within 7 days of disease onset.

2) To evaluate whether tecovirimat (+SC) improves time to lesion resolution compared placebo (+SC) for patients who present with Monkeypox disease after 7 days of disease onset.

3) To evaluate the safety of tecovirimat relative to placebo for patients with monkeypox

4) To evaluate the virologic efficacy, as assessed by time to resolution of viremia, of tecovirimat relative to placebo for patients with monkeypox.

5) To describe lesion progression longitudinally over the study period.

6) To evaluate the clinical efficacy of tecovirimat (+SOC) versus placebo (+SOC) in patients with monkeypox as assessed by mortality, clinical severity, and duration of symptoms.
Exploratory Objectives

Clinical
- To evaluate the frequency and characteristics of persistent lesions.
- To develop a baseline disease severity metric for monkeypox.
- To assess the effect of HIV infection on monkeypox clinical outcomes and treatment effect.

Viral
- To evaluate viral persistence in skin lesions and in the oropharynx.
- To assess genomic variability in monkeypox virus isolated from participants based on geographic and clinical differences.
- To assess if viral resistance develops due to selective pressure by treatment.

Serologic
- To evaluate the impact of anti-OPXV antibodies on the course of disease and the clinical efficacy of tecovirimat.
- To evaluate the trajectory of monkeypox IgM and IgG during infection.

Epidemiologic
- To evaluate exposure history of confirmed monkeypox cases and to identify risk factors for monkeypox infection.