*This is ACTG A5418 SAP Version 4.0 with names of authors redacted.*

# A5418

# Primary Statistical Analysis Plan

# Version 4.0

## August 19, 2025

**A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Mpox Virus Disease**

***Study of Tecovirimat for Human Mpox Virus (STOMP)***

**ClinicalTrials.gov Identifier: NCT05534984**

**Protocol Version 3.0**

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**Version History**

| Version | Changes Made | Date Finalized |
|---|---|---|
| 1.0 | Original Version. Version 1.0 of the Primary SAP was finalized prior to access to study data including treatment codes. | September 23, 2022 |
| 2.0 | Amended Version 1.0 to:<br>• adjust stratification factors for randomization (remove presence of severe pain and add remote enrollment)<br>• include an additional interim efficacy review<br>• add clarifying language to Sections 2.5, 4, and 5<br>• add one outcome measure | December 9, 2022 |
| 3.0 | • Clarification of information fraction used in interim efficacy reviews<br>• Added plans to summarize impact of institutional balancing<br>• Addressed handling of eligibility and stratification errors in analysis report(s) | April 4, 2024 |
| 4.0 | • Described purpose of analyses covered by this SAP revision and data cutoffs that will be used for the analyses<br>• Added approaches for handling post-DSMB follow-up<br>• Added exploratory objectives and analysis plans for those objectives<br>• Clarified definition of baseline<br>• Added definition of analysis visit windows for additional sampling time points<br>• Removed supportive analysis estimating cause-specific instantaneous risk ratio for the primary outcome<br>• Modified approach to adherence analysis, which was removed from protocol version 3.0<br>• Added plans for addressing intercurrent events in analyses of participant-reported outcomes | August 19, 2025 |

# 1 Introduction

## 1.1 Purpose

The Primary Statistical Analysis Plan (SAP) was updated to version 4.0 to facilitate discussion of the statistical analysis components of the A5418 study among lead study investigators and statisticians, helping them agree on the analyses to be performed and presented in the secondary analysis report based on the final locked study database.

The primary analysis report was completed under version 3.0 of the Primary SAP. Following the second planned interim efficacy review on November 26, 2024, the Data and Safety Monitoring Board (DSMB) recommended stopping accrual because of statistical futility and publishing results as soon as possible. A5418 closed to accrual on November 27, 2024 and the primary analysis was completed using data from follow-up visits occurring through October 23, 2024, the data cutoff for the November 2024 DSMB review. The Primary SAP was updated to version 4.0 to include analysis considerations for a final look at the primary outcome data that was presented in the primary manuscript, including full trial follow-up, as well as analysis plans for secondary outcomes that will be submitted to ClinicalTrials.gov and other exploratory outcomes.

Detailed outlines and coding descriptions of tables and figures that will be included in the secondary analysis report are provided in the Analysis Implementation Plan (AIP). Separate SAP(s) will provide outlines of analyses for exploratory objectives and outcome measures not included in the Primary SAP.

## 1.2 Version History

Version 1.0 of the Primary SAP was finalized prior to access to study data including treatment codes.

Version 2.0 incorporates changes implemented in protocol version 3.0, in particular, changes to the stratification factors and DSMB review schedule.

Version 3.0 specifies additional listings related to institutional balancing, eligibility and stratification errors and handling of such errors.

Version 4.0 adds analysis approaches for handling post-DSMB follow-up and plans for other exploratory outcome measures that will be included in the secondary analysis report based on the locked database. Version 4.0 was finalized after study completion but prior to access to treatment codes.

# 2 Study Overview

## 2.1 Overview of Study Design

A5418 is a Phase 3, randomized, placebo-controlled, double-blind trial to establish the efficacy of tecovirimat for the treatment of human mpox virus (HMPXV) disease. The study also includes a cohort of people who will receive open-label tecovirimat, including people with protocol-defined severe HMPXV, who are pregnant or breastfeeding, who are less than 18 years of age, who are on potent inducing concomitant medications, or who have severe immune suppression or skin conditions placing them at higher risk for severe HMPXV disease.

Participants who do not meet the criteria for the open-label cohort (Arm C) will be randomized in a 2:1 ratio to tecovirimat (Arm A) or placebo (Arm B) for 14 days. Randomization will be stratified by duration of symptoms (≤5 or >5 days) and remote vs. in-person enrollment and will be balanced by site.

Randomized participants who stop study drug because of negative confirmatory testing will be replaced. Randomized participants who progress to severe disease post-randomization or who report severe pain from HMPXV five days post-randomization will be offered open-label tecovirimat.

The primary outcome measure is time to clinical resolution up to 28 days post-randomization (Day 29). All participants will be followed to 56 days post-randomization (Day 57).

## 2.2 Hypotheses

Tecovirimat will lead to faster clinical resolution of HMPXV disease (all skin lesions scabbed, desquamated or healed and all visible mucosal lesions healed) compared to placebo.

## 2.3 Study Objectives

This Primary SAP addresses the following study objectives, including the primary and secondary objectives, for the randomized arms; the secondary objectives for the open-label cohort, including the PK and safety objectives for children less than 18 years of age, will be addressed in separate SAP(s).

Analysis of the study objectives below in the randomized arms will be performed under a superiority framework. These analyses will be finalized after the last participant enrolled to the randomized arms has completed the Day 57 study visit and all queries have been resolved.

### 2.3.1 Primary Objective

To compare the clinical efficacy, as assessed by time to clinical resolution of skin and visible mucosal lesions, between participants with HMPXV randomized to tecovirimat versus placebo.

### 2.3.2 Secondary Objectives

1. [Protocol secondary objective 1.3.1] To compare pain scores between randomized arms.
2. [Protocol secondary objective 1.3.2] To compare rates of progression to severe HMPXV disease between randomized arms.
3. [Protocol secondary objective 1.3.3] To compare clearance of HMPXV between randomized arms in various compartments including blood, skin lesions, oropharynx, rectum, and genital secretions.
4. [Protocol secondary objective 1.3.4] To compare time to complete lesion healing between randomized arms.
5. [Protocol secondary objective 1.3.5] To compare participant-reported outcomes including adherence and EQ-5D-5L between randomized arms.
6. [Protocol secondary objective 1.3.6] To evaluate the safety of tecovirimat as compared to placebo.

### 2.3.3 Exploratory Objectives

1. [Protocol exploratory objective 1.4.3] To describe lesion progression longitudinally over the study period.
2. [Protocol exploratory objective 1.4.7] To describe the clinical efficacy of tecovirimat in various subgroups including those with shorter or longer duration of symptoms at baseline, people presenting with proctitis, and persons living with HIV.
3. [Protocol exploratory objective 1.4.8] To explore the relationship between bacterial sexually transmitted infections (gonorrhea, chlamydia and syphilis), HSV, and HMPXV.
4. [Protocol exploratory objective 1.4.11] To explore new HMPXV positivity among household contacts through to 28 days from start of investigational agent or placebo.
5. [Protocol exploratory objective 1.4.12] To describe rates and patterns of recrudescent infection and disease.

## 2.4 Overview of Sample Size Considerations

A total sample size of 530 participants is planned in the randomized arms. The sample size has been chosen to provide 85% power to detect a 40% improvement in the instantaneous risk of clinical resolution up to 28 days after randomization in the tecovirimat arm compared to the placebo arm, while also taking into account the following:

- Two planned interim analyses
- Potential loss to follow-up
- Participants who enroll with proctitis without any skin or visible mucosal lesions
- Participants switched to open-label tecovirimat due to disease progression or severe pain.

The sample size calculation used a two-sided Type I error rate of 5% and assumed an event rate of 77% pooled over arms at Day 29. Further details on the assumptions and sample size calculation are provided in protocol section 10.4.

**Sample size re-estimation**

Given the uncertainty of the event rate, a blinded sample size re-estimation will be conducted at the midpoint of the trial when 178 participants have clinical resolution events (i.e., at 50% information). The blinded overall rate of events will be computed and used to determine whether the sample size should increase in order to reach the 357 total events needed to power the trial. The following table shows the different potential scenarios at sample time re-estimation. If the observed overall rate is higher than 77%, the target sample size will remain unchanged in order to maintain power for the key secondary outcome measure of pain reduction.

| Observed overall event rate at Day 29 | Number of participants needed to reach the 357 total events | Suggested number of participants (after adjusting for interim review, potential drop out, participants enrolled with proctitis without any skin or visible mucosal lesions, and switch to open-label) |
|---|---|---|
| 60% | 357/0.60 = 595 | 680 |
| 70% | 357/0.70 = 510 | 583 |
| 80% | 357/0.80 = 447 | No change |

## 2.5 Overview of Formal Interim Monitoring

The study will undergo interim review at least annually by the NIAID-appointed DAIDS Therapeutics and Prevention DSMB. Two interim efficacy reviews are planned when approximately 33% and 67% of total information is available (i.e., when 119 and 238 participants experienced clinical resolution events) unless otherwise recommended by the DSMB. Specifically, the information fraction at each interim efficacy review will be the number of clinical resolution events observed at the time of data freeze divided by the expected total number of clinical resolution events, 357. If the study accrues at a slower pace than anticipated, the first safety review by the DSMB may occur approximately 6 months after the enrollment of the first study participant. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team.

With respect to efficacy, the DSMB will be asked to recommend stopping the study early only when there is substantial evidence of a treatment benefit. As a guideline, the Lan-DeMets spending function analog of the O'Brien-Fleming boundaries with an overall two-sided Type I error rate of 5% will be used to monitor the primary outcome measure. In the absence of a significant difference between randomized groups that leads to termination of the randomized comparison, the study team believes there is value in continuing the randomized comparison of tecovirimat versus placebo to full enrollment in order to obtain as much precision as possible and to provide maximal information to inform the field.

With respect to operational futility, the DSMB may recommend modification to the study if the proportion of participants who switch to open-label tecovirimat due to disease progression or severe pain is unexpectedly high (>20%). In addition, the DSMB will monitor the loss to follow-up rate (LTFU). An overall LTFU rate in the randomized groups of over 10% would be cause for concern.

Further details on interim monitoring guidelines are provided in protocol section 10.5.1.

# 3 Outcome Measures

These outcome measures will be included in the primary analysis report. The outcome measures in Sections 3.1 and 3.2 will be submitted to ClinicalTrials.gov within one year after the primary completion date (PCD).

## 3.1 Primary Outcome Measure

Time to clinical resolution, defined as the first day on which all skin lesions are scabbed, desquamated or healed, and visible mucosal lesions are healed, up to 28 days.

- Addresses the primary objective and protocol exploratory objective 1.4.7

## 3.2 Secondary Outcome Measures

1. [Protocol secondary outcome measure 10.2.2.1] Pain assessed by 11-point numerical rating scale for pain
    - Addresses protocol secondary objectives 1.3.1
2. [Protocol secondary outcome measure 10.2.2.2] Development of severe HMPXV in those without severe HMPXV at baseline
    - Addresses protocol secondary objective 1.3.2
3. [Protocol secondary outcome measure 10.2.2.3] Levels of HMPXV in various compartments
    - Addresses protocol secondary objectives 1.3.3
4. [Protocol secondary outcome measure 10.2.2.4] Time to complete lesion healing defined as all lesions being re-epithelialized
    - Addresses protocol secondary objectives 1.3.4
5. [Protocol secondary outcome measure 10.2.2.5] Self-reported adherence
    - Addresses protocol secondary objectives 1.3.5
6. [Protocol secondary outcome measure 10.2.2.6] Summaries of quality-of-life measures by EQ-5D-5L
    - Addresses protocol secondary objectives 1.3.5
7. [Protocol secondary outcome measure 10.2.2.7] Occurrence of Grade 3 or greater adverse events
    - Addresses protocol secondary objectives 1.3.6
8. [Protocol secondary outcome measure 10.2.2.8] All-cause mortality

### 3.3 Other Outcome Measures

1. [Protocol outcome measure 10.2.3.4] Number of lesions tracked longitudinally over the study period
    - Addresses protocol exploratory objective 1.4.3
2. [Protocol outcome measure 10.2.3.8] Summary measures of the Anal Health-Related Symptom Index (A-HRSI) QoL assessment in participants reporting proctitis
3. [Protocol outcome measure 10.2.3.9] Presence of bacterial sexually transmitted infections
    - Addresses protocol exploratory objective 1.4.8
4. [Protocol outcome measure 10.2.3.12] Occurrence of new HMPXV positivity among household contacts
    - Addresses protocol exploratory objective 1.4.11
5. [Protocol outcome measure 10.2.3.13] Occurrence of lesions that occur after initial resolution of symptoms and skin lesions
    - Address protocol exploratory objective 1.4.12

# 4 General Considerations

Analyses covered by this SAP will be presented on two sets of data. To support the CT.gov submission, which will be based on results presented in the primary manuscript, analyses of secondary objectives that were not included in the primary manuscript (specifically, self-reported adherence and EQ-5D-5L outcomes) will use data from follow-up visits occurring through October 23, 2024, the data cutoff for the November 2024 DSMB review. All analyses will then be updated using the final locked data from follow-up visits occurring on or before November 26, 2024, the date of the DSMB recommendation. The exception to the latter will be the safety analyses, which will include all available follow-up.

Discrete variables will be described using frequencies and percentages. Continuous variables will be described using percentiles (e.g., median, $25^{th}$ and $75^{th}$ percentiles).

Time-to-event variables with competing events will be summarized using the Fine and Gray approach for competing risks; the subdistribution hazard ratio will be estimated with the 95% confidence interval; the cumulative incidence of participants experiencing the event will be estimated using the Aalen-Johanson estimator. All other time-to-event outcomes will be summarized using Kaplan-Meier methods. Censoring details vary by analysis and are described in Sections **5** and **6**.

Statistical comparisons will be performed using two-sided significance tests with a 5% Type I error rate. Comparisons across treatment arms for baseline characteristics are not planned because the study is randomized (and hence any differences should reflect chance variation).

To minimize imbalances in the number assigned to active treatment versus placebo at any clinical site, a dynamic institutional balancing approach is used. This is in addition to randomization using permuted blocks within each of the four strata defined by duration of symptoms and remote versus in-person enrollment. Specifically, if a participant's randomization based on the permuted block current at the time of randomization would create an imbalance at a site larger than some pre-specified difference (e.g., $| N_{Tec} - 2*N_{placebo} | > 2$), then the alternate assignment would be made for this person. The number of participants assigned alternative treatment using institutional balancing will be summarized at the end of the study.

A summary of participants with eligibility errors and stratification errors will be provided. Participants who were enrolled and were later found to be ineligible by the site, study statisticians, or data managers will be reviewed by the study chairs/co-chairs for confirmation of their ineligibility and for determination of their inclusion in the analyses. Participants who were assigned to the wrong strata will be analyzed according to their correct strata of symptom duration and remote versus in-person enrollment.

## 4.1 Analysis Sets

Primary Efficacy Set: All randomized participants with laboratory-confirmed mpox with one or more skin or visible mucosal lesions

Secondary Efficacy Set: All randomized participants with laboratory-confirmed mpox

Safety Set: All randomized participants who took at least one dose of tecovirimat or placebo

### 4.2 Analysis Visits

Key time points are defined as follows.

Day 1: Study entry, i.e., the date of randomization

Note: For the purpose of statistical analysis, baseline measurements will be the last available pre-dose measurement.

Day 6: Last day that data contributing to key secondary estimand can be observed

Day 15: Last day of study treatment

Day 29: Last day that data contributing to primary outcome can be observed

Day 57: Study completion

Study visits will be derived using the difference in days between the evaluation/specimen date and the date of randomization (Day 1). The protocol requires post-entry evaluations to be within +/- 1 day at Day 6, +/- 2 days at visits occurring after Day 6 and before Day 29, within +/- 4 days at Day 29, and within +/-7 days at Day 57 (note at Day 6, only the participant-completed study diary, pain scale and A-HRSI for participants reporting anal pain or proctitis at baseline are collected). For the purpose of statistical analysis, broader windows will be used to minimize the impact of deviations from the desired schedule (see table below). In general, if there are multiple results within an analysis visit window then the evaluation closest to the scheduled study day will be used (if results are equidistant, then the earliest result will be used). However, if it happens that a result obtained before and a result obtained after the DSMB recommendation occur in the same analysis visit window, then the result obtained before the DSMB recommendation will be used to maximize the available data. The windows described below do not apply to data collected daily, e.g., pain scores.

In-Person/Remote Study Visits for All Enrolled Participants:

| Study Visit | Protocol Visit Window | Analysis Visit Window |
|---|---|---|
| Screening | -7, +0 days (Day -6 to Day 1) | -7, +0 days (Day -6 to Day 1) |
| Entry (Day 1) | ±0 days (Day 1) | ±0 days (Day 1) |
| Day 3* | ±2 days (Day 1 to Day 5) | -1, +2 days (Day 2 to Day 5) |
| Day 6† | ±1 day (Day 5 to Day 7) | ±4 days (Day 2 to Day 10) |
| Day 8 | ±2 days (Day 6 to Day 10) | -2, +3 days (Day 6 to Day 11) |
| Day 15 | ±2 days (Day 13 to Day 17) | ±3 days (Day 12 to Day 18) |
| Day 22 | ±2 days (Day 20 to Day 24) | -3, +2 days (Day 19 to Day 24) |
| Day 29 | ±4 days (Day 25 to Day 33) | -4, +13 days (Day 25 to Day 42) |
| Day 57 | ±7 days (Day 50 to Day 64) | ±14 days (Day 43 to Day 71) |

* Day 3 visit is for additional sampling cohort only.
† At Day 6, aside from the daily evaluations, only the A-HRSI is collected.

Participants who consented to additional sampling had an additional set of remote visits where they obtained swabs at home. Since the protocol visit windows for these additional visits overlap with the protocol visit windows listed above, samples collected in-person in the clinic and samples collected at home by the participant will be handled separately, i.e., the following study visits will be derived only for results labeled as "PARTICIPANT COLLECTED" in the study database.

Remote Visits for Additional Sampling Cohort:

| Study Visit | Protocol Visit Window | Analysis Visit Window |
|---|---|---|
| Day 2 | ±1 day (Day 1 to Day 3) | ±1 day (Day 1 to Day 3) |
| Day 5 | ±2 days (Day 3 to Day 7) | -1, +2 days (Day 4 to Day 7) |
| Day 11 | ±2 days (Day 9 to Day 13) | ±3 days (Day 8 to Day 14) |
| Day 18 | ±2 days (Day 16 to Day 20) | ±3 days (Day 15 to Day 21) |
| Day 25 | ±2 days (Day 23 to Day 27) | ±3 days (Day 22 to Day 28) |

### 4.3 Analysis Adjustment for Interim Review

The nominal significance level used at the final analysis will be derived based on the O'Brien and Fleming guideline implemented using the Lan and DeMets spending function approach.

### 4.4 Adjustment for Multiple Testing

A hierarchical testing approach will be used to control the family-wise error rate across the primary outcome measure and the secondary pain outcome measures. Hypothesis testing will first be conducted for the primary outcome measure. If the null hypothesis is rejected at the nominal significance level derived as described in protocol section 10.5.1, confirmatory analysis of the secondary pain outcome measures will be performed at the same nominal significance level. A total of nine tests will be conducted for the secondary pain outcome measures (see section 5.2; note the fourth supplementary estimands describe five tests). The Benjamini-Hochberg method will be used to account for multiplicity of testing of pain outcome measures with the false discovery rate set to 5%. If the null hypothesis is not rejected, analysis of the secondary pain outcome measures will be considered exploratory and no formal conclusion will be drawn. Analysis of all other outcome measures will be considered supportive and no formal adjustment for multiplicity will be undertaken.

# 5 Estimands and Analysis

## 5.1 Primary Estimand of the Primary Objective

| **Primary Objective: To compare the clinical efficacy, as assessed by time to clinical resolution of skin and visible mucosal lesions, between participants with HMPXV randomized to tecovirimat versus placebo.** | |
|---|---|
| Estimand | The instantaneous risk ratio of clinical resolution of skin or visible mucosal lesions among people with laboratory-confirmed mpox with 1 or more skin or visible mucosal lesions in those prescribed to Tecovirimat relative to no treatment |
| Treatment | Tecovirimat for 14 days |

| Target population | Analysis set |
|---|---|
| People aged 18 or older with laboratory-confirmed HMPXV disease with 1 or more skin or visible mucosal lesions | Primary Efficacy Set (see section **4.1**) |
| **Variable(s)** | **Outcome measure(s)** |
| Time to clinical resolution up to 28 days | Time to clinical resolution is measured from randomization to the first day on which all skin and visible mucosal lesions are scabbed, desquamated, or healed, up to 28 days after randomization (Day 29) |
| **Handling of intercurrent events** | **Handling of missing data** |
| All-cause death, treatment change due to disease progression or severe pain, use of other antivirals with expected activity against HMPXV: these events are considered competing events. Individuals experiencing these events will be retained in the risk set through 28 days under subdistribution hazard model (Composite strategy)<br><br>Discontinuation of treatment for reasons other than death, disease progression or severe pain: all follow-up included regardless of treatment status (Treatment policy strategy) | Participants who are lost to follow up will be censored at the earlier of time of last visit with lesion evaluation and November 26, 2024, the date of the DSMB recommendation. |
| **Population-level summary measure** | **Analysis approach** |
| Instantaneous risk ratio (subdistribution hazard ratio) of Tecovirimat relative to no treatment | Instantaneous risk ratio (subdistribution hazard ratio) will be estimated with the associated 95% confidence interval and tested using a subdistribution proportional hazards model |

The primary analysis of time to clinical resolution will be assessed using the subdistribution proportional hazards model (Fine and Gray, 1999) where all cause death, switch to open-label tecovirimat and use of other antivirals with expected activity against HMPXV are considered as competing events. Instantaneous risk ratio (subdistribution hazard ratio) will be tested and estimated with a two-sided Wald 95% CI. Cumulative incidence functions (CIFs) will be used to estimate the incidence of clinical resolution and other competing events. Gray's test (Gray, 1988) will be used to test the equality of cumulative incidence functions between treatment groups.

Follow-up will be censored at earlier of time of last evaluation of lesions and November 26, 2024, with censoring assumed to be non-informative.

Subgroup Analyses:

Treatment interactions will be tested for the primary outcome measure in separate subdistribution proportional hazards models to evaluate whether the treatment effect varies among levels of a subgroup. More specifically, subdistribution proportional hazards models will be implemented for each subgroup. Within each subgroup, the instantaneous risk ratio of tecovirimat vs. placebo will be estimated, and compared between subgroups by constructing a test of interaction and 95% confidence interval. This will be implemented by determining the difference between subgroups of the instantaneous risk ratio of tecovirimat vs. placebo, and the variance of the difference will be determined by summing the variance of the subgroup-specific variances.

The following subgroup variables are pre-specified:

1. Duration of symptoms (≤5 days or >5 days)
2. Enrollment type (remote vs. in-person)
3. Presence of severe pain (<7 or 7-10 on the 11-point numerical rating scale for pain)
4. Receipt of smallpox/mpox vaccine prior to entry (yes, no)
5. Age (<40, ≥40 years)
6. Sex (male sex at birth, female sex at birth)
7. Race (White, Non-White)
8. Ethnicity (Hispanic, Non-Hispanic)
9. Presence of proctitis (yes, no)
10. HIV status (living with HIV, not living with HIV)

The following subgroup variables were explored in post-hoc analyses for the primary analysis publication; these analyses will also be updated using the full trial follow-up.

11. Duration of symptoms (≤3 days, >3 days)
12. Lesion count (<10, ≥10)
13. HMPXV DNA in index lesion (detected, not detected)

For Phase 3 NIH-funded clinical trials, NIH requires primary analyses of treatment comparisons to be summarized by sex/gender and by race/ethnicity and treatment interactions with sex/gender and race/ethnicity to be tested. Note, however, the study has not been powered to evaluate treatment differences within these subgroups nor to evaluate treatment by subgroup interactions. Further, numbers may be too small in some cases for meaningful statistical analysis beyond a descriptive analysis (for example, if the study enrolls mostly men or if there are less than 5 events in one arm).

### 5.2 Secondary Estimand of Secondary Objective 1.3.1

| **Secondary Objective 1.3.1: To compare pain scores between randomized arms** | |
|---|---|
| Estimand | The difference of the mean time-weighted average of pain intensity difference (pre-treatment – post treatment) over 5 days among people with laboratory-confirmed mpox who reported severe pain between those prescribed to Tecovirimat relative to no treatment |
| Treatment | Tecovirimat for 14 days |

| Target population | Analysis set |
|---|---|
| People aged 18 or older with laboratory-confirmed HMPXV disease who reported severe pain (7-10 on the numerical rating scale [NRS]) | The subset of the Secondary Efficacy Set (see section **4.1**) who reported severe pain at entry (7-10 on the NRS) |
| **Variable(s)** | **Outcome measure(s)** |
| Time-weighted average of pain intensity difference from pre-treatment to each day post treatment over 5 days measured by NRS | 11-point NRS<br><br>Pain intensity difference at $i^{th}$ day is defined as NRS difference of baseline and on ith day (baseline – $i^{th}$ day) where i = 2, …, 6<br><br>Time-weighted average of pain intensity difference is defined as the average of the sum of the pain intensity difference (SPID) at each measurement multiplied by the duration in days since the previous measurement from Day 2 to Day 6 |
| **Handling of intercurrent events** | **Handling of missing data** |
| All-cause death: all NRS measures included up to death (While on treatment strategy)<br><br>Treatment change due to disease progression or severe pain: all NRS measures included up to treatment change (While on treatment strategy)<br><br>Discontinuation of treatment for reasons other than death, disease progression or severe pain: all NRS measures included up to treatment discontinuation (While on treatment strategy) | Participants who are lost to follow up will have their measurements included through to last available measurement at or before Day 6 |
| **Population-level summary measure** | **Analysis approach** |
| Difference (Tecovirimat - no treatment) in mean time-weighted average of pain intensity difference over 5 days | Two-sample t-test for the comparison between the randomized groups. Two-sided 95% confidence interval for the difference will be calculated.<br><br>Sensitivity analysis: None |

### 5.2.1 First Supplementary Estimand of Secondary Objective 1.3.1

This supplementary analysis of protocol secondary objective 1.3.1 focuses on a different target population, i.e., people who report moderate or severe pain at baseline. Differences from the secondary estimand are noted in bold italics in the estimand-to-analysis table below and only rows with differences are shown.

| **Secondary Objective 1.3.1: To compare pain scores between randomized arms** | |
|---|---|
| Estimand | The difference of mean time-weighted average of pain intensity difference (pre-treatment – post-treatment) over 5 days among people with laboratory-confirmed mpox who reported ***moderate or*** severe pain between those prescribed to Tecovirimat relative to no treatment |
| Target population | Analysis set |
| People aged 18 or older with laboratory-confirmed HMPXV disease who reported ***moderate or*** severe pain (***4***-10 on the numerical rating scale) | The subset of the Secondary Efficacy Set (see section **4.1**) who reported moderate or severe pain at entry (***4***-10 on the NRS) |

### 5.2.2 Second Supplementary Estimand of Secondary Objective 1.3.1

This supplementary analysis of protocol secondary objective 1.3.1 focuses on a different target population, i.e., all randomized participants, regardless of pain score reported at baseline. Only rows with differences in the estimand-to-analysis table are shown.

| **Secondary Objective 1.3.1: To compare pain scores between randomized arms** | |
|---|---|
| Estimand | The difference of mean time-weighted average of pain intensity difference (pre-treatment – post-treatment) over 5 days versus pre-treatment among people with laboratory-confirmed mpox between those prescribed to Tecovirimat relative to no treatment |
| Target population | Analysis set |
| People aged 18 or older with laboratory-confirmed HMPXV disease | Secondary Efficacy Set (see section **4.1**) |

### 5.2.3 Third Supplementary Estimand of Secondary Objective 1.3.1

This supplementary analysis of protocol secondary objective 1.3.1 uses a different population-level summary measure that considers pain intensity over 14 days. Differences from the secondary estimand are noted in bold italics in the estimand-to-analysis table below and only rows with differences are shown.

| **Secondary Objective 1.3.1: To compare pain scores between randomized arms** | |
|---|---|
| Estimand | The difference of mean time-weighted average of pain intensity difference (pre-treatment – post-treatment) over ***14*** days among people with laboratory-confirmed mpox who reported severe pain between those prescribed to Tecovirimat relative to no treatment |
| Variable(s) | Outcome measure(s) |
| Time-weighted average of pain intensity difference from pre-treatment to each day post treatment over ***14*** days measured by NRS | 11-point NRS<br><br>Pain intensity difference at $i^{th}$ day is defined as NRS difference of baseline and on ith day (baseline – $i^{th}$ day) where i = 2, …, ***15***<br><br>Time-weighted average of pain intensity difference is defined as the average of the sum of the pain intensity difference (SPID) at each measurement multiplied by the duration in days since the previous measurement from Day 2 to Day ***15*** |
| Population-level summary measure | Analysis approach |
| Difference (Tecovirimat – no treatment) in mean time-weighted average of pain intensity difference over ***14*** days | Two-sample t-test for the comparison between the randomized groups. Two-sided 95% confidence interval for the difference will be calculated.<br><br>Sensitivity analysis: None |

### 5.2.4 Fourth Supplementary Estimands of Secondary Objective 1.3.1

This supplementary analysis of protocol secondary objective 1.3.1 uses a different population-level summary measure that considers absolute changes from baseline in pain intensity. Differences from the secondary estimand are noted in bold italics in the estimand-to-analysis table below and only rows with differences are shown.

| **Secondary Objective 1.3.1: To compare pain scores between randomized arms** | |
|---|---|
| Estimands | The differences of mean ***pain intensity difference from pre-treatment to each of the first 5 days post treatment*** among people with laboratory-confirmed mpox who reported severe pain between those prescribed to Tecovirimat relative to no treatment |
| Variable(s) | Outcome measure(s) |
| ***Pain intensity difference from pre-treatment to each day post treatment*** | 11-point NRS<br><br>Pain intensity difference at $i^{th}$ day is defined as NRS difference of baseline and on ith day (baseline – $i^{th}$ day) where i = 2, …, 6 |
| Population-level summary measure | Analysis approach |
| ***Difference (Tecovirimat – no treatment) of mean pain intensity difference from pre-treatment to post treatment*** | Two-sample t-tests for the comparison between the randomized groups at Day 2 - 6. Two-sided 95% confidence interval for the differences will be calculated.<br><br>Sensitivity analysis: None |

# 6 Analysis of Other Secondary and Exploratory Objectives

Unless otherwise specified, the following approaches will be taken:

- Analyses of secondary and other outcome measures will use the Secondary Efficacy Set.
- Missing outcome data will be assumed to be missing completely at random and ignored in analysis.

## 6.1 Progression to Severe HMPXV Disease

Development of severe HMPXV will be summarized by randomized groups and time to development of severe HMPXV will be analyzed using Kaplan-Meier methods.

## 6.2 HMPXV Clearance

The proportion of participants with undetectable HMPXV at each evaluation time point and sampling location will be estimated with the associated Wald-based 95% confidence interval where appropriate. Comparisons between randomized groups will use a two-sample Z-test and a Wald-based 95% CI on the difference in proportions will be calculated. If there is insufficient undetectable HMPXV (less than 5 in one or both groups), Fisher's exact test and associated exact 95% CI using the melded confidence interval method [Fay 2015] will be used. Additional summaries of HMPXV at each of the additional sampling time points will be provided for those participants who consented to additional sampling, with the caveat that numbers may be too small for meaningful statistical analysis beyond a descriptive analysis.

A sensitivity analysis adjusting for baseline HMPXV level will be done using a logistic regression model where undetectable HMPXV is the dependent variable with treatment assignment and baseline HMPXV level as the independent variables.

## 6.3 Time to Complete Lesion Healing

Time to complete lesion healing is defined as the first day on which all skin and mucosal lesions are healed up to 28 days. Analysis will be restricted to the Primary Efficacy Set using the same approach for the primary outcome measure.

## 6.4 Participant-Reported Outcomes

Self-reported adherence will be analyzed separately in three analysis sets, i.e., in the subsets of the Primary Efficacy Set and the Secondary Efficacy Set who took at least one dose of tecovirimat or placebo, and in the Safety Set. The proportion of participants reporting no missed doses (of the last three prescribed doses) will be summarized at each evaluation time point. Since the adherence assessment was removed from protocol version 3.0, the number of participants with adherence data is expected to be small. Therefore, no formal statistical comparison will be carried out.

The EQ VAS score will be summarized at each evaluation time point by randomized arms and changes from baseline will be compared using the Wilcoxon rank-sum test as appropriate. For each of the five dimensions of the EQ-5D-5L, the number and percentage of participants reporting each level of problem will be described and compared between arms using a

Chi-square test as appropriate. If there are few or zero events in both arms (which may be likely for worse responses at later study visits), response categories may be collapsed into two levels (no problems, any problems) to facilitate analysis, and the proportion with any problems may be compared between arms using the same approach as the HMPXV clearance and adverse event analyses.

Health-related quality of life (HRQoL) as measured by the Anal Health-Related Symptom Index (A-HRSI) will be analyzed in all randomized participants with laboratory-confirmed mpox who reported anal pain or proctitis at baseline. The A-HRSI asks participants to rate the degree of prevalence or impact on morbidity of their physical symptoms, physical impacts, or psychological symptoms. Items are averaged across each domain, with higher scores indicative of worse HRQoL. Missing answers will be ignored. Sensitivity analysis will restrict to participants who completed all 25 questions. A-HRSI scores will be summarized at each evaluation time point by randomized arms and changes from baseline will be compared using the Wilcoxon rank-sum test.

For all participant-reported outcomes, intercurrent events, including all-cause death, treatment change due to disease progression or severe pain, and discontinuation of treatment for reasons other than death, disease progression or severe pain, will be handled using the while-on-treatment strategy, i.e., all responses will be included up to the time of the event.

## 6.5 Safety

### 6.5.1 Adverse Events

Occurrence of Grade 3 or higher treatment-emergent adverse events (AE) will be analyzed in the Safety Set according to the actual treatment received, i.e., participants who switched to open-label tecovirimat will be included in the tecovirimat group regardless of their initial treatment taken. All observations through Day 57, regardless of treatment status, will be used to determine the variable. Participants who discontinue follow-up before Day 57 will have their outcome determined based on data available until the time of discontinuation (i.e., a participant who discontinued follow-up without a prior AE is assumed not to have had an AE had they been observed through Day 57). The proportion of participants who had a Grade 3 or higher treatment-emergent AE reported will be estimated with a two-sided Wald-based 95% confidence interval and compared between randomized arms using a two-sample Z-test. A Wald-based 95% CI on the difference in proportions will be calculated. If there are fewer than 5 events in either group, exact confidence intervals for the proportion in each arm will be calculated using the Clopper-Pearson method, inference will use Fisher’s exact test, and an exact 95% CI on the difference in proportions will be calculated using the melded confidence interval method.

### 6.5.2 Mortality

All-cause mortality will be summarized in all participants who were randomized and will be primarily descriptive as it is anticipated there will be very few deaths in this study. However, if there are enough events (greater than 10 in both groups combined) to warrant formal statistical analysis, the following approach will be taken separately in the Secondary Efficacy Set and in the Safety Set. All observations through Day 57, regardless of treatment status, will be used to determine the variable. Participants who discontinue follow-up before Day 57 will have their outcome determined based on data available until the time of discontinuation (i.e., will be

censored at last contact). Participants who are alive and on-study through Day 57 will be censored at Day 57. Comparison of time to death between randomized groups will be made using Kaplan-Meier methods.

### 6.6 Lesion Progression

The number and percentage of participants who developed new lesions will be summarized by evaluation time point. HMPXV in new skin lesion swabs will be described by evaluation time point and sampling location.

### 6.7 STIs

The number and percentage of participants presenting with each STI at baseline will be reported.

### 6.8 HMPX Occurrence Among Household Contacts

The number and percentage of participants who had at least one household contact diagnosed with mpox will be summarized by evaluation time point.

### 6.9 Recrudescence

The number and percentage of participants who had new active lesions after clinical resolution will be reported. Clinical and virologic characteristics of all participants who were not resolved by Day 57 will be provided.

## 7 Report Contents

- CONSORT diagram
- Accrual, summarized by month of enrollment and by site/country
- Baseline characteristics
- Study retention
- Treatment status
- Mortality
- Adverse events
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- Pain reduction
- Progression to severe HMPXV disease
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- Participant-reported outcomes, including summaries of self-reported adherence and quality of life as measured by the EQ-5D-5L and A-HRSI
- Lesion progression
- HMPX occurrence among household contacts
- Recrudescence

# 8 References

Gray, RJ. “A class of K-sample tests for comparing the cumulative incidence of a competing risk.” The Annals of statistics (1988): 1141-1154.

Fine, JP, and Gray, RJ. “A proportional hazards model for the subdistribution of a competing risk.” Journal of the American Statistical Association 94.446 (1999): 496-509.

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