A5418

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

Study of Tecovirimat for Human Monkeypox Virus (STOMP)

A *Multicenter* Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
National Institute of Allergy and Infectious Diseases

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SIGA Pharmaceutical

***IND* # 163182**

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I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (U.S.) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., U.S. National Institutes of Health, Division of AIDS) and institutional policies.

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Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5418 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management committee (CMC).

- Send an e-mail message to actg.cmcA5418@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

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- Send an e-mail message to actg.teamA5418@fstrf.org (ATTENTION: Cheryl Day/Alex Greninger, Christine Johnston/Davey Smith, and Jennifer Kiser/**Edmund Capparelli,** respectively).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Stephanie Caruso**, Elizabeth Siciliano, and Alexander Watson** directly.
- For other questions, send an e-mail message to actg.teamA5418@fstrf.org (ATTENTION: Stephanie Caruso, **Elizabeth Siciliano, and Alexander Watson**).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
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- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
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Copies of the Protocol
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Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
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Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

A-HRSI	Anal Health-Related Symptom Index
AUC	area under the curve
CD4	cluster of differentiation 4
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EA-IND	expanded-access investigational new drug
EC	ethics committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMPXV	Human monkeypox virus
IND	investigational new drug (application)
IRB	institutional review board
LPV	lab processing chart
MOP	manual of procedures
MVA	modified vaccinia virus Ankara
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OPXV	orthopoxvirus
PCR	polymerase chain reaction
PK	pharmacokinetic
PSWP	protocol-specific web page
PLWH	persons living with HIV
SAE	serious adverse event
SOE	schedule of evaluations
SUSAR	serious and unexpected suspected adverse reaction
WHO	World Health Organization

SCHEMA

A5418

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

DESIGN
Phase 3, randomized, placebo-controlled, double-blind trial of tecovirimat for the treatment of human monkeypox virus (HMPXV) disease. The study will also include a cohort of people who will receive open-label tecovirimat including people with protocol-defined severe HMPXV, pregnant and breastfeeding individuals, individuals less than 18 years of age, individuals on potent inducing concomitant medications, people with severe immune suppression or skin conditions placing them at higher risk for severe disease (see section 4.3).

Participants with symptomatic HMPXV who do not meet criteria for the open-label cohort will be randomized in a 2:1 ratio to tecovirimat or matching placebo for 14 days. All participants will be followed through a combination of virtual assessments, in-person visits, and daily self-reports for resolution of clinical disease, specimen collection to assess viral clearance, and participant reported outcomes through day 57. **Participants will have the option of completely remote participation.**

Participants who progress to severe disease post-randomization will be offered open-label tecovirimat. Participants who report severe pain from HMPXV will be offered open-label tecovirimat as early as 5 days post-randomization.

The primary **outcome measure** is the time to clinical resolution defined as all skin lesions being scabbed, desquamated, or healed, and all visible mucosal lesions being healed.

DURATION
57 days

SAMPLE SIZE
530 Arms A+B (subject to re-estimation); Arm C sample size not specified

POPULATION
People with laboratory-confirmed or presumptive HMPXV disease with 1 or more skin or mucosal lesions or symptoms of mucosal lesions that are able to be followed for resolution and those with proctitis with or **without** mucosal lesions.

STRATIFICATION
Randomization (Arms A and B) will be stratified by duration of symptoms (≤5 or >5 days) **and remote enrollment**. Arm C will be non-randomized.

REGIMEN

Arm A:

- 25 kg to <40 kg: Tecovirimat 400 mg by mouth within 30 minutes after food every 12 hours for 14 days
- 40 kg to <120 kg: Tecovirimat 600 mg by mouth within 30 minutes after food every 12 hours for 14 days
- ≥120 kg: Tecovirimat 600 mg by mouth within 30 minutes after food every 8 hours for 14 days

Arm B: Matching placebos for the doses described for Arm A

Arm C: Open label tecovirimat at the doses described for Arm A plus the following for participants <25 kg:

- <6 kg: Dosing based on weight (see Table 5.1-2)
- 6 kg to <13 kg: Tecovirimat 100 mg by mouth within 30 minutes after food every 12 hours for 14 days
- 13 kg to <25 kg: Tecovirimat 200 mg by mouth within 30 minutes after food every 12 hours for 14 days

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

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.

1.2 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.

1.3 Secondary Objectives

1.3.1 To compare pain scores between randomized arms.

1.3.2 To compare rates of progression to severe HMPXV disease between randomized arms.

1.3.3 To compare clearance of HMPXV between randomized arms in various compartments including blood, skin lesions, oropharynx, rectum, and genital secretions.

1.3.4 To compare time to complete lesion healing between randomized arms.

1.3.5 To compare participant-reported outcomes including adherence and EQ-5D-5L between randomized arms.

1.3.6 To evaluate the safety of tecovirimat as compared to placebo.

1.3.7 To describe time to lesion resolution, pain, clearance of HMPXV, time to complete lesion healing, participant-reported outcomes, and safety of tecovirimat in participants who receive open-label tecovirimat

1.3.8 To determine the steady-state tecovirimat AUC_{tau} and C_{tau} in children less than 18 years of age.

1.3.9 To evaluate the safety profile of 14 days of tecovirimat in children less than 18 years of age.

1.4 Exploratory Objectives

1.4.1 In a subset of participants, to define the natural history of HMPXV oral, rectal, vaginal, urine, and lesion shedding in the presence and absence of tecovirimat.

1.4.2 In a subset of participants, to determine virologic and immune correlates of disease severity.

1.4.3 To describe lesion progression longitudinally over the study period.

1.4.4 To investigate orthopoxvirus (OPXV) immunity and its impact on the course of HMPXV disease between tecovirimat and placebo groups.

1.4.5 To assess genomic variability in MPXV isolated from participants based on geographic and clinical differences.

1.4.6 To describe the presence of resistance at baseline and emergence of viral resistance during tecovirimat treatment.

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.

1.4.8 To explore the relationship between bacterial sexually transmitted infections (gonorrhea, chlamydia and syphilis), HSV, and HMPXV.

1.4.9 To define the pharmacokinetic (PK) profile and PK-pharmacodynamic (PD) associations for tecovirimat in HMPXV.

1.4.10 To assess the potential for drug interactions between tecovirimat and antiretrovirals among persons living with HIV (PLWH).

1.4.11 To explore new HMPXV positivity among household contacts through to 28 days from start of investigational agent or placebo.

1.4.12 To describe rates and patterns of recrudescent infection and disease.

1.4.13 To describe the steady-state tecovirimat AUC_{tau} and C_{tau} in pregnant participants.

2.0 INTRODUCTION

2.1 Background

Human Monkeypox Virus (HMPXV)

HMPXV is an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family, which also includes Variola and Vaccinia [Parker 2007]. The viral genome is composed of core, lateral bodies, outer membrane, and the outer lipoprotein envelope elements [Laliberte 2010]. There are two distinct genetic clades: the central African (Congo Basin) clade 1 and the West African clade 3. In general, clade 3 infections cause a less severe disease than clade 1 [Bunge 2022]. Interestingly, isolates from the 2022 outbreak shared 40 mutations that distinguish it from its closest variant

[Isidro 2022; Figure 1]. Such variation may impact infectiousness, immune evasion, pathogenesis, and treatment susceptibility.

Epidemiology and Recent Outbreak

First discovered in laboratory monkeys in 1958, the primary carriers of monkeypox today are rodents. Zoonotic transmissions from infected animals are possible through animal bites, feces, or uncooked meat. Human to human transmission occurs from close physical contact with the virus entering through the oropharynx, nasopharynx, anorectal, or intradermal routes.

Since Spring 2022, monkeypox has rapidly spread throughout the world, with more than **70,000** cases in **107** countries and more than **26,000** cases in the United States reported as of **September** 2022 [CDC 2022c]. This new outbreak has been concentrated among men who have sex with men (MSM) [Thornhill 2022].

HMPXV Infection and Disease

In the HMPXV Clade 1 disease, the time from exposure to onset of symptoms ranges from 5 to 21 days, with a median time of onset of 7 days [Thornhill 2022]. The virus replicates at the inoculation site then spreads to regional lymph nodes. Following a period of initial viremia, the virus spreads to other body organs. HMPXV can be found in blood, semen, throat, rectum, and skin lesions (Figure 2.1-1) [Noe 2022]. Common symptoms include fever, headache, muscle aches, backache, swollen lymph nodes, malaise, fatigue, and pustular rash. Duration of symptoms is typically 2 to 4 weeks [Kumar 2022]. Symptoms usually include fevers, myalgias, and lymphadenopathy followed by a centrifugally appearing “pox” rash, often with numerous lesions. These lesions progress through the vesiculopustular to ulcerative stage and then spontaneously resolve. The disease caused by HMPXV can be rarely serious and life-threatening, and most infections are self-limited. Previous studies of HMPXV in Central Africa, where people are often medically underserved, found a mortality up to 10% among people infected [Adler 2022].

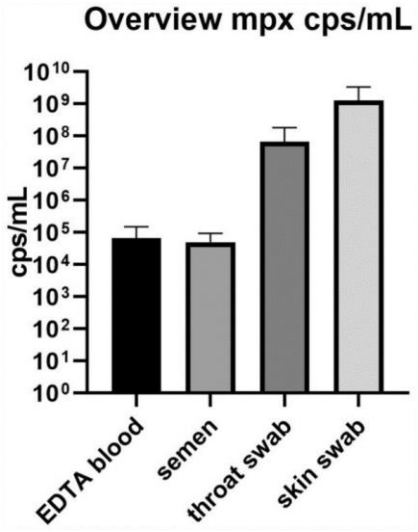

Figure 2.1-1: HMPXV genome copies per mL found in samples from two persons with active and symptomatic HMPXV infection (viral genome copies/mL of two participants averaged per sample type) [Noe 2022; Figure 2].

A recent report of 528 cases of HMPXV infection (Clade 3) from five continents, 16 countries, and 43 clinical sites provides the most robust assessment of the current outbreak of HMPXV in MSM. Systemic features during the infection included fever (62%), lethargy (41%), myalgia (31%), headache (27%), and lymphadenopathy (56%). These systemic symptoms frequently preceded a generalized rash. In this case series, skin lesions were noted in 95%, and the most common sites were: anogenital area (73%); the trunk, arms, or legs (55%); the face (25%); and the palms and soles (10%). Among persons with skin lesions, 58% had lesions that were described as “vesiculopustular.” The number of lesions varied, and most persons had fewer than 10 lesions, and 54 presented with only a single genital ulcer. Mucosal lesions were reported in 41% of the persons. The anorectal mucosa involvement was the presenting symptom in 61 persons, which was associated with a combination of anorectal pain, proctitis, tenesmus, or diarrhea. The oropharyngeal mucosa involvement was reported as the initial symptoms in 26 persons, with symptoms including a combination of pharyngitis, odynophagia, epiglottitis, and oral or tonsillar lesions. Close to 50% of cases are among PLWH, although clinical presentation was similar among persons with and without HIV. Sexually transmitted infections (STI) were reported at the time of HMPXV diagnosis in 109 of the 377 persons who were tested, gonorrhea (8%), chlamydia (5%), and syphilis (9%). Three new cases of HIV infection were identified.

Seventy persons (13%) became hospitalized, most often for anorectal pain management (n=21) and treatment of soft-tissue superinfection (n=18). Other reasons for hospitalization included severe pharyngitis, which limited oral intake (n=5), treatment of eye lesions (n=2), acute kidney injury (n=2), myocarditis (n=2), and infection-control purposes (n=13). No difference in the frequency of hospitalization was observed based on presence of HIV. Additionally, almost all people with HIV were experiencing virologic control and immune reconstitution with antiretroviral therapy (median CD4 cell count of 680 cells/mL). Despite some hospitalizations, there were no deaths reported in this

series; however, five deaths have been reported as of August 1, 2022 [Bisset 2022; University of Minnesota CIDRAP 2022].

Tecovirimat

To date, most persons with HMPXV infection in the current pandemic have received only supportive and symptomatic care, but antivirals have been FDA approved for smallpox that should have activity against HMPXV [Adler 2022; Parker 2008]. One of these drugs, tecovirimat, is beginning clinical studies against HMPXV in Africa and Europe [ISARIC 2022]. Tecovirimat was developed by SIGA Technologies, Inc. (SIGA) [SIGA Technologies, Inc. 2022]. Tecovirimat exerts antiviral activity on the exit of viral particles from an HMPXV-infected cell based on the viral p37 protein target, which is highly conserved across all species of orthopoxviruses, including those in clades 1 and 3 of HMPXV. Additionally, there are no mammalian homologs to p37. There are also no orthologous genes outside the Poxviridae family, therefore no off-target activity should be observed. In vivo efficacy studies of tecovirimat were conducted in non-human primates and rabbits, showing antiviral activity, and results from these studies were encouraging [Grosenbach 2018]. Also, safe administration of tecovirimat for treatment of HMPXV has been recently reported in some of the recent confirmed cases of HMPXV [Adler 2022; CDC 2022b].

Risks of Tecovirimat

The safety of tecovirimat is currently being evaluated or will be evaluated in several trials of HMPXV disease, including an expanded–access IND (EA-IND) protocol being conducted by the U.S. CDC, although safety data are not yet available from these studies. The EA-IND protocol is not designed to yield data on efficacy and there is no control group included. Tecovirimat has not been studied in patients with smallpox disease, but it was studied in 359 healthy adults (18-79 years). Participants who received at least one 600 mg dose of tecovirimat were 59% female, 69% White, 28% Black/African American, 1% Asian, and 12% Hispanic or Latino ethnicity. Ten percent of the participants were 65 or older. Also, 336 participants received at least 23 of 28 doses of 600 mg tecovirimat in a twice daily regimen for 14 days. Most frequently reported adverse reactions were headache and nausea. See Table 2.1-1 adapted from [Gibson and Leibowitz 2019].

Table 2.1-1: Adverse Reactions Reported in ≥2% of Healthy Adult Subjects Receiving at Least One Dose of Tecovirimat 600 mg

Adverse Reaction	Tecovirimat 600 mg n=359 (%)	Placebo n=90 (%)
Headache	12	8
Nausea	5	4
Abdominal pain	2	1
Vomiting	2	0

Children and HMPXV

Historically HMPXV in endemic regions has involved children and adolescents. While the 2022 HMPXV outbreak started primarily among adult MSM, secondary infections among

household contacts, including children, have been reported [Goodman 2022]. This is not unexpected as the household attack rate has been reported as high as 50% [Nolen 2016] with a large number of those being childhood household contacts. For example, in a 2013 outbreak in the Democratic Republic of Congo the median age of case-patients was 10 years and 17.7% were under the age of 5 [Nolen 2016]. Once infected with HMPXV the clinical course appears similar to adults although children under age 8 may have more severe disease [Huhn 2005; Jezek 1987]. In the 2003 United States outbreak, 10 cases were in individuals less than 18 year of age and while overall severity was similar to that of adults there was an increase in pediatric patients (50%) requiring ICU admission [Huhn 2005]. In the 1980-1985 HMPXV outbreak in Zaire, children aged 14 and under made up 93% of cases with high mortality in those under age 4 (14.9%) and those aged 5-9 (6.5%) [Jezek 1987]. As with adults there is little known about the duration and sites of viral shedding among pediatric patients with HMPXV.

Tecovirimat and Children

No studies of tecovirimat have been conducted in pediatric patients and there are therefore no human data to assess the risk and benefits. Currently the CDC recommends treatment with tecovirimat for children under age 8 and those meeting the same severe disease or risk of severe disease criteria as adults [CDC 2022a]. Currently tecovirimat pharmacokinetics has not been evaluated in pediatric patients. The current pediatric dosing regimen is based on a population pharmacokinetic modeling and simulation approach that is expected to produce tecovirimat exposures comparable to those in adults [SIGA Technologies, Inc. 2018]. Based on the potential benefit and the critical need to establish optimal dosing, pediatric patients will be enrolled into Arm C (open label tecovirimat plus standard of care) to ensure access and to collect the data on the pharmacokinetic, safety, and efficacy of tecovirimat in this population.

Pregnancy and HMPXV

Given limited diagnostics and the austere environments in which the majority of monkeypox infections occur, data on monkeypox infection in pregnant and breastfeeding women are limited. However, case reports of HMPXV infected pregnant persons and reports from other orthopox infections including smallpox, cowpox, and vaccinia virus infection suggest that pregnant women potentially represent a high-risk population with increased risk of maternal and perinatal morbidity and mortality [Meaney-Delman 2022].

Data on monkeypox infection in pregnancy is limited to five laboratory confirmed cases in the Democratic Republic of Congo (DRC). Four pregnant women with monkeypox infection were described in an observational study of 222 hospitalized patients who were isolated based on clinical suspicion of HMPXV infection and confirmed by polymerase chain reaction (PCR) [Khalil 2022; Mbala 2017; Meaney-Delman 2022]. While all four pregnant women survived, three of the four women who had moderate to severe monkeypox infection, by a WHO lesion number and activity-based severity score, experienced fetal demise, including two that occurred as first trimester miscarriages and one intrauterine fetal demise at 18 weeks gestation. While confirmatory testing of pregnancy tissues was not conducted in the two first trimester miscarriages, the intrauterine fetal demise had clinical, virological, histological, and serological evidence consistent with vertical transmission of HMPXV. The fetus displayed diffuse cutaneous

maculopapillary skin lesions on the abdomen, back, chest, and extremities including the palms and soles of the feet consistent with monkeypox infection. A rise in HMPX viral load from 10^2 copies/mL to 10^6 copies/mL was temporally associated with cessation of fetal movement. Monkeypox virus was found in amniotic fluid (2.6x107copies/mL), fetal tissue (1.7x107copies/mL), and umbilical cord vein blood (2.5x107copies/mL). The fourth pregnant woman experienced a mild monkeypox infection by WHO severity score which resulted in the live birth of a reportedly healthy neonate at term [Mbala 2017; Meaney-Delman 2022]. A fifth case of maternal monkeypox diagnosed in the second trimester was reported in Zaire in 1983 resulting in the delivery of a preterm neonate with a generalized rash consistent with congenital monkeypox infection, but no confirmatory testing was available. At 6 weeks of age, the infant subsequently died from malnutrition [Mbala 2017; Meaney-Delman 2022].

Tecovirimat and Pregnancy

No studies of tecovirimat have been conducted in pregnant women, therefore there is no human data to establish the presence or absence of tecovirimat-associated risk in pregnancy.

Reproduction studies in animals have found no embryofetal development toxicity in pregnant mice treated with tecovirimat at exposures up to 23 times higher than human exposure at the recommended human dose. Similarly, embryofetal development toxicity was not observed during organogenesis in rabbits at tecovirimat exposures less than human exposure at the **recommended human dose**.

Based on the potential increased risk of maternal and fetal morbidity and mortality and the lack of embryofetal development toxicity in animal studies, pregnant woman, in any trimester and after a discussion of the risks associated with tecovirimat, will be enrolled into Arm C (open label tecovirimat plus standard of care) to ensure access to investigational therapeutics and to collect the data needed to establish the safety and efficacy of tecovirimat in this population [Birmingham Health Partners 2022]. The schedule of events will remain the same in both the double-blind randomized controlled trial and the open label pregnancy registry.

Similarly, there are no available data on the effect of tecovirimat on milk production, the presence of the tecovirimat in human milk, and/or the effects on the breastfed child. When administered to lactating mice, tecovirimat was present in milk [SIGA Technologies 2022]. Since HMPXV is spread by close contact and neonates are at high risk for severe disease, women in the United States who are breastfeeding will be counseled to pump and discard breastmilk until all lesions have resolved, the scabs have fallen off and a fresh layer of intact skin has formed, consistent with CDC guidance [CDC 2022d].

Vaccination Against HMPXV

Because HMPXV is closely related to the virus that causes smallpox, the smallpox vaccine can protect people from getting HMPXV. Past data from experiences in Africa suggests that the smallpox vaccine is at least 85% effective in preventing HMPXV infection [Jezek 1988]. There is one vaccine approved to prevent HMPXV-caused

disease, JYNNEOS. The JYNNEOS vaccine is based on the highly attenuated Modified Vaccinia Ankara (MVA) virus and is felt to be safer than other replicating smallpox vaccines [CDC 2022d]. MVA has demonstrated protective efficacy in animal models of HMPXV [SIGA Technologies, Inc. 2022], older human adults (56-80 years old) [CDC 2022d], and persons living with HIV (PLWH) [CDC 2022d].

2.2 Rationale

Human Monkeypox virus is currently the cause of a multi-country outbreak and represents the most recent infectious threat to global public health. Given the dramatic increase in the numbers of infections (>28,000 in the past three months) and spread to more than 80 countries in which HMPXV is not considered endemic, the WHO declared a public health emergency of international concern [CDC 2022c; WHO 2022]. Along with preventative strategies including vaccination, contact tracing, and social mobilization, safe and effective therapeutics are urgently needed to improve clinical outcomes and control this and future outbreaks.

While there are no therapeutics currently approved for HMPXV infection, tecovirimat has been FDA approved for use against another highly lethal Orthopox virus, variola virus, based on its efficacy against monkeypox virus infection of non-human primates (NHP) and rabbitpox in rabbits consistent with the FDA animal rule [Grosenbach 2018; Sherwat 2022]. Case reports of antiviral efficacy in HMPXV-infected individuals treated with tecovirimat provide further support but are insufficient alone to demonstrate safety and efficacy in HMPXV infection [Adler 2022; Matias 2022; Rao 2022]. As a result, this randomized, double-blind, placebo controlled clinical trial is designed to provide safety and efficacy data on the use of tecovirimat in HMPXV infection. Ultimately, data from a rigorous placebo controlled RCT is needed to inform clinical care and accelerate regulatory pathways required to increase access to safe and effective therapeutics for people suffering in the current public health epidemic of international concern and for those in persistent threat of infection in endemic countries.

Rationale for Placebo-Controlled Design

Currently, there is no drug approved for HMPXV infection. Non-randomized, unblinded investigation of the efficacy of tecovirimat against HMPXV infection is encouraging, but the data are extremely limited (TPOXX, Siga) [Adler 2022; SIGA Technologies 2022]. In 2017, tecovirimat was approved by the FDA for the treatment of smallpox using a regulatory pathway known as the “animal rule.” This allows the FDA to approve a drug based on controlled studies in animals when studies in humans are not possible because of ethical issues or the rarity of the disease being studied [FDA 2018; FDA 2022].

Additionally, the U.S. CDC currently recommends tecovirimat be used under an EA-IND for 14 days for patients with severe HMPXV infection or those who are at risk for severe HMPXV infection (SIGA’s Marketing Application) [CDC 2022b]. Since no randomized controlled clinical trial has yet evaluated the efficacy of tecovirimat for treatment of HMPXV, especially among MSM with clade 3 infection, this protocol will be conducted to gather additional data.

A randomized, placebo-controlled trial is the optimal design to show efficacy, especially when including subjective outcomes including resolution of skin lesions and pain. Convincing evidence of safety and efficacy will be critical to efforts to combat the disease around the world, especially if the epidemic generalizes to a world-wide endemic infection. However, the current fund of knowledge suggests the risk-benefit ratio favors access to tecovirimat. Indeed, the CDC has provided access to tecovirimat through an EA-IND. This study maximizes access to tecovirimat by using a 2:1 allocation ratio. The study also allows access to open-label tecovirimat should the disease progress or should participants experience severe pain post-randomization. The study also provides open-label tecovirimat for those at highest risk of complications such as those having facial lesions or ocular infection.

Importantly, this RCT was developed in parallel with and will complement other clinical trials evaluating the safety and efficacy of tecovirimat in the treatment of HMPXV infection including the PALM007 trial in the Democratic Republic of Congo in which HMPXV infection is endemic, the PLATINUM study in the UK, a Canadian Clinical Trials Study, and the WHO Global Core Protocol which is an international adaptive multi-country placebo-controlled therapeutics platform trial.

Rationale for Open-Label Populations

Access to tecovirimat is currently restricted to an EA-IND pathway for patients with severe HMPXV infection or those at risk for severe HMPXV infection. Even for patients that meet these criteria, regulatory challenges have limited access to tecovirimat. The inclusion of an open-label arm for specific high-risk patients and those with severe disease will not only increase access to tecovirimat but will enable the collection of data to inform safety and efficacy of this therapeutic.

Pregnancy and Breastfeeding

This trial will provide open-label tecovirimat to pregnant persons and persons who are breastfeeding. This rationale is described above. In addition, the approach to inclusions of this population is consistent with the ethical principles set forth by the Councils for International Organizations for Medical Sciences in collaboration with the World Health Organization (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf).

Highly Immunosuppressed Individuals (See section 4.3.2 for definition)

Although data on HMPXV infection is lacking in immunocompromised persons, severe complications including progressive vaccinia [CDC 2009; Hopkins 2004; Lederman 2012] have been reported in immunocompromised individuals with smallpox infection and those who receive smallpox vaccination with the replication competent vaccinia virus.

Suspected or Confirmed Ocular Involvement

Corneal scarring and loss of vision represent one of the most significant and permanent complications of orthopox infection. Of 294 confirmed monkeypox infections followed in the DRC 2010-2013, 68 (23%) persons reported the presence of conjunctivitis among their symptoms [Reynolds 2017]. In a separate study of 338 persons with HMPXV in Zaire diagnosed between 1981 and 1986 [Jezek 1988; p 459], 10% of primary and 5% of

secondary cases were reported to have serious complications including “unilateral or bilateral blindness, weak vision, and deforming scars”.

Skin Conditions Placing Individuals at a Higher Risk for Disseminated Infection
Individuals with a history or presence of exfoliative skin conditions (eczema, atopic dermatitis, burns, impetigo, varicella zoster virus infection, psoriasis, or Darier disease [keratosis follicularis]) are potentially at higher risk for disseminated HMPXV infection. Eczema vaccinatum, a complication of smallpox vaccination that occurs in persons with exfoliative skin conditions, including those in complete remission at the time of vaccination, resulted in increased hospitalization and mortality [CDC 2007; Lane 1969; Reed 2012].

Lesions Requiring Surgical Intervention and Hospitalization
A small minority of persons with HMPXV during the current epidemic have experienced severe genital lesions (typically on the penile foreskin) that have extended beyond the subdermal layers and have required surgical debridement. Some participants have even required hospitalization. The inclusion of these small subsets into an open-label cohort will not appreciably impact the overall ability of the trial to rigorously test the efficacy and safety of tecovirimat and will perhaps reduce the likelihood of severe and long-term adverse outcomes for the study population in general.

Children Under the Age of 18
To date, tecovirimat has been approved for smallpox in all ages. However, it has only been studied for safety in adults, and pediatric PK used for dosing is based on modeling studies. Through this study, we will evaluate the PK and safety of tecovirimat in children less than 18 years. Tecovirimat is metabolized by uridine glucuronosyltransferase enzymes which are not fully functional at birth but rapidly increase in activity during the first few weeks to months of life [Kawade 1981; Krekels 2012]. Given this, initial tecovirimat doses for neonates <6kg are provided in Table 5.1-2. PK for each neonate will be used to inform dosing of subsequent neonates enrolled.

People Receiving Potent Inducing Concomitant Medications
There are very limited data on drug-drug interactions between tecovirimat and many concomitant medications. It is possible that strong inducing medications such as rifampin may decrease the exposure to tecovirimat by inducing UGT1A, it is not clear to what extent this will affect tecovirimat exposures. It appeared that tecovirimat was effective in animal models at lower-than-expected concentrations in humans [Grosenbach 2018]. Given the uncertainty, participants receiving these inducing medications will be placed in Arm C so that we can focus on determining the magnitude of interaction. This will provide important data to guide future use of tecovirimat, should it be found to be efficacious, and will help prioritize which additional drug-drug interaction studies are needed.

Rationale for Additional Sampling Cohort
Systematically collected data regarding the natural history of HMPXV dynamics in the current epidemic are urgently needed. The duration and quantity of viral shedding from rash, mucosal sites and blood will inform prevention messages and provide guidance for isolation among people with HMPXV. Understanding how viral shedding is impacted by

tecovirimat administration will help us understand the impact of more aggressive treatment with antivirals for all people with HMPXV and may have both individual and public health impacts through faster clearance of virus (analogous to HIV Treatment as Prevention). In addition, by collecting blood samples during infection and clearance of virus, we can study whether viremia and the development of the humoral and cellular immune response are associated with severity and duration of disease; through understanding correlates of disease severity, we can develop additional interventions and have better data to direct when to deploy medical countermeasures.

There is little known about the duration and sites of viral shedding among people with HMPXV. A case series of 7 people with HMPXV infection in the UK in 2018-2021 demonstrated detection of virus from multiple sites, including ulcerated skin lesions, upper respiratory tract secretions, blood and urine [Adler 2022]. Although shedding patterns were highly variable per patient, patients had HMPXV detected via PCR from ulcerated lesions, blood, and upper respiratory secretions for up to 28 days, with even more prolonged detection, particularly from upper respiratory tract secretions, among some participants. A second study enrolled 12 untreated participants from Spain in the context of the current global HMPXV outbreak. Samples were collected for up to 16 days post symptom onset from multiple sites including saliva, rectum, nasopharynx, semen, urine, and feces and tested for HMPXV by PCR [Peiró-Mestres 2022]. All participants had HMPXV shedding from saliva, and viral shedding was detected in most participants (>75%) from rectal, nasopharyngeal, semen, and urine sites. All participants had viral detection from at least one site at the time of last sample collection, suggesting prolonged viral shedding in the absence of antiviral therapy.

Rationale for PK Sampling

Pharmacokinetic data with tecovirimat were primarily generated in healthy volunteers. PK data in individuals with active disease are extremely limited. This study will determine the pharmacokinetics of tecovirimat using a combination of intensive and sparse sampling. A minimum of 24 participants in Arms A and B will undergo intensive PK sampling at steady state (day 8). Given the 2:1 randomization, it is expected that ~16 participants will be on tecovirimat. Complete, evaluable intensive PK data are expected in ≥10 of these participants.

Intensive PK will be performed in the first 8 pregnant participants enrolled in each trimester of pregnancy, at least the first 8 children in each weight band, individuals on potent inducing medications with the potential to lower tecovirimat exposures (these participants are encouraged but not required to participate in intensive PK sampling), and additional adult participants who agree to this sampling. The relationship between PK and response to tecovirimat will also be assessed.

Anal Health-Related Symptom Index (A-HRSI)

The Anal Health-Related Symptom Index (A-HRSI) will be administered to participants reporting proctitis at baseline. The A-HRSI was developed in a substudy of the ANCHOR study [NCT01946139 (https://clinicaltrials.gov/show/NCT01946139); Palefsky 2022] and included a four-phase process to establish content validity. Forty-one study participants who were eligible for ANCHOR were interviewed to inform the instrument developed and these

interviews were used to create a 23-item measure draft tool that was then tested in a second cohort of 45 participants eligible for ANCHOR in a process of cognitive interviewing. This process resulted in a 25-item content-valid measure of physical symptoms, physical impacts and psychological symptoms [Burkhalter 2018]. Reliability was assessed in 100 ANCHOR participants across a 7–10-day timeframe, with Cronbach's α in the fair to good range across the three domains (i.e., 0.79–0.82), indicating internal consistency for the measure [Atkinson 2019]. The test-retest reliability was good across each of the three domains (intraclass correlation coefficients = 0.80–0.84). Construct validity of the measure was then established in a fourth cohort of individuals enrolled in ANCHOR (n=303) who completed A-HRSI at a single time point, with the three-domain model (i.e., physical symptoms, physical impacts, psychological symptoms) confirmed via confirmatory factor analysis. These three domains strongly associated (Pearson's *r*) with corresponding domains from the well-established MD Anderson Symptom Inventory and Functional Assessment of Cancer Therapy – General tools.

3.0 STUDY DESIGN

This is a randomized, placebo-controlled, double-blind study to establish the efficacy of tecovirimat for the treatment of people with laboratory-confirmed or presumptive HMPXV disease**. (See section 4.1.1 for the definitions of confirmed and presumptive disease.)** Potential participants will be approached for informed consent and then assessed for eligibility.

Participants should be assessed for the presence of HMPXV, the extent, duration and severity of disease, and the presence of any conditions necessitating enrollment into Arm C (open-label arm) as opposed to the randomized arms (Arms A and B). **(See section 4.3 for the criteria for Arm C.)**

Enrollment of those with presumptive disease is allowed. For those with severe disease, enrollment based on presumptive diagnosis is strongly encouraged. Delaying enrollment for receipt of laboratory confirmation can be considered for those who have only mild symptoms whose confirmatory test results are expected within 24 hours.

For **participants who are** enrolled (i.e., randomized to Arm A or B, or registered to Arm C) **in person** based on a presumptive HMPXV diagnosis, sites should send diagnostic specimens to the central laboratory for a clinical report as described in section 6.3.6 whether or not there is a pending local test. **Participants enrolled in person for whom** both the local test (if one was obtained) and all clinically reported HMPXV tests from the central laboratory are negative should stop study drug. **Follow up through remote or in person contact will occur 7 days after stopping study drug to assess for AEs. Participants randomized to Arms A and B will be replaced.** If any of these tests are positive, then the person should complete the study as planned.

For participants who are enrolled remotely, sites should verify that the local laboratory test confirmed HMPXV or verify that a local laboratory test confirming HMPXV is pending. No additional diagnostic testing is required. Participants enrolled remotely for whom the local HMPXV testing is negative should stop study

drug. Follow up through remote contact will occur 7 days after stopping study drug to assess for AEs. Participants randomized to Arms A and B will be replaced.

Eligible and consented participants for the randomized arms (N=530) will be randomized 2:1 to receive either tecovirimat or placebo (Arms A and B); participants with severe disease, significant skin conditions, participants with severe immune suppression (see section 4.3.2) will be enrolled to Arm C. Participants who are pregnant or breastfeeding will be enrolled into Arm C after discussion of the potential risks and benefits of tecovirimat. Participants less than 18 years of age will be enrolled to Arm C. Participants receiving a potent inducing concomitant medication will also be enrolled to Arm C.

All participants will receive standard-of-care treatment according to local/site practice and suggested approaches to supportive care are described in a protocol manual of procedures (MOP). Randomization between Arms A and B will be stratified according to time since prodromal symptom onset (≤5 days or >5 days) **and remote enrollment**.

Baseline evaluations for all adult **participants** and sexually active adolescents **enrolled/followed in person** will include an assessment for bacterial sexually transmitted infections, chronic viral hepatitis, and HIV testing as described in section 6.1 (Schedules of Evaluations). Participants with genital, anal, perianal, or perioral ulcerative lesions or proctitis should be tested for HSV if not done within 7 days prior to enrollment. This testing is available through the central laboratory to be used for clinical management. **Participants enrolled remotely will be advised of the recommended STI testing and HIV testing (if not known to have HIV).**

Participants **seen for in-person visits** will have baseline samples for HMPXV collected including blood, oropharyngeal swabs, swabs of a representative lesion to be designated the “index lesion”, rectal swabs, eye fluid (if having suspected ocular infection) and self-collected vaginal swabs (cisgender women and transgender men only). Participants with suspected HMPXV infection in the eye should be considered for referral to ophthalmology. Note there are specific recommendations for treating ocular HMPXV (see MOP). Participants **seen in person** agreeing to semen collection will be provided a kit for home collection.

Participants enrolled remotely may elect to have follow up visits in person. In this event, these participants would sign the consent form for in person follow up.

Participants enrolled in person may elect to have follow up visits remotely. In this event, participants will continue to follow the SOEs for in-person participants with evaluations that are required to be done in person marked as missed evaluations. Missed evaluations due to a remote visit are not protocol deviations.

Regardless of whether participants are enrolled/followed in person or remotely, they should have a plan for accessing care for their monkeypox virus outside of the study, if necessary.

Once enrolled, study drug administration will begin according to study group assignment. Tecovirimat will be administered as described below (section 5.0). Study drug or placebo administration will be for 14 days. Participants should be counseled on how to avoid transmitting HMPXV to others. **Participants who are enrolled/followed remotely will be sent the study product via mail or courier service.**

Participants who progress to develop one of the conditions for severe HMPXV disease (as defined in section 4.3.**2**) will **have** a **visit to** confirm progression. **For participants enrolled/followed in person, this visit should be done in person, if feasible. For participants enrolled/followed remotely, this visit will be conducted remotely (i.e., via telemedicine) unless the participant prefers to come into the site.** If severe disease is confirmed, participants will stop blinded study treatment and start a 14-day course of open-label tecovirimat.

Participants reporting severe pain (7 or greater on the numerical rating scale) 5 days after randomization will **have a visit to confirm indication for open-label tecovirimat. This includes participants who report persistent severe pain since baseline or pain that worsens and becomes severe. For participants enrolled/followed in person, this visit should be done in person, if feasible. For participants enrolled/followed remotely, this visit will be conducted remotely (i.e., via telemedicine) unless the participant prefers to come into the site.** These participants **will stop blinded study treatment and start a 14-day course of open-label tecovirimat.** Of note, participants randomized to Arm A who subsequently receive open-label tecovirimat will receive a total course of tecovirimat longer than 14 days. These participants will continue to be followed according to their original schedule of events. If participants become hospitalized, study staff should continue to follow the schedule of events as feasible. If in person visits for hospitalized participants are not possible, study staff should conduct remote assessments to ascertain study outcomes as allowed.

Participants will self-monitor skin and/or mucosal lesions daily through 29 days or resolution (whichever comes first), complete a daily diary of symptoms and complete a daily numerical rating scale for pain assessment. Participants will be instructed on the criteria for lesion resolution. Participants will be **requested** to take serial photographs of lesions as described in the MOP, **but these photographs are not required.** If reporting lesion resolution, participants will be seen for a remote visit (or in person whichever is preferred by the participant) as soon as possible for study staff to confirm status.

Participants **enrolled/followed in person** will be seen weekly through day 29 for assessment of HMPXV disease, safety assessments, HMPXV sampling similar to that described for entry, and swabbing of new HMPXV lesions. Participants will be seen at day 57 to assess for possible recrudescence of infection (i.e., new lesions occurring after initial resolution of disease.

Participants over the age of 18 in Arms A/B/C **who are enrolled/followed in person** will have the option to undergo additional mucosal and lesional viral sampling while on study drug in addition to optional PBMC collection, with the goal of having up to 100 participants enrolled in this cohort.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria (All participants; Arms A, B, and C)

4.1.1 Laboratory-confirmed or presumptive HMPXV infection:

Laboratory-confirmed HMPXV infection is defined as determined by PCR, culture, or antigen test obtained from a sample collected from a skin lesion, oropharynx, or rectal swab obtained within 7 days prior to study entry

OR

Presumptive diagnosis:

- Skin lesion(s), mucosal lesion(s) or proctitis consistent with a high probability of HMPXV in the opinion of the site investigator
  AND
- Sexual contact with 1 or more persons in the 21 days prior to symptom onset or close exposure to another person known to be infected with HMPXV.

OR

- **Neonates (<4 weeks of age) born to mothers with monkeypox infection. These neonates are assumed to have monkeypox and no confirmatory testing is required.**

4.1.2 HMPXV illness of <14 days duration immediately prior to study entry.

4.1.3 At least one active (not yet scabbed) skin lesion, mouth lesion, or proctitis with or without visible ulcers.

4.1.4 Non-pregnant people of reproductive potential must agree to use at least one effective means of contraception when engaging in sexual activities that can result in pregnancy, from the time of enrollment through the end of study participation. Acceptable methods of contraception include the following:

- Abstinence
- Hormonal contraception
- Male or female condom
- Diaphragm or cervical cap with a spermicide
- Intrauterine device

NOTE: Reproductive potential is defined as:

- Participants who have reached menarche
- Participants who have not been post-menopausal for at least 12 consecutive months with follicle-stimulating hormone (FSH) ≥40 IU/mL or 24 consecutive months if an FSH is not available
- Participants who have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or bilateral salpingectomy)
- For individuals with permanent infertility due to an alternate medical cause (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

4.1.5 Ability to provide informed consent (for those above the legal age of consent and those providing consent for minors) and assent (for those **who have reached** the age of **assent**, **but not the** legal age of consent)**, as allowed by local ethics committees.**

4.1.6 For participants to be enrolled/followed remotely, ability and willingness to participate in remote telehealth assessments (i.e., video visits).

4.2 Additional Inclusion Criteria for Arms A and B

4.2.1 Age ≥18 years at the time of study entry.

4.3 Additional Inclusion Criteria for Arm C

Participants who meet the above entry criteria (section 4.1) who also meet any of the following criteria will be registered to Arm C.

4.3.1 Participants age <18 years at the time of study entry

4.3.2 Those with severe HMPXV disease defined as having one or more of the following conditions:

- Suspected or confirmed ocular involvement
- Facial lesions on the malar, nose, or eyelid region
- Confluent facial lesions
- Hospitalization due to HMPXV infection or its complications
- Lesions that require surgical intervention including debridement, urinary catheterization or sigmoidoscopy, or lesions extending below the dermis

Those with or without severe disease and with one or more of the following will also be enrolled into Arm C:

- Severe immunosuppression defined as:
  - HIV with CD4 <200 cells/mm^3 or plasma HIV-1 RNA >1000 copies/mL
  - Leukemia
  - Lymphoma

- Generalized malignancy
- Solid organ transplantation
- Therapy with alkylating agents within 180 days prior to study entry
- Antimetabolites within 180 days prior to study entry
- Radiation therapy within 180 days prior to study entry
- Tumor necrosis factor inhibitors within 180 days prior to study entry
- High-dose corticosteroids (equivalent of 20 mg or greater of prednisone for at least 14 days) within 90 days prior to study entry
- Being a recipient with hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component)
- Other severe immunosuppression in the opinion of the site investigator

- **Active s**kin conditions placing the person at higher risk for disseminated infection as defined as:
  - Atopic dermatitis
  - Active exfoliative skin condition(s) such as eczema, burns, impetigo, active varicella zoster virus infection, psoriasis, or Darier disease (keratosis follicularis)
- Breastfeeding
- Pregnancy
- Receipt of potent inducers, including rifampin, rifapentine, rifabutin, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir
- Current or planned use of another investigational drug at any point during tecovirimat/placebo dosing that would be predicted to have a significant drug-drug interaction with tecovirimat therapeutics.

4.4 Exclusion Criteria (All participants; Arms A, B, and C)

4.4.1 Prior or concomitant receipt of tecovirimat (e.g., under an alternative access mechanism**)**.

NOTE: Participants <18 years of age, pregnant, and/or breastfeeding in Arm C are allowed up to 3 days of tecovirimat immediately prior to entry.

4.4.2 Planned initiation of intramuscular cabotegravir/rilpivirine during study drug administration or for two weeks following completion of study drug administration. Participants who are stable on long-acting intramuscular cabotegravir/rilpivirine may enroll.

4.4.3 Participants who, in the judgement of the investigator, will be at significantly increased risk as a result of participation in the study.

4.4.4 Participants who require intravenous dosing of tecovirimat.

4.5 Study Enrollment Procedures

4.5.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the IRB of record as well as any required local institutional review board (IRB)/ethics committee (EC) approvals and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) WILL NOT be reviewed or approved by the DAIDS PRO. Sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.
Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC Study Enrollment System.

4.5.2 Consent Process

<u>If the potential participant is not of legal age to provide independent informed consent</u>
Written informed consent for study participation will be obtained from each potential participant’s parent or legal guardian before any study-specific procedures are performed. It is generally expected that the consent of one parent (or legal guardian) will be sufficient for child participation in this study. However, consenting requirements at each site will depend on the IRB/EC risk determination.

When applicable per IRB/EC policies and procedures, written assent will also be obtained from the potential participant before any study-specific procedures are

performed. If the parent/guardian does not provide consent, or the potential participant does not provide assent when applicable, the potential participant will not be screened or enrolled. Minor participants who assent to the study and later withdraw that assent will not be maintained in the study against their will, even if their parent/guardian still wants them to participate.

If the potential participant is of legal age or circumstance to provide independent informed consent or, if applicable per local regulations, is considered a minor who is legally able to provide informed consent
Written informed consent for study participation will be obtained from each potential participant before any study-specific procedures are performed.

4.5.3 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.5.4 Randomization/Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database. Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

4.6 Co-enrollment Guidelines

- Sites in the U.S. are strongly encouraged to co-enroll participants **enrolled/followed** in **person in** A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials for Currently Unspecified Analyses”, Co-enrollment in A5128 does not require permission from the A5418 protocol chairs.
- Sites outside of the U.S. are strongly encouraged to co-enroll participants **enrolled/followed** in **person in** A5243, “Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses“. Co-enrollment in A5243 does not require permission from the A5418 protocol chairs.
- Request for continued participation in non-interventional studies is not required.
- For specific questions and approval for co-enrollment in other interventional studies, sites should first check the protocol-specific web page (PSWP) or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study-provided treatment is defined as Tecovirimat or Placebo for Tecovirimat.

5.1 Regimens and Duration

Participants randomized to either Arm A or B to receive one of two regimens as shown in Table 5.1-1. Participants in Arm A and Arm B may change to a 14-day course of open label tecovirimat as described in section 3.0. Participants in Arm C will receive tecovirimat for 14 days as described in Table 5.1-1.

Table 5.1-1: Treatment Regimens for Participants **≥6kg**

Arm	Weight Band	Dose	Duration
Arm A	25 kg to less than 40 kg	Tecovirimat 400 mg (2 capsules) every 12 hours	14 days
	40 kg to less than 120 kg	Tecovirimat 600 mg (3 capsules) every 12 hours	14 days
	120 kg and over	Tecovirimat 600 mg (3 capsules) every 8 hours	14 days
Arm B	25 kg to less than 40 kg	Placebo for Tecovirimat 400 mg (2 capsules) every 12 hours	14 days
	40 kg to less than 120 kg	Placebo for Tecovirimat 600 mg (3 capsules) every 12 hours	14 days
	120 kg and over	Placebo for Tecovirimat 600 mg (3 capsules) every 8 hours	14 days
Arm C	Less than 6 kg	See Table 5.1-2	14 days
	6 kg to less than 13 kg	Tecovirimat 100 mg (1/2 capsule) every 12 hours	14 days
	13 kg to less than 25 kg	Tecovirimat 200 mg (1 capsule) every 12 hours	14 days
	25 kg to less than 40 kg	Tecovirimat 400 mg (2 capsules) every 12 hours	14 days
	40 kg to less than 120 kg	Tecovirimat 600 mg (3 capsules) every 12 hours	14 days
	120 kg and over	Tecovirimat 600 mg (3 capsules) every 8 hours	14 days

Table 5.1-2: Initial Treatment Regimens for Participants <6kg

Weight	Dose	Duration
<3kg	Tecovirimat **33.3** mg (**3.3** mL) every 12 hours	14 days
3 to **<6**kg	Tecovirimat **50** mg (**5** mL) every 12 hours	14 days

Sites should contact the Clinical Management Committee (CMC) when enrolling children <6 kg. The available PK data will be discussed with the site investigator and the dose will be confirmed with the site. We are performing pharmacokinetic analyses in near real time for pediatric **participants** (results obtained approximately 1 week after shipment of

specimen). The initial dosing regimens are listed above. These doses will be updated (in the protocol MOP) based on available data as described in section 11.0.

5.1.1 Dispensing

Tecovirimat **33.3** mg: Administer as **33.3mg/3.3mL** – 200mg capsule (20mg total dose) orally every 12 hours

Tecovirimat 50 mg: Administer as one-quarter (1/4) – 200 mg (50 mg total dose) orally every 12 hours for participants older than 7 days)

Tecovirimat 100 mg: Administer as one-half (1/2) – 200 mg (100 mg total dose) orally every 12 hours

Tecovirimat 200 mg: Administer as one – 200 mg (200 mg total dose) orally every 12 hours

Tecovirimat 400 mg/Placebo for Tecovirimat: Administer as two – 200 mg/matching placebo capsules (400 mg total dose) orally every 12 hours

Tecovirimat 600 mg/Placebo for Tecovirimat: Administer as three – 200 mg/matching placebo capsules (600 mg total dose) orally every 12 hours

Tecovirimat 600 mg/Placebo for Tecovirimat: Administer as three – 200 mg/matching placebo capsule (600 mg total dose) orally every 8 hours (for 120kg and over)

5.1.2 Administration

Oral Therapy for Adults
Tecovirimat capsules or placebo should be taken by mouth with a full glass of water within 30 minutes after eating a meal of moderate or high fat (ideally about 600 calories and 25 grams of fat) in order to improve bioavailability. See MOP for a list of suggested meals meeting the caloric and fat criteria. Tecovirimat or placebo capsules can be opened and mixed in liquid for adults who cannot swallow capsules. Instructions for capsule opening and mixing are described in the MOP.

Oral Therapy for Children
For children <13kg, the contents of one- 200mg capsule should be mixed with 20mL of water and a fraction of the water and drug mixture withdrawn to match the desired dosing. The prepared dose may be orally administered directly or further mixed with 1-2 teaspoons of liquid or soft food.

For children ≥13kg, the contents of the specified number of capsules required for

the desired dose should be mixed with 30mL of liquid **(e.g., milk, chocolate milk, water)** or soft food **(e.g., apple sauce, yogurt).**

Instructions for capsule opening, mixing, and administration are described in the MOP.

Children capable of taking tecovirimat with a meal will take the capsules within 30 minutes after eating a meal of moderate or high fat based on their age and weight in order to improve bioavailability. For younger children, we will investigate the PK based on their typical consumption including for those who are formula or breastfed.

For children who may spit out a dose of study product or vomit within 15 minutes after taking study product, parents or guardians will be instructed to administer a replacement dose. If vomiting occurs more than 15 minutes after taking study product, a replacement dose should not be administered (the next scheduled dose should be taken as scheduled).

Instructions for capsule opening and mixing are described in the MOP.

Missed Dose
If a dose of Tecovirimat or Placebo for Tecovirimat is missed, the participant should take the dose as soon as possible and anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next scheduled dose, the participant should not take the missed dose, and should resume dosing at the next scheduled dose.

If the participant is scheduled for every 8-hour dosing and a dose of Tecovirimat or Placebo for Tecovirimat is missed, the participant should take the dose as soon as possible and anytime up to 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next scheduled dose, the participant should not take the missed dose, and should resume dosing at the next scheduled dose.

5.2 Study Product Formulation and Storage

5.2.1 Tecovirimat

The oral formulation of Tecovirimat is provided as oral capsules containing white to off-white powder in orange and black hard gelatin capsules. Each capsule contains 200 mg of Tecovirimat active ingredient and comes in a bottle containing 42 capsules. Tecovirimat capsules should be stored at room temperature at 20−25°C (68−77°F), with excursions permitted to 15−30°C (59−86°F) [see USP Controlled Room Temperature].

5.2.2 Placebo for Tecovirimat

The oral formulation of the placebo for Tecovirimat is provided as oral capsules

containing white to off-white powder in orange and black hard gelatin capsules. The placebo comes in a bottle containing 42 capsules. Placebo for Tecovirimat should be stored at 20−25°C (68−77°F), [USP controlled room temperature].

5.3 Study Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply and Distribution

Study products will be made available to sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, the product may be obtained by the investigational pharmacist by following the instructions provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

All study products will be donated by SIGA.

5.3.2 Study Product Accountability

The investigational pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All study products must be stored in the investigational pharmacy.

5.3.3 Final Disposition of Study Product

For U.S. clinical research sites, all unused study product remaining at sites after the study is completed or terminated must be returned to the NIAID CRPMC (unless otherwise directed by the sponsor). Study products may also be returned to the CRPMC for other reasons, as requested by the sponsor. Investigational pharmacists will follow the relevant instructions for return of unused study products provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

At non-U.S. clinical research sites, the investigational pharmacist must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for the destruction of unused study products remaining at the site.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication’s and study agent’s most recent package insert, Investigator’s Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

5.4.1 Prohibited Medications

Drug interaction data with tecovirimat are evolving. Study personnel are required to review the most updated interactions on the PSWP. There are no prohibited medications.

5.4.2 Precautionary Medications

Tecovirimat is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19. Participants taking drugs that are substrates of CYP3A should be monitored for reduced efficacy and participants who are taking drugs that are substrates for CYP2C8 and/or CYP2C19 should be monitored for side effects. Please see the PSWP for a table of CYP3A, CYP2C8, and CYP2C19 substrates which may be altered by tecovirimat.

Avoid initiation of intramuscular cabotegravir/ritonavir during study drug administration and for two weeks following completion of study drug administration.

Use of other antivirals with expected activity against HMPXV (i.e., cidofovir and brincidofovir) is strongly discouraged for Arms A and B. Sites should contact the CMC prior to use in Arms A and B.

For those with severe immunosuppression, concomitant treatment with cidofovir or brincidofovir can be considered at the discretion of the local investigator. Please note that these medications are not provided by the study.

An increase in dose for doravirine, rilpivirine, or maraviroc is not warranted, as it may lead to unnecessary confusion, dosing errors, and pill burden.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Participants 18 Years of Age or Older; Arms A, B, and C **– ENROLLED/FOLLOWED IN PERSON**

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± 2	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Clinical Evaluations – see section 6.3.1										
Medical History	X									
Medication History	X									
Complete Physical Exam	X									
Targeted Physical Exam		X		X	X	X	X	X	(X)	X
Skin/HMPXV Assessment	X			X	X	X	X	X	X	X
Concomitant Medications	X			X	X	X	X	X	X	X
Study Treatment Modifications			X	X	X					
Clinical/Safety/Laboratory Evaluations – see section 6.3.2										
Hematology		X		X						
Serum Chemistries		X		X						

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± 2	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Urine or Serum Pregnancy	X			Whenever pregnancy is suspected						X
Syphilis Serology with Reflex to Confirmatory Testing		X								
Chlamydia and Gonorrhea (Swab)		X								
Chlamydia and Gonorrhea (Urine)		X								
HSV PCR Testing	X									
Anti-HIV-1/HIV-2		X								
HIV-1 RNA (for PLWH or on HIV PrEP)		X								
Absolute CD4 (for PLWH)		X								
HBsAg, Anti HBs, Anti HBc		X								
Hepatitis C Virus Antibody with Reflex		X								
HMPXV Diagnostic Skin Swab (Presumptive Diagnosis Only)	X									
HMPXV Diagnostic Oral Swab (Presumptive Diagnosis Only)	X									

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± 2	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
HMPXV Diagnostic Rectal Swab (Presumptive Diagnosis Only)	X									
Study Drug Administration – see section 6.3.3										
Study Drug Administration		Daily on days 1 - 15								
Telephone Check			X							
Open-Label Dispensing of Tecovirimat										X
Participant-Completed Evaluations – see section 6.3.4										
Participant-Completed Study Diary		Daily self-assessment days 1 - 29								
Participant-Completed Pain Scale (NRS)	X	Daily self-assessment days 1 - 29								
Participant-Collected Photographs of Lesions **(optional)**		Daily self-assessment days 1 - 29								
Participant-Completed Study Dosing Diary		**Daily on days 1 - 15**								
Semen Collection (optional)		X			X			X		X
Questionnaires – see section 6.3.5										
HMPXV Transmission Questionnaire		X					X			

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± 2	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Household Transmission Questionnaire		X					X	X		
EQ-5D-5L Questionnaire		X		X	X		X			
Anal Health Related Symptom Index (if indicated)		X	X		X			X		
Samples Collected at Clinic – see section 6.3.6										
HMPXV Index/New Skin Lesion Swab		X		X	X	X	X	X		X
HMPXV Oral Swab		X		X	X	X	X	X		X
HMPXV Rectal Swab		X		X	X	X	X	X		X
HMPXV Vaginal Swab		X		X	X	X	X	X		X
Breastmilk Collection (breastfeeding only)		X		X	X	X	X	X		
Ocular Fluid (suspected eye disease only)		X		X	X	X	X	X		X
Whole Blood (HMPXV DNA)		X		X	X	X	X	X		X
Pharmacokinetic Samples - see section 6.3.7										
ARV Trough PK (Plasma) (for participants on ARVs)		X		X	X					

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± 2	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Sparse Tecovirimat PK				X	X					X
Intensive PK				X						
Stored Samples – see section 6.3.8										
Stored Plasma and DBS		X		X	X		X	X		X
Stored Serum		X		X	X		X	X		X

Table 6.1-2: Participants 18 Years of Age or Older; Arms A, B, and C – ENROLLED/FOLLOWED REMOTELY

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	**-7**		**± 1**	**± 2**	**± 2**	**± 2**	**± 4**	**± 7**		
Clinical Evaluations – see section 6.3.1										
Capture from clinical care, if available										
Complete Physical Exam	**X**									
Collect at the visit										
Medical History	**X**									
Medication History	**X**									
Skin/HMPXV Assessment	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment Modifications			**X**	**X**	**X**					
Clinical/Safety/Laboratory Evaluations – see section 6.3.2										
Capture from clinical care, if available										
Hematology		**X**								
Serum Chemistries		**X**								

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	**-7**		**± 1**	**± 2**	**± 2**	**± 2**	**± 4**	**± 7**		
Urine or Serum Pregnancy	**X**	**Any time pregnancy testing is performed**								**X**
Syphilis Serology with Reflex to Confirmatory Testing		**X**								
Chlamydia and Gonorrhea (Swab)		**X**								
Chlamydia and Gonorrhea (Urine)		**X**								
HSV PCR Testing	**X**									
Anti-HIV-1/HIV-2		**X**								
HIV-1 RNA (for PLWH or on HIV PrEP)		**X**								
Absolute CD4 (for PLWH)		**X**								
HBsAg, Anti HBs, Anti HBc		**X**								
Hepatitis C Virus Antibody with Reflex		**X**								
Study Drug Administration – see section 6.3.3										
Study Drug Administration		**Daily on days 1 - 15**								
Telephone Check			**X**							

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	**-7**		**± 1**	**± 2**	**± 2**	**± 2**	**± 4**	**± 7**		
Open-Label Dispensing of Tecovirimat										**X**
Participant-Completed Evaluations – see section 6.3.4										
Participant-Completed Study Diary		**Daily self-assessment days 1 - 29**								
Participant-Completed Pain Scale (NRS)	**X**	**Daily self-assessment days 1 - 29**								
Participant-Collected Photographs of Lesions (optional)		**At least twice a week**								
Participant-Completed Study Dosing Diary		**Daily on days 1 - 15**								
Questionnaires – see section 6.3.5										
HMPXV Transmission Questionnaire		**X**					**X**			
Household Transmission Questionnaire		**X**					**X**	**X**		
EQ-5D-5L Questionnaire		**X**		**X**	**X**		**X**			
Anal Health Related Symptom Index (if indicated)		**X**	**X**		**X**			**X**		
Samples Collected – see section 6.6										
HMPXV Index/New Skin Lesion Swab		**X**		**X**	**New lesion occurring on day 6 or later**					

Table 6.1-**3**: Additional Sampling Cohort; Participants 18 Years of Age or Older **– ENROLLED/FOLLOWED IN PERSON ONLY**

Evaluations on this schedule are IN ADDITION to those indicated in Table 6.1-1.

Evaluation (see section 6.4)	Entry (Day 1)	Post-Entry Evaluations (Days)										
		2	3	5	8	11	15	18	22	25	29	57
Visit Windows (Days)		± 1	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 4	± 7
Visit Location (R: Remote, P: In Person)		R	P	R	P	R	P	R	P	R	P	P
Informed Consent for Additional Sampling	X											
Teach Oral, Rectal, Vaginal, and Skin Lesion Swabs	X											
HMPXV Oral Swab		X	X	X		X		X		X		
HMPXV Rectal Swab		X	X	X		X		X		X		
HMPXV Vaginal Swab		X	X	X		X		X		X		
HMPXV Index Skin Lesion Swab		X	X	X		X		X		X		
Return/Review Swabs			X		X		X		X		X	
Urine	X		X		X		X				X	
Whole Blood for HMPXV DNA			X									
Sparse Tecovirimat PK			X									
Stored PBMCs (optional)	X						X					X

Table 6.1-**4**: Participants Younger Than 18 Years of Age; Arm C **– ENROLLED/FOLLOWED IN PERSON**

Evaluation (SA = perform only for sexually-active participants; X= perform for all participants)	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± **2**	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Clinical Evaluations – see section 6.3.1										
Medical History	X									
Medication History	X									
Complete Physical Exam	X									
Targeted Physical Exam		X		X	X	X	X	X		X
Skin/HMPXV Assessment	X			X	X	X	X	X	X	X
Concomitant Medications	X			X	X	X	X	X	X	X
Study Treatment Modifications			X	X	X					
Safety or Clinical Laboratory Evaluations – see section 6.3.2										
Hematology		X		X						
Serum Chemistries		X		X						
Urine or Serum Pregnancy Testing	SA			Whenever pregnancy is suspected						

Evaluation (SA = perform only for sexually-active participants; X= perform for all participants)	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± **2**	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Syphilis Serology with Reflex to Confirmatory Testing		X								
Chlamydia and Gonorrhea (Swab)		SA								
Chlamydia and Gonorrhea (Urine)		SA								
HSV PCR Testing	SA									
Anti-HIV-1/HIV-2		SA								
HIV-1 RNA (for PLWH or on HIV PrEP)		X								
Absolute $CD4^+$ (for PLWH)		X								
HBsAg, Anti HBs, Anti HBc		SA								
Hepatitis C Virus Antibody with Reflex		SA								
HMPXV Diagnostic Skin Swab (Presumptive Diagnosis Only)	X									
HMPXV Diagnostic Oral Swab (Presumptive Diagnosis Only)	X									

Evaluation (SA = perform only for sexually-active participants; X= perform for all participants)	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± **2**	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
Study Drug Administration – see section 6.3.3										
Study Drug Administration		Daily on days 1 - 15								
Telephone Check			X							
Open-Label Dispensing of Tecovirimat										X
Participant-Completed Evaluations – see section 6.3.4										
Participant-Completed Study Diary		Daily self-assessment days 1 - 29								
Participant-Completed Pain Scale	X	Daily self-assessment days 1 - 29								
Participant-Collected Photographs of Lesions **(optional)**		Daily self-assessment days 1 - 29								
Participant-Completed Study Dosing Diary		**Daily on days 1 - 15**								
Questionnaires – see section 6.3.5										
Household Transmission Questionnaire		X					X	X		
Samples Collected at Clinic – see section 6.3.6										
HMPXV Index/New Skin Lesion Swab		X		X	X	X	X	X		X

Evaluation (SA = perform only for sexually-active participants; X= perform for all participants)	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	-7		± 1	± **2**	± 2	± 2	± 4	± 7		
Visit Location (R: Remote, P: In Person)			R	P	P	P	P	P	P/R	P
HMPXV Oral Swab		X		X	X	X	X	X		X
Ocular Fluid (suspected eye disease only)		X		X	X	X	X	X		X
Whole Blood for HMPXV DNA		X		X	X	X	X	X		X
Pharmacokinetic Samples - see section 6.3.7										
ARV Trough PK (Plasma) (for participants on ARVs)		X		X	X					
Sparse Tecovirimat PK		**(X)**		X	X					X
Intensive PK				X						
Stored Samples – see section 6.3.8										
Stored Serum		X			X					X

Table 6.1-5: Participants Younger Than 18 Years of Age; Arm C – ENROLLED/FOLLOWED REMOTELY

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	**-7**		**± 1**	**± 2**	**± 2**	**± 2**	**± 4**	**± 7**		
Clinical Evaluations – see section 6.3.1										
Capture from clinical care, if available										
Complete Physical Exam	**X**									
Collect at the visit										
Medical History	**X**									
Medication History	**X**									
Skin/HMPXV Assessment	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment Modifications			**X**	**X**	**X**					
Clinical/Safety/Laboratory Evaluations – see section 6.3.2										
Capture from clinical care, if available										
Hematology		**X**								
Serum Chemistries		**X**								

Evaluation	Screening	Entry (Day 1)	Post-Entry Evaluations (Days)						Confirmation of Lesion Resolution	Confirmation of Disease Progression
			6	8	15	22	29	57		
Visit Windows (Days)	**-7**		**± 1**	**± 2**	**± 2**	**± 2**	**± 4**	**± 7**		
Urine or Serum Pregnancy	**X**	**Any time pregnancy testing is performed**								**X**
Study Drug Administration – see section 6.3.3										
Study Drug Administration		**Daily on days 1 - 15**								
Telephone Check			**X**							
Open-Label Dispensing of Tecovirimat										**X**
Participant-Completed Evaluations – see section 6.3.4										
Participant-Completed Study Diary		**Daily self-assessment days 1 - 29**								
Participant-Completed Pain Scale (NRS)	**X**	**Daily self-assessment days 1 - 29**								
Participant-Collected Photographs of Lesions (optional)		**At least twice a week**								
Participant-Completed Study Dosing Diary		**Daily on days 1 - 15**								
Questionnaires – see section 6.3.5										
Household Transmission Questionnaire		**X**					**X**	**X**		
Samples Collected – see section 6.6										
HMPXV Index/New Skin Lesion Swab		**X**		**X**	**New lesion occurring on Day 6 or later**					

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Evaluations needed to determine eligibility and stratification for randomization to arms A or B or registration to Arm C must occur prior to the participant starting any study medications, treatments, or interventions. These assessments are included in the "Screening" column in the Schedule of Evaluations (SOE).

Screening
Screening evaluations to determine eligibility must be completed within 7 days prior to study entry unless otherwise specified. Screening evaluations will generally occur on the day of randomization with the possible exception of local HMPXV diagnostic testing.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

Entry evaluations can occur at the time of screening or the day of randomization or registration. Participants should begin treatment the same day as randomization. Treatment must begin within 3 days after randomization or registration. **For those enrolled/followed remotely, treatment must begin within 5 days after randomization or registration.**

6.2.3 Post-Entry Evaluations

On-Treatment/Post-Treatment Evaluations
Evaluations should occur in the visit windows described in section 6.1.

Study Completion Evaluations
Day 57 evaluations will serve as the study completion evaluations.

Confirmation of Disease Progression
Participants in Arms A or B who develop severe disease (as defined in section 4.3.**2**) should be seen **in person or through telemedicine** for a confirmation of disease progression visit. This can occur at any point after randomization. If severe disease is confirmed by study personnel, participants should stop blinded study treatment and start a 14-day course of open-label tecovirimat. Participants should continue to be followed according to the SOE. Participants do not change to Arm C. If these participants are hospitalized and the study staff are unable to conduct an in-person visit, study staff should make efforts to ensure access to open-label tecovirimat. Sites should continue to follow participants **according to** the SOE when able to do so.

If participants progress to severe disease after day 7 while on blinded study medication or after blinded study medication has stopped, the site investigator should contact the CMC to discuss management.

Participants who report severe pain (7 or greater on the 11-point numerical rating scale) on day 6 or later should be seen **in person or through telemedicine** for a confirmation of disease progression visit. Participants should stop blinded study treatment and start a 14-day course of open-label tecovirimat. Participants should continue to be followed according to the SOE. Participants do not change to Arm C.

Of note, participants randomized to Arm A who subsequently receive open-label tecovirimat will receive a total course of tecovirimat longer than 14 days.

Confirmation of Lesion Resolution
If a participant reports lesion resolution, then a remote or in-person visit should be performed as soon as possible to confirm lesion resolution.

If the visit is done remotely, a targeted physical exam is not required.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized or Registered Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the entry visit.

Premature Study Discontinuation Evaluations
Evaluations **performed at the participant's last remote or in person visit** will serve as the study discontinuation evaluations for participants who prematurely discontinue from the study**; there are no additional premature discontinuation evaluations required.**

6.3 Instructions for Evaluations (Arms A, B, and C)

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the DAIDS AE Grading Table and AE reporting of adverse events requirements.

6.3.1 Clinical Evaluations

Medical History
The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days.

In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- HIV
- Diagnoses listed in section 4.3.2

Any allergies to any medications and their formulations must also be documented.

Medication History
A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Medication Category	Complete History or Timeframe
Antiretroviral therapy or pre-exposure prophylaxis	Within 30 days prior to study entry
Long-acting cabotegravir or rilpivirine	Within one year prior to study entry
Immune-based therapy, cancer therapy, immunosuppressants	Within 90 days prior to study entry
Prescription drugs (other)	Within 14 days prior to entry
Treatment for STIs	Within 30 days prior to study entry
Smallpox/HMPXV/MVA vaccine (childhood and recent receipt)	Complete history
Childhood vaccinations	Within 30 days prior to study entry
Prescription or over the counter medications or supplements listed in section 4.3.2 or section 5.4.2	Within 30 days prior to study entry

Complete Physical Examination
A complete physical examination at **screening for those seen in person should** include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac examination; abdominal examination; examination of the lower extremities for edema. The complete physical examination will also include signs and symptoms, diagnoses, and vital signs (height, weight, temperature, pulse, and blood pressure). **For those enrolled/followed remotely, sites should attempt to locate clinical care records including physical examinations.**

Targeted Physical Examination
A targeted physical examination is to include vital signs (weight, temperature, pulse, and blood pressure), and is to be driven by any previously identified or new adverse event, that the participant has experienced since the last visit or at this visit. **This examination is not required for those enrolled/followed remotely.**

Post entry, see section 8.2 for collection requirements for pregnancy.

Refer to section 7.2 for AE collection requirements.

Skin/HMPXV Assessment
This assessment will include:

- A comprehensive skin assessment to locate all HMPXV skin lesions (see MOP for details). This assessment should include numbers of lesions, location of lesions (face, eyes, scalp, neck, arms, legs, trunk, penis, other genital area, vulva, buttock, perianus, and oropharynx) and description of lesions (including presence of bacterial superinfection).
- Representative photos of lesions **either in person or via telemedicine (optional)**
- Recording of the location of sampled lesions.
- Designation of a lesion as the “Index Lesion” for the purposes of frequent sampling in the Additional Sampling cohort and for all participants to follow through the participant diary.
- An examination of the lymph nodes (femoral, axillary, cervical) **for in person assessments only**.
- An assessment for potential ocular complications including assessing for eye redness, eye pain, floaters, and any changes in vision.

Concomitant Medications
Post-entry, the following new and discontinued concomitant medications must be recorded:

- Changes in ART
- Treatment of STIs
- Opioid use
- Medications listed in section 4.3.2 or section 5.4.2.
- Any prescription or over the counter medications initiated during the 14 days of study drug treatment
- Other analgesics (e.g., acetaminophen, NSAIDS, topical analgesics) will be captured on Patient Diaries only
- Medications or treatments with expected activity against HMPXV (e.g., cidofovir, brincidofovir, trifluridine eye drops)
- Smallpox vaccination or vaccinia immune globulin

Study Treatment Modifications
Record all study drug modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than two consecutive doses since the last visit. Record any permanent discontinuation of treatment.

6.3.2 Laboratory Evaluations

At screening/entry all laboratory values must be recorded. **For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.** For post-entry assessments **conducted during in person visits**, record all laboratory values for AST, ALT, albumin, bilirubin (total and direct) regardless of grade; record abnormal laboratory findings as per section 7.2.

Hematology
Participants will have blood drawn for hemoglobin, hematocrit, WBC with differential, platelets, and RBC per the SOE. Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

At Entry/Day 1, blood should be drawn before study drug administration.

Serum Chemistries
Participants will have blood drawn for liver function tests (albumin, ALT, ALP, AST, total bilirubin, direct bilirubin, and total protein), and renal function tests (BUN, creatinine, potassium, and sodium) per the SOE. Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

At Entry/Day 1, blood should be drawn before study drug administration.

Urine or Serum Pregnancy
For participants of reproductive potential: Serum or urine b-HCG. (Urine test must have a sensitivity of ≤25 mIU/mL). Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs Pregnancy testing results must be obtained prior to randomization/registration.

Urine or serum pregnancy testing should be collected from clinical care if available but is not required for those followed remotely if it is not available. If pregnancy is suspected, then the participant is encouraged to obtain pregnancy testing.

Post-screening, pregnancy testing should be done any time pregnancy is suspected.

In the event of pregnancy occurring during the study, record pregnancy on an eCRF and record pregnancy outcome per section 8.2.

Syphilis Serology with Reflex to Confirmatory Testing
RPR or EIA will be performed in real time at a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. If the initial test yields positive results the alternate treponema test must be performed for confirmation. Positive syphilis tests should be treated locally with treatment of STIs captured on the CRF. Samples do not need to be repeated if they are available within 7 days prior to entry, but the results should be recorded on the CRF.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

Sites should provide appropriate STI treatment or refer as needed.

Gonorrhea and Chlamydia (Swab)
Oropharyngeal and rectal swabs (rectal swabs will only be done for participants ≥ 18 years of age) for gonorrhea and chlamydia will be performed in real time using a nucleic acid amplification testing (NAAT) or culture. Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Positive gonorrhea and chlamydia tests should be treated locally with treatment of STIs captured on the CRF. Samples do not need to be repeated if they are available within 7 days prior to entry, but the results should be recorded on the CRF.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

Sites should provide appropriate STI treatment or refer as needed.

Gonorrhea and Chlamydia (Urine)
Urine testing for gonorrhea and chlamydia will be performed in real time using a nucleic acid amplification testing (NAAT). Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any

network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Positive gonorrhea and chlamydia tests should be treated locally with treatment of STIs captured on the CRF. Samples do not need to be repeated if they are available within 7 days of entry, but the results should be recorded on the CRF.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

Sites should provide appropriate STI treatment or refer as needed.

HSV Testing (if indicated)
Swabs of genital, perianal, perioral or other ulcerative lesions suspicious for HSV should be swabbed and tested for HSV for participants with proctitis, swabs of the rectum should be obtained for HSV testing. Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Sites may obtain testing through the central laboratory for this study, which will generate a clinical laboratory report that can be used for management of the participant. Samples do not need to be repeated if they are available within 7 days prior to entry, but the results should be recorded on the CRF.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

Sites should provide appropriate STI treatment or refer as needed.

Anti-HIV-1/HIV-2
HIV-1/HIV-2 antibody testing will be done at a laboratory that possesses a CLIA certification, waiver, or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Samples do not need to be repeated if they are available within 7 days prior to entry, but the results should be recorded on the CRF. **For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.**

Participants should be referred for treatment of HIV as required.

HIV-1 RNA (for PLWH or on HIV PrEP)
Participants with HIV and those on HIV pre-exposure prophylaxis should have plasma HIV-1 testing per the SOE. Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in VQA and is currently certified.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

Absolute CD4 (for PLWH)
Obtain absolute CD4 testing per the SOE from a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or IQA certification (non-U.S. sites).

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

HBsAg, Anti HBs, Anti HBc
NOTE: Prior documentation of positive HBsAb is acceptable evidence that hepatitis B is not present.

In the absence of documented positive HBsAb, obtain HBsAb, HBsAg, and HBcAb prior to study entry. Samples must be tested by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

Hepatitis C Virus (HCV) Antibody with Reflex
Anti HCV with reflex to HCV RNA as part of screening/entry from a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs

If Anti HCV is positive, HCV RNA should be performed by a laboratory that possesses a CLIA certification or equivalent (U.S. sites) or at any network-approved non-U.S. laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. Samples do not need to be repeated if they are available within 7 days prior to entry, but the results should be recorded on the CRF.

For participants enrolled/followed remotely, values from clinical care assessments should be entered if available.

HMPXV Diagnostic Swabs (Skin, Oral, Rectal) (Presumptive Diagnosis Only)
Participants enrolled with laboratory-confirmed HMPXV do not need this testing.

Participants **seen in person** who have a pending test obtained locally should send samples for diagnostic testing to the designated central laboratory testing in real-time. This will generate a laboratory report that should be placed in the participant's medical record. Up to 3 samples should be submitted: 1) swab of skin lesions: If 3 or more skin lesions are present, then up to 3 lesions should each be swabbed with a

unique swab and the 3 swabs placed together in one tube of viral transport media (see the Lab Processing Chart (LPC)). If one lesion is present, then only 1 swab should be obtained. If no lesions are present (e.g., isolated proctitis or mouth lesions), then only the other two samples should be submitted, 2) rectal swab (if reporting rectal symptoms), 3) oropharyngeal swab (if reporting mouth lesions, mouth pain or sore throat).

NOTE: These specimens are in addition to the other specimens that are required by the protocol. For example, these participants will have skin lesion swabs sent for diagnostic testing in real time in addition to separate skin swabs sent for other protocol objectives to be batch tested.

Participants enrolled in person for whom both the local test (if one was obtained) and all clinically reported HMPXV tests from the central laboratory are negative should stop study drug. Follow up through remote or in person contact will occur 7 days after stopping study drug to assess for AEs.

For participants who are enrolled remotely, sites should verify that the local laboratory test confirmed HMPXV or verify that a local laboratory test confirming HMPXV is pending. No additional diagnostic testing is required. Participants enrolled remotely for whom the local HMPXV testing is negative should stop study drug. Follow up through remote contact will occur 7 days after stopping study drug to assess for AEs.

6.3.3 Study Drug Administration

Study Drug Administration
Study drug will be self-administered for 14 days with the exception of intensive PK visits where participants will be instructed to hold the morning doses of study drug and bring study drug to the research center in the original container.

Caregivers will assist with tecovirimat dosing for children who are unable to self-administer the tecovirimat capsules and those who require opening of the tecovirimat capsules and dissolution in water. Instructions for opening capsules and preparing and administering the tecovirimat solution are provided in the MOP.

Telephone Check
Study staff will perform a telephone check per the SOE to assess participant's symptoms and level of reported pain (on a numerical rating scale for adults and on a face scale for pediatric participants under the age of 18).

Open-Label Administration of Tecovirimat
Participants in Arms A and B reporting severe pain (7 or greater on the numerical rating scale) at day 6 will stop blinded study treatment and start a 14-day course

of open-label tecovirimat. Participants in Arms A and B who progress to severe disease as defined in section 4.3.**2** will stop blinded study treatment and start a 14-day course of open-label tecovirimat. These participants will be seen for an in-person visit to confirm indication for open-label tecovirimat and to receive a 14-day course of unblinded tecovirimat. These participants will continue to be followed per the SOE.

6.3.4 Participant-Completed Evaluations

Any evaluation listed as "participant completed" on the Schedule of Evaluations can be understood to be "participant or parent/guardian completed" in the case of pediatric participants requiring assistance.

Participant-Completed Study Diary
This will be completed per the SOE. The diary will collect the occurrence of new lesions, overall progress of lesions, clinical resolution (primary endpoint), and complete healing. The diary will track the progress of the designated "Index lesion" daily. This diary will collect the presence of specified HMPXV symptoms and the use of concomitant therapies to treat symptoms.

Participant-Completed Pain Scale
This will be a single item, the numeric rating scale for overall pain (on a numerical rating scale for adults and on a face scale **[the Wong-Baker FACES Pain Rating Scale]** for pediatric participants under the age of 18).

Participant-Collected Photographs of Lesions **(optional)**
Photographs of the index lesions, and other representative, new, or worrisome lesions will be obtained by participants **per the SOE** (see MOP for details). These photographs should be available to study staff to help determine whether clinical resolution has been achieved. Sites may be requested to submit certain photographs to the central database.

Participant-Completed Study Dosing Diary
This will be completed per the SOE. The dosing diary will collect the date and time of study drug doses.

Semen Collection (Optional)
Males will provide semen specimens as described in the MOP.

6.3.5 Questionnaires

Questionnaires are posted on the DMC Portal in the Forms Management Utility.

HMPXV Transmission Questionnaire
This questionnaire will assess **HMPXV exposure and** recent sexual activity.

Household Contact Questionnaire
This questionnaire will ask about household contacts of participants and additional cases of HMPXV within the household. This questionnaire will be updated during the protocol to ascertain the new cases within the household during study follow-up.

EQ-5D-5L Questionnaire
Participants will be asked about symptoms and diagnoses experienced using the EQ-5D-5L instrument.

Anal Health-Related Symptom Index (if indicated)
The A-HRSI asks participants to rate the degree of prevalence or impact of their physical symptoms, physical impacts, or psychological symptoms. Items are averaged across each domain, with higher scores indicative of worse health-related quality of life (HRQoL). The measure takes approximately 6-10 minutes to complete in person or either via telephone-facilitated interview or participant completed electronic form. This will be done in participants reporting anal pain or proctitis at baseline.

6.3.6 Samples Collected at Clinic **(in person visits only)**

Oropharyngeal Swabs, Rectal Swabs, and/or Skin Lesion Swabs
Oropharyngeal, rectal, and/or skin lesion swabs will be collected by site staff per the SOE (see MOP for details). Swabs will be collected for HMPXV testing, including viral levels, sequencing, and culture. For storage and shipping instructions, refer to the LPC.

The skin lesion swabs should include the “Index Lesion”. This lesion will be swabbed throughout study follow-up.

New skin lesions that have appeared since the participant’s last study visit should be swabbed (starting with in person visits after entry).

At Entry/Day 1, the swabs should be collected prior to the first dose of investigational agent/placebo.

Self-Collected Vaginal Swab
Self-collected vaginal swabs (see MOP for details). Collect before any gynecologic exam with cervical cytology at visits where both procedures are scheduled. Swabs should not be obtained during the 14 days after any cervical or vaginal biopsy or procedure. For storage and shipping instructions, refer to the LPC.

Breastmilk
Lactating women will be asked to express breastmilk during study visits per the SOE, if able. For interpretation, this sample should be collected as close to the PK blood draw as possible at day 8 and 15.

For storage and shipping instructions, refer to the LPC. Any remaining expressed milk should be discarded.

Ocular Fluid (For Eye Disease Only)
For participants with ocular involvement with HMPXV (i.e., conjunctivitis, ocular lesion, vision change), collect tear fluid **if possible** (see MOP for details). If bilateral disease is present, then collect two independent samples. For storage and shipping instructions, refer to the LPC.

Whole Blood for HMPXV DNA Levels
Whole blood HMPXV DNA levels will be performed per the SOE. For storage and shipping instructions, refer to the LPC.

6.3.7 Pharmacokinetics

See the A5418 Lab Processing Chart for instructions on PK sample collection, processing, and shipment.

ARV Trough PK (Plasma)
Collected only from participants on ARVs. Trough samples for ARV PK will be obtained per the SOE. The time of prior ARV dosing for all ARV will be carefully recorded. If participant's ARV regimen is twice daily, schedule the trough around the ARV metabolized by CYP3A4 (e.g., HIV protease inhibitors, cobicistat, maraviroc, NNRTIs). If an ARV trough is not possible because of evening dosing of daily ARV, attempt to obtain the samples at the same time post-ARV dose. For storage and shipping instructions, refer to the LPC.

Sparse PK
Entry/Day 1. **The first 8 participants <6 kg will have a single blood draw 2-4 hours after the first dose of study drug. This blood draw should only be performed if the participant is hospitalized and the blood draw will not result in exceeding maximum blood volume allowances. For storage and shipping instructions, refer to the LPC.**

Day 8. All participants not undergoing intensive PK will have a study drug trough obtained on day 8. This blood draw should occur 12 hours (+/- 2 hours) after study drug dosing for every 12-hour study product dosing and 8 hours (+/- 2 hours) for every 8-hour study product dosing. **Sparse PK sampling should be omitted if the participant has been off study drug >24 hours.** The time of prior study product dosing should be carefully recorded. For storage and shipping instructions, refer to the LPC.

Day 15. All participants will have a single blood sample obtained within 4 hours of study product administration. **Sparse PK sampling should be omitted if the participant has been off study drug >24 hours.** For storage and shipping instructions, refer to the LPC.

Confirmation of Disease Progression. Participants that complete this visit will have a single blood sample obtained. The time of prior study product dose will be carefully recorded. For storage and shipping instructions, refer to the LPC.

Intensive Pharmacokinetics including Children, Pregnant Participants, and Individuals taking Potent Inducting Concomitant Medications

A subset of participants will undergo intensive PK sampling per the SOE. The intensive PK visit should be performed within the protocol-specified window for day 8 if feasible. However, the intensive PK can be performed as early as the 8th dose of study drug (1st sample prior to 8th dose and intensive sampling after the 8th dose) for logistical issues. This subset will include:

- The first 8 pregnant persons enrolled in each trimester of pregnancy:
  - TM1: <13 weeks
  - TM2: ≥13 weeks to <27 weeks
  - TM3: ≥27 weeks
- At least the first 8 children enrolled in each weight band:
  - Weight Band 1: <6 kg
  - Weight Band 2: 6 kg to <13 kg
  - Weight Band 3: 13 kg to <25 kg
  - Weight Band 4: 25 kg to <40 kg
  - Weight Band 5: ≥40 kg
- Participants on potent inducers including rifampin, rifapentine, rifabutin, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir (these participants are encouraged but are not required to participate in intensive PK sampling)
- Any additional participants ≥18 years of age that agree to participate in this sampling (goal 24 participants).

Additional children may also undergo intensive PK sampling if, in the opinion of the protocol team, a confident determination regarding achievement of PK targets cannot be made based on the first 8 dose-evaluable children in a given weight band. The protocol team will provide frequent updates to all study sites via email regarding the number of dose-evaluable children enrolled in each weight band and will notify all sites when intensive PK sampling should be discontinued in each weight band. In the event that the protocol team determines that additional intensive PK sampling is required in a given weight band, all sites will be similarly notified.

Site staff will contact participants the day before their intensive PK visit to assess their recent adherence, remind them of the evening dose, to hold the morning dose, and to bring their study drug in the original container with them to their PK visit.

Participants will be asked to have nothing to eat or drink except for water for 8 hours before their visit. They will arrive at the facility in the morning. They will have a blood sample drawn **(pre-dose)**, eat a standardized meal, and then take

their study drug. Additional blood samples will be obtained at 1, 2, 3, 4, 6-, 8-, and 10-hours after dose of study drug. The intensive sampling will end at 8 hours for those taking study drug every 8 hours. **C**hildren who cannot fast for 8 hours are asked to fast for at least 2 hours prior to study drug administration. The time and type of last food should be recorded on the **eCRF**. Children will take the study drug with liquid or food appropriate for their age and size. The type of liquid or food consumed with the study drug will be recorded on the **eCRF**.

For storage and shipping instructions, refer to the LPC.

6.3.8 Stored Samples

Stored Plasma and DBS **(in person visits only)**
Blood plasma will be collected and stored for future testing, including but not limited to:

- Immunologic studies including markers linked to systemic inflammation (IL-6, TNF-a), inflammasome activation (IL-1beta, IL-18), interferon pathways (IP-10, type I interferon), neutrophil activation (MPO), monocyte activation (sCD14), as well as markers associated with coagulation or endothelial cell dysfunction (VWF, P-selectin, tissue factor)
- HMPXV seroconversion and antibody titers (among seroconverters)
- Additional quantitative HMPXV DNA
- Full viral genome sequencing will be performed from select samples that are detectable for HMPXV DNA to assess for signs of viral evolution and resistance to the investigational agent or immune responses. If sequence analysis suggests viral escape from the investigational agent (e.g., mutations in putative binding regions or epitopes), then phenotypic analyses may be pursued.

All Entry/Day 1 samples should be collected prior to the first dose of study drug.

For storage and shipping instructions, refer to the LPC.

Stored Serum **(in person visits only)**
Blood sera will be collected and stored for future testing, including but not limited to:

- Total and neutralizing antibody assays
- In vitro phenotypic analysis of drug susceptibility to investigational agent or other agents

All Entry/Day 1 samples should be collected prior to the first dose of study drug.

For storage and shipping instructions, refer to the LPC.

6.4 Instructions for Evaluations (Additional Sampling Cohort**, in person visits only**)

6.4.1 Informed Consent for Additional Sampling

Participants will provide consent **for additional sampling.**

6.4.2 Participant-Collected Samples and Assessments

Teach Oral, Rectal, Vaginal, and Index Lesion Swabs
Participants will be instructed on at-home collection of oropharyngeal, rectal, vaginal, and index skin lesion swabs (see MOP for details). The index skin lesion will be identified at baseline and swabbed longitudinally. Swabs will be collected per the SOE. Documentation that these instructions took place will not be recorded on an eCRF.

Oral, Rectal, Vaginal, and Index Lesion Swabs
Swabs will be self-collected by the participants as instructed per the SOE. See MOP for details. Swabs will be stored at the participant's home

Return/Review Swabs
Sites should remind participants of the need to return samples prior to the visit. Participants will return all samples stored at home at each in-person visit. For storage and shipping instructions, refer to the LPC.

6.4.3 Sample Collection

Urine
Urine specimens will be obtained per the SOE. For storage and shipping instructions, refer to the LPC.

Whole Blood for HMPXV DNA Levels
Whole blood will be collected for HMPXV DNA per the SOE. For storage and shipping instructions, refer to the LPC.

Sparse PK
Day 3. Participants in the Additional Sampling cohort will have a single sparse/convenience blood sample obtained for PK. The time of prior study product dose will be carefully recorded. For storage and shipping instructions, refer to the LPC.

Stored Peripheral Blood Mononuclear Cells (PBMCs) (optional)
Blood will be collected for PBMC isolation per the SOE. For storage and shipping instructions, refer to the LPC.

PBMCs will be collected only at select sites. Only sites certified by the IQA Cryopreservation PT Program at the Duke Human Vaccine Institute are required to collect PBMCs. Collection of PBMCs will be optional

PBMCs will be stored for future testing, which may include, but is not limited to, the following:

- Cellular immune responses between treatment and control samples, including assessment of T-cell responses to HMXPV proteins
- Cellular activation/exhaustion/memory differentiation phenotypes among innate or adaptive immune cells
- Host genetics

All Entry/Day 1 samples should be collected prior to the first dose of study drug.

6.5 Modifications for Participants **under 18 Years of Age**

At entry, pediatric participants **enrolled/followed in person** will be assessed as being sexually active or not sexually active.

Pediatric participants **enrolled/followed in person** will follow **Table 6.1-4**, with evaluations completed according to whether they are sexually active or not.

Pediatric participants enrolled/followed remotely will follow Table 6.1-5.

Pediatric laboratory evaluations **and collections** will vary according to weight band (see the LPC for details).

6.6 Virologic Assessments for Participants Enrolled/Followed Remotely

Skin Lesion Swabs
The index skin lesion will be swabbed by the participant at home at the times indicated in the SOE using the collection kit provided by the study (see MOP for details). In addition, the participant should swab a new skin lesion should one appear on day 6 or later. Only one new skin lesion should be swabbed. These samples may be omitted if testing kits/shipping kits are not available or if health ordinances preclude shipment of such samples by participants. Instructions for storage and shipment of samples will be provided to the participants.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for This Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met:

- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement
- All AEs Grade ≥3

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are:
  - Tecovirimat
  - Placebo for Tecovirimat

7.3.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Follow-up of Participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, the event is considered to be stable, or the participant is lost to follow-up. Study staff should obtain additional laboratory testing as needed to evaluate AE and confirm resolution. If an AE is ongoing at completion of participation in the study, only those that are investigational agent-related SAEs need continued follow-up to resolution or stability until 30 days past the last study visit.

7.5 Study Monitoring

The protocol leadership team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, data completeness, **and** adverse events pooled over arms.

The DAIDS Clinical Representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable.

The study will be reviewed by a NIAID-appointed DSMB at least annually. **Two** interim efficacy review**s are** planned **at** approximate**ly 33% and 67%** of total information (**i.e.,**

when 119 and 238 participants experienced clinical resolution events) **unless otherwise recommended by the DSMB**. In the event **that 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 statistician in consultation with the team. See section 10.0 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring are outlined in a Study Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Overdose
An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the dose described in the protocol.

Any overdose must be reported within 24 hours (follow the directions described in the Study Management section). The overdose itself is not to be reported as an AE. However, any AEs associated with the overdose are to be reported on relevant AE/SAE sections in the eCRF.

In the event of an overdose, the site investigator should:
1. Contact the protocol team immediately
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities
3. Obtain a plasma sample for PK analysis within 3 days of the date of the last dose of investigational agent/placebo if requested by the medical monitor
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Adverse Events
It is possible that some participants will experience transient or prolonged AEs during the trial. To minimize the effects on the eventual evaluation of the safety and efficacy of study treatment, the following principles will be used to determine study drug discontinuation.

Grade 1 or 2
Participants who develop Grade 1 or 2 AE or toxicity felt to be related to study treatment may continue study treatment at the discretion of the site investigator with close follow up. If a participant chooses to discontinue study treatment, the site should notify the CMC within 72 hours. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1 through completion of the study.

Symptoms that may be related to HMPXV should prompt **provision of or referral for** supportive care (see MOP for details).

Grade 3 or 4
Participants who develop a Grade 3 or 4 AE or toxicity thought by the site investigator to be related to study treatment should permanently discontinue study treatment and the site should consult with the CMC. The participant should be reevaluated weekly until the AE returns to Grade ≤2. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1 through completion of the study.

8.2 Pregnancy

Participants who are pregnant at the time of study entry will be assigned to Arm C.

Participants who become pregnant while on study should continue evaluations according to the section 6.1. Participants who become pregnant prior to day 29 can request unblinding to help guide decision making about their treatment of HMPXV.

At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome eCRF. If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact them regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Participants will be asked to bring the infant for a study visit four weeks after birth for a physical exam.

Participants who are enrolled/followed remotely will be asked to participate in a telemedicine visit to assess outcomes and to provide any relevant documentation of medical encounters to assess outcomes.

8.3 Breastfeeding

Given that HMPXV is spread by close contact and neonates are at high risk for severe disease, the CDC recommends that breastfeeding should be delayed until all lesions have resolved, the scabs have fallen off and a fresh layer of intact skin has formed.

At sites outside of the U.S. this is a more complex decision and the WHO recommends that breastfeeding practices be assessed on a case-by-case status accounting for the physical status of the mother and severity of disease. Protecting the child's survival while maintaining the nutritional intake of the infant is the priority [WHO 2022]. International sites will make the decision regarding breastfeeding on a case-by-case basis accounting for local recommendations.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see section 8.1 Toxicity).

- Request by participant to terminate treatment.
- Clinical reasons believed life-threatening by the physician, even if not addressed in the Toxicity section of the protocol.
- Found to be HMPXV negative on all diagnostic tests.
- Unable to take enteral medications. Intravenous formulations of tecovirimat may be obtained outside of the trial.
- Receipt of tecovirimat through a mechanism outside the trial (participants should still continue to be followed on study/off treatment).

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5418 is a randomized, placebo-controlled, double-blind study to establish the efficacy of tecovirimat for the treatment of individuals with laboratory-confirmed or presumptive HMPXV disease. Eligible participants will be randomized 2:1 to receive either tecovirimat or placebo for 14 days stratified according to time since prodromal symptom onset (≤5 days or >5 days) **and remote enrollment**. Participants enrolled with presumptive HMPXV diseases with both negative results from local tests and diagnostic testing through the central laboratory will stop study drug and continue to be followed per the SOE for 7 days after stopping study drug. These participants**, if enrolled in the randomized arms,** will be replaced.

Participants who progress to severe disease post-randomization as defined in section 4.3.2 will stop blinded study treatment and start a 14-day course of open-label tecovirimat. Participants who report severe pain from HMPXV at day 6 should stop blinded study treatment and start a 14-day course of open-label tecovirimat. Participants who switch to open-label tecovirimat will be followed per the SOE for randomized arms.

Participants will monitor skin lesions daily for 28 days after study entry with confirmation of the lesion resolution via remote or in person visit. Primary outcome measure is time to clinical resolution (all lesions scabbed, desquamated, or healed). Since primary outcome measure is only observable among participants with 1 or more skin or visible mucosal lesions that are able to be followed for resolution, participants who enroll with proctitis without any visible mucosal lesions or skin lesions will be excluded from the analysis of primary outcome measure.

Participants with severe disease, significant immunosuppression or skin conditions, who are pregnant, breastfeeding and children under age 18 will be enrolled to an open-label Arm C.

10.1.1 Estimand for Primary Objective

Table 10.1.1-1: Estimand Description and Attributes for Primary Objective 1.2

Estimand Description	The instantaneous risk ratio of clinical resolution of skin or visible mucosal lesions among people with laboratory-confirmed monkeypox 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	People aged 18 or older with laboratory-confirmed HMPXV disease with 1 or more skin or visible mucosal lesions
Variable(s)	Time to clinical resolution up to 28 days
Handling of Intercurrent Events	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. I**ndividuals **experiencing these events will be retained in the risk set through 28 days under subdistribution hazard model** (Composite strategy) Discontinuation of treatment for reasons other than disease progression or severe pain or death: all follow-up included regardless of treatment status (Treatment strategy)
Population-Level Summary Measure	Instantaneous risk ratio of Tecovirimat relative to no treatment

10.1.2 Estimand for Key Secondary Objective

Table 10.1.2-1: Estimand Description and Attributes for Secondary Objective 1.3.1

Estimand Description	The difference of **the mean** time-weighted average of pain intensity difference (**pre-treatment - post treatment)** over 5 days among people with laboratory-confirmed monkeypox who reported severe pain between those prescribed to Tecovirimat relative to no treatment
Treatment	Tecovirimat for 14 days
Target Population	People aged 18 or older with laboratory-confirmed HMPXV disease who reported severe pain (7-10 on the numerical rating scale)

Variable(s)	**Time-weighted average of pain intensity difference from pre-treatment to each day post treatment over 5 days measured** by 11-point **NRS**
Handling of Intercurrent Events	All-cause death: all **NRS measures** included up to death (While on treatment strategy) Treatment change due to disease progression or severe pain: all **NRS measures** included up to treatment change (While on treatment strategy) Discontinuation of treatment for reasons other than disease progression or severe pain or death: all **NRS measures** included up to treatment discontinuation (While on treatment strategy)
Population-Level Summary Measure	Difference **(Tecovirimat – no treatment)** in **mean** time-weighted average of pain intensity difference over 5 days

10.2 Outcome Measures

10.2.1 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.

10.2.2 Secondary Outcome Measures

10.2.2.1 Pain assessed by 11-point numerical rating scale for pain

10.2.2.2 Development of severe HMPXV in those without severe HMPXV at baseline

10.2.2.3 Levels of HMPXV in various compartments

10.2.2.4 Time to complete lesion healing defined as all lesions being re-epithelialized

10.2.2.5 Self-reported adherence

10.2.2.6 Summaries of Quality-of-life measures by EQ-5D-5L

10.2.2.7 Occurrence of Grade 3 or greater adverse events

10.2.2.8 All-cause mortality

10.2.2.9 Tecovirimat blood concentrations in children less than 18 years of age

10.2.3 Other Outcome Measures

10.2.3.1 Frequency and quantity of HMPXV oral, rectal, vaginal, urine, and lesion shedding in the presence and absence of tecovirimat treatment

10.2.3.2 HMPXV isolation by culture from oral, rectal, vagina and lesion in the presence and absence of tecovirimat

10.2.3.3 Virologic and immunologic measurements that correlate with disease severity

10.2.3.4 Number of lesions tracked longitudinally over the study period

10.2.3.5 Cellular and humoral immune responses to OPXV that are associated with disease progression and clinical efficacy of tecovirimat

10.2.3.6 Genomic variability in MPXV isolated from participants based on geographic and clinical differences

10.2.3.7 Presence of resistance at baseline and emergence of viral resistance during tecovirimat treatment

10.2.3.8 Summary measures of A-HRSI QoL assessment in participants reporting proctitis

10.2.3.9 Presence of bacterial sexually transmitted infections

10.2.3.10 Tecovirimat blood concentrations

10.2.3.11 ARV blood concentrations

10.2.3.12 Occurrence of new HMPXV positivity among household contacts

10.2.3.13 Occurrence of lesions that occur after initial resolution of symptoms and skin lesions

10.3 Randomization and Stratification

Eligible participants will be assigned using permuted block randomization in a 2:1 ratio to tecovirimat or placebo with dynamic institutional balancing to minimize imbalances at any clinical site. The randomization will be stratified by days from onset of symptoms (≤5 days or >5 days) **and remote enrollment**.

10.4 Sample Size and Accrual

Sample size estimation is based on the comparison of the primary outcome measure "time to clinical resolution" using log-rank test. The two key determinants of power are the total number of lesion resolution events, *E*, and the treatment-to-control ratio of the instantaneous risk (hazard) of lesion resolution, θ. The number of events required to achieve power $1-\beta$ to detect a ratio of θ using a two-tailed test with type I error rate α=0.05 is approximately

$$E = \frac{\left(1.96 + z_{\beta}\right)^2}{\{\ln(\theta)\}^2 q_0 q_1},$$

where z_{β} is the $100(1-\beta)$th percentile of the standard normal distribution and q_0 and q_1 are the treatment allocation [Schoenfeld 1983].

Table 10.4.1 displays the numbers of events and participants needed to achieve 80% and 85% power with 2:1 allocation for various scenarios. In total, 357 participants with clinical resolution up to 28 days after randomization are needed to detect a 40% improvement in the instantaneous risk of clinical resolution as measured by the instantaneous risk ratio (akin to a "hazard ratio" but for a positive outcome; values greater than one indicate improved outcomes) with 85% power and a two-sided type one error rate of α=0.05. Extrapolating the observed event rate of 77% from the 2007-2011 INRB/USAMRIID observational study yields a total targeted sample size of 464 participants.

Note that the 77% event rate is used to determine the sample size as a conservative approach. Assuming the hypothesized instantaneous risk ratio of 1.4 is accurate, the event rate on the tecovirimat arm will be higher than 77%. It was also taken into consideration of participants switching to open-label tecovirimat due to disease progression or severe pain as these participants will be considered as not achieving the clinical resolution, hence potentially lower the event rate.

A total sample size of 530 is planned while taking into account the following:

- **Two** planned interim **analyses**
- Potential loss to follow-up
- Participants enrolled with proctitis without any skin or visible mucosal lesions
- Participants switch**ed** to open-label tecovirimat due to disease progression or severe pain

Table 10.4-1: Number of Events and Participants Needed (assumed 77% will experience the event) to Have 80% and 85% Power with 2:1 Allocation before Accounting for Potential Drop-out

Instantaneous Risk Ratio	Scenario for 80% power		Scenario for 85% power	
	# Of Events Needed	# Of Participants Needed	# Of Events Needed	# Of Participants Needed
1.3	514	668	587	763
1.4	312	406	357	464
1.5	215	280	246	320

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 lesion resolution events have occurred (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. For example, if the overall event rate is 60%, then the suggested number of participants would be 357/0.60 = 595 (before accounting for potential drop out). Because this is an event-driven trial, increasing the sample size the midway point will not change the planned timing of future interim analyses (since these are fixed based on the 357 events needed to power the trial) and will not require an update to any pre-specified interim monitoring bounds discussed below. Full details of the sample size re-estimation plan will be provided in the statistical analysis plan.

Pain Intensity Reduction

Pain intensity is assessed by participants using an 11-point NRS from 0=no pain to 10=worst possible pain. Pain intensity scores were collected at Baseline (prior to treatment initiation**, Day 1**) and daily after for 28 days. Pain intensity difference is calculated by subtracting the pain intensity at each time point from the pain intensity at baseline. Positive numbers indicate a reduction in pain [maximum (max)=10 at each time point] and negative numbers indicate an increase in pain [minimum (min)=-10 at each time point]. Since the protocol requires participants to switch to open-label tecovirimat on **D**ay **6** due to severe pain, the primary pain intensity difference will be summarized over the first 5 days after treatment initiation using an average summed pain intensity difference (SPID). The average SPID5d score is the time-weighted average of the pain intensity difference from **D**ay **2** to **D**ay **6**, more specifically it is defined as the average of the sum of the pain intensity differences at each measurement multiplied by the duration in days since the previous measurement from **D**ay **2** to **D**ay **6**. The range of average SPID5d is -10 to 10. Comparisons of the average SPID5d between the two randomized arms will use a two-sample t-test.

Conservatively assuming 50% of enrolled participants in Arms A and B reporting pain at baseline with approximately 10% reporting severe pain (7-10), and approximately 30% reporting moderate pain (4-6), N=213 (and separately in each pain category) are used as subpopulations for evaluating the pain reduction between the two randomized arms. The table below shows the effect size of the difference to be detected with at least 80% power using a two-sided t-test at 5% significance level. Any labeling claim based on pain

assessment as a secondary endpoint will be made only if the primary endpoint demonstrates statistically significant treatment effect on symptom resolution as a sequential testing strategy. This is to account for any potential multiplicity or type-I error inflation due to testing multiple endpoints.

Table 10.4-2: Effect size to be detected with at least 80% power under various assumed SD.

Pain Categories Reported at Baseline	Tecovirimat (N)	Placebo (N)	SD*	Difference to be Detected in SPID5d
Severe	36	18	1.5	1.30
			2.0	1.72
Moderate	106	53	1.5	0.73
			2.0	1.00
Moderate/severe	142	71	1.5	0.63
			2.0	0.85

* SD estimated from Farrar, 2001.

Sample Size Justification for Intensive Virologic Sampling Group

With 100 participants undergoing intensive daily mucosal and lesional viral sampling, assuming 85% with evaluable measures (approximately 56 in tecovirimat group and 28 in placebo group), the study will have at least 80% power to detect a difference of 0.7 SD in time-weighted average of viral reduction in HMPXV log10 viral load from day 1 to day 15 between treatment groups using a 2-sided 5% t-test. For example, assuming the time-weighted average change in HMPXV from **D**ay 1 to **D**ay 15 in the placebo group will be -1.5 log10 copies/mL with a corresponding SD of 1, the study will have at least 80% to detect a 0.7 log difference in time-weighted average change in log 10 viral load between the treatment groups.

Accrual

The study accrual rate will depend on the status of the monkeypox outbreak at each site, as estimated based on the number of sites, the study is expected to complete accrual of randomized groups in approximately **20** weeks with weekly enrollment projections below:

Week	Enrollment
1	**3**
2	**5**
3	**8**
4	**13**
5	**21**
6	**34**
7-**20**	**34**

10.5 Data and Safety Monitoring

A NIAID-appointed Data and Safety Monitoring Board (DSMB) will monitor ongoing results to ensure the well-being and safety of participants as well as study integrity. The DSMB will be asked to recommend stopping the study early for efficacy only when there is substantial

evidence of a treatment benefit. The operation of the DSMB is governed by the NIAID DSMB Charter.

10.5.1 Interim Monitoring Guidelines

The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor the primary outcome measure as a guide for the DSMB **with** an overall two-sided type-I error rate of **5%**. **Two** interim efficacy **analyses are planned** at approximately **33**% **and 67%** of total information unless otherwise recommended by the DSMB. The statistical analysis plan will provide a more detailed description of the stopping boundaries used for interim analyses.

Table 10.5.1-1: Efficacy Boundaries Based on Planned Timing of Interim reviews using O'Brien-Fleming Spending Function

Analysis	Number of Participants with Lesion Resolution Events	Efficacy Boundary	Nominal α Level
Interim **#1**	**119**	**3.371**	**0.0002**
Interim #2	**238**	**2.511**	**0.012**
Final	357	**1.993**	**0.046**

Efficacy boundaries estimated using East 6.

In the absence of a significant difference between randomized groups that leads to termination of the randomized comparison, the study team believes that 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.

The DSMB will monitor operational futility. 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. As a benchmark, a switch rate to open-label tecovirimat of more than 20% would be cause for concern. In addition, the DSMB will monitor the loss to follow-up (LTFU) rate. As a benchmark, an overall LTFU rate in the randomized groups of more than 10% would be cause for concern.

A separate unblinded statistical team will prepare these closed reports for DSMB review and recommendations. In considering its recommendations, the DSMB may also take into account the totality of the evidence from the trial data (including effects on secondary and other outcomes and in key participant subgroups) and any other information from external sources it considers relevant (e.g., results from other trials, emerging information on the nature of the disease and its epidemiology). For example, the DSMB might make recommendations based on substantial evidence for a difference between randomized arms in pain reduction **or recommend modification to study**

follow-up based on evidence of a difference in treatment effect between participants who were enrolled remotely versus in-person.

10.6 Analyses

The following sections provide a brief overview of the analysis considerations. Prior to the start of enrollment, a detailed Statistical Analysis Plan fully delineates all planned statistical analyses. In the event of a DSMB recommendation to stop the trial for efficacy at interim review, full analysis and publication of the primary trial results will be prepared based on the frozen data for the DSMB meeting. Subsequent analyses (including a database prepared for future data-sharing requests) will be performed based on the final trial database including all final study termination visits. In the event of a DSMB recommendation to stop for operational futility, full analysis and publication of the primary trial results will be performed based on the final trial database including all final study termination visits

Descriptive summaries of the distribution of continuous baseline variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages. Statistical comparisons will be performed using two-sided significance tests with a 5% Type I error **rate**.

The following study populations or analysis sets are used for addressing the study objectives. This terminology is used throughout this protocol and the Statistical Analysis Plan.

Safety **set** for the randomized groups: all participants who (i) were randomized and (ii) take at least 1 dose of tecovirimat or placebo.

Primary efficacy **set** for the randomized groups: all participants who (i) were randomized; (ii) with laboratory-confirmed monkeypox; (iii) with 1 or more skin or visible mucosal lesions that are able to be followed for resolution.

Secondary efficacy **set** for the randomized groups: all participants who (i) were randomized; (ii) with laboratory-confirmed monkeypox.

Open-label **set**: all participants who (i) enrolled to Arm C and (ii) take at least 1 dose of tecovirimat.

10.6.1 Primary Outcome Measure

Analysis of the time to clinical resolution will be restricted to the primary efficacy population for the randomized groups as defined above. As outlined in primary estimand 10.1.1, intercurrent events of all-cause death, use of other antivirals with expected activity against HMPXV, and disease progression or severe pain leading to treatment change will be considered as **competing events under the subdistribution proportional hazard model (Fine and Gray, 1999)** using a composite variable strategy. More specifically, those who died, used other antivirals with expected activity against HMPXV, or experienced disease progression or severe pain leading to treatment change will remain in the risk set

with their time to clinical resolution censored at 28 days. The intercurrent event of discontinuation of randomized treatment for reasons other than disease progression or severe pain or death will be treated using a treatment policy strategy where all follow-up is included regardless of treatment status. Instantaneous risk ratio of clinical resolution will be **tested and** estimated with its confidence interval using a **subdistribution** proportional hazards model. **Cumulative incidence functions (CIFs) will be used to estimate the incidence of clinical resolution and tested between the two treatment groups using Gray's test accounting for competing risk.** For handling of missing data, participants' losses to follow-up will be assumed as non-informative and will have their time to clinical resolution censored at the time of last **evaluation of lesions**.

As a supportive analysis, **cause-specific instantaneous risk ratio will be estimated to aid the understanding of the effect of tecovirimat on the incidence and the instantaneous risk of clinical resolution. For this analysis,** all-cause death, use of antivirals with expected activity against HMPXV, and switching to open-label tecovirimat due to disease progression or severe pain will be **censored at the time of event.**

Pre-specified subgroup analysis will be conducted for the primary outcome measure using the statistical test for interaction for the following: duration of symptoms (≤5 or >5 days), presence of moderate to severe pain (<7 or 7-10 on the 11-point NRS for pain), **remote enrollment,** receipt of monkeypox or smallpox vaccine, age, sex, and race. Additional subgroups may be identified and evaluated. Full details of planned subgroup analyses will be provided in the statistical analysis plan.

10.6.2 Secondary Outcome Measure

Unless otherwise specified, analyses of secondary outcome measures will use secondary efficacy population as defined above.

Pain intensity reduction will be assessed using time-weighted average of sum pain intensity difference (SPID). Average SPID5d (SPID from study day 2 to day 6) will be calculated in all enrolled participants. The primary analysis will be restricted to those who reported severe pain (NRS 7-10) at baseline. Calculation of SPID5d for participants who switched to open-label tecovirimat or discontinued randomized treatment prior to study day 6 will include NRS reported prior to open-label tecovirimat initiation or discontinuation of randomized treatment. Comparison between the randomized arms will use a two-sample t-test. Two-sided 95% confidence interval on the difference between randomized groups will be calculated. Secondary analysis will compare the average SPID5d separately in those reported moderate or severe pain (NRS 4-10) at baseline and in all enrolled participants. Average SPID over the treatment period and absolute change from baseline to day 2 through day 6 will also be evaluated.

Time to complete lesion healing will be restricted to the primary efficacy population and analyzed using the same approach for the primary outcome measure.

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

Levels of HMPXV will be summarized by randomized groups and by sampling locations. The proportion of participants with undetectable HMPXV at each evaluation time point will be estimated with 95% confidence intervals where appropriate and plotted over time. Comparisons between randomized groups will use a **two-sample Z-test**.

Analysis of occurrence of grade 3 or greater adverse events will be limited to safety population as defined above. Grade 3 or greater adverse events will be tabulated by randomized groups and proportion of participants reporting such AE will be compared using **a two-sample Z-test**.

All-cause mortality will be summarized by randomized groups and described in detail. Comparison of time to death between randomized groups will be made using a logrank test if there are enough events warrant such analysis.

Self-reported adherence, summaries of quality-of-life measures by EQ-5D-5L, and summaries of A-HRSI QoL assessment will be summarized by randomized groups and compared using Wilcoxon rank-sum test **or Chi-square test as appropriate**.

As Arm C is an open-label arm, analyses of all outcomes will be restricted to the open-label population as defined above and will be descriptive only.

Please see section 11.0 for analyses of PK outcomes.

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 **measure**. 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 section 10.5.1**, confirmatory analysis of the secondary pain outcome **measures** will be performed **at the same nominal significance level; the Benjamini-Hochberg method will be used to account for multiplicity of testing of pain outcome measures**. 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.**

10.7 Unblinding

Planned Unblinding
Participants will be unblinded at completion of the study. Please refer to ACTG SOP-123 Unblinding Participants for details.

Sudden/Unplanned Unblinding
The decision to unblind one or more arms of an ongoing study is made by the team in conjunction with the relevant Scientific Committee and the Executive Committee. This can occur based on a recommendation from the DSMB or an SMC or the results of another trial (also see the DAIDS SOP "Termination of a Trial or a Single Treatment Arm").

If the decision is made to unblind, participants should be unblinded as soon as possible. Unblinding is conducted through the DMC, which sends treatment assignments to the sites soon after the unblinding decision. Every effort should be made by the sites to contact participants who have completed follow-up in order to explain the study results.

When a treatment comparison is unblinded based on an interim analysis, the results of that interim analysis must be reported in publications. Data from visits that occurred before the interim review but that were not in the database at the data cutoff date have little potential for bias and may be reported with a comment. Data from visits that occurred after unblinding are potentially biased and must not be used if the intent is to claim that all the data are from a blinded study. In unblinding due to both "interim analysis" and the "other trial results" situations, if analyses are reported on clinical data or samples taken after the unblinding date, the conditions under which these data were gathered must be made clear in any publication.

11.0 PHARMACOLOGY PLAN

The pharmacokinetics of tecovirimat have been established in healthy volunteers receiving 600 mg every 12 hours (shown in Table 11.0-1). Pharmacokinetic data with tecovirimat were primarily generated in healthy volunteers. PK data in individuals with active disease are extremely limited. This study will determine the pharmacokinetics of tecovirimat using a combination of intensive and sparse sampling. Intensive PK sampling will be optional for participants in Arms A/B, with a goal of having complete, evaluable PK profiles for 10 participants on active tecovirimat at day 8.

Table 11.0-1: Tecovirimat Pharmacokinetics in Healthy Volunteers

PK Parameter	
AUC (ng*hr/mL), mean (CV%)	28,791 (35%)
C_{max} (ng/mL), mean (CV%)	2106 (33%)
C_{min} (ng/mL), mean (CV%)	587 (38%)
Protein binding	77-82%
Half life	20 hours
CL/F (L/hr)	31
V/F (L)	1030

The pharmacokinetics of tecovirimat have not been assessed in pregnant persons. Intensive PK sampling will be performed in the first 8 pregnant persons enrolled in each trimester. The PK will be compared with historical data and values obtained from participants intensively sampled in Arms A/B.

There are very limited PK data for tecovirimat in children. Tecovirimat weight-band doses and administration methods for children in this study mirror those recommended by CDC for children ≥6 kg, but modeling and simulation indicated some refinements to dose and frequency for those <6 kg (described below). Intensive PK sampling will be performed in the first 8 children enrolled in each weight band. The weight bands are: (WB1 <6 kg, WB2 6 kg to <13 kg, WB3 13 kg to <25 kg, and WB4 25 kg to <40 kg, WB5 ≥40 kg) The PK in each weight band will be compared to historical data and values obtained from participants intensively samples in Arms A/B. Tecovirimat doses may be adjusted and additional intensive PK data performed if the PK, safety and efficacy data in the first 8 children suggest dose adjustments are needed. Sites must notify the CMC prior to initiating tecovirimat in children <6kg to verify the starting dose.

Tecovirimat is metabolized by uridine glucuronosyl transferase (UGT) enzymes 1A1 and 1A4. Tecovirimat is not a substrate for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Tecovirimat is not a substrate for P-gp, BCRP, OATP1B1, or OATP1B3. Potent inducers such as rifampin, rifapentine, rifabutin, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir may lower exposures of tecovirimat. Participants on these potent inducers will enroll into Arm C and strongly encouraged to undergo intensive PK sampling.

Tecovirimat is not an inhibitor of CYP1A2, CYP2D6, CYP2E1 or CYP3A4, and is not an inducer of CYP1A2. Tecovirimat inhibits BCRP in vitro, but is not an inhibitor of P-gp, OATP1B1 and OATP1B3, OAT1, OAT3, or OCT2.

There are limited in vivo data on the drug interaction potential of tecovirimat. The potential for tecovirimat to act as a perpetrator in drug interactions has been evaluated in healthy volunteers using five CYP probe substrates: flurbiprofen (CYP2C9), bupropion (CYP2B6), repaglinide (CYP2C8), omeprazole (CYP2C19), and midazolam (CYP3A4). The AUC for flurbiprofen was not altered, indicating no impact on CYP2C9. Bupropion was minimally altered (16% reduction), indicating no significant impact of tecovirimat on CYP2B6 substrates. However, AUCs of the other three drugs were altered. Repaglinide AUC was increased 29% and there was a high incidence of hypoglycemia with the combination. Omeprazole AUC was increased 73%, and while this is not a clinically significant impact for omeprazole, other CYP2C19 substrates with narrow therapeutic indices may have increased exposures. Midazolam AUC was reduced 32%, indicating tecovirimat has CYP3A induction potential. This is relevant for drugs that are substrates for CYP3A4 which may have reduced exposures and compromised therapeutic effects (e.g., HIV protease inhibitors, cobicistat, maraviroc, some NNRTIs). While a 30% reduction has historically been considered a clinically relevant threshold for reduced ARV exposures, newer ARV

have wider therapeutic indices and tecovirimat is administered for a relatively short duration (14 days). PWH are disproportionally affected by HMPXV and likely to receive tecovirimat in the absence of interaction data in practice and thus, this controlled clinical trial represents a unique and important opportunity to assess the interaction potential. This study will compare ARV concentrations with and without tecovirimat and measure HIV-1 RNA during study drug administration.

Selection of Pediatric Doses

The tecovirimat doses selected for pediatric participants in this study include the FDA approved doses for older, larger children which had dosing down to 13kg. These doses were determined through extrapolation from adult PK data with the goal of achieving exposures comparable to the observed exposure from 600mg every 12 hours. A similar approach was taken to doses for pediatric patients less than 13 kg for this study. We used standard allometric scaling to extrapolate to lighter pediatric participants using the weight allometric exponent of 0.75 for CL and Q and 1.0 for V1 and V2. However, in addition to PK differences based on size, in newborns and young infants, immature metabolism also needs to be considered. Since tecovirimat is primarily eliminated through metabolism by the UGT1 family, we applied the ontogeny pattern of raltegravir metabolism, also a UGT1A substrate [Clark, 2019], in combination with allometric scaling to assess potential dosing regimens. Absorption was assumed to be similar to adults. The WHO weight band groups were used to the extent possible and median values from CDC NHANES growth data base used to link age and weight in simulations.

The reported CL/F in adults is 31 L/h in the tecovirimat package insert. This projects an $AUC_{0\text{-}24}$ at steady of 38.7 mcg*h/mL with 600mg given orally every 12 hours in adults (AUC=F*Dose/CL). This equates to an average concentration (Cave) at steady-state of 1.6 mcg/mL (Cave= AUC/Dose Rate). The reported steady state trough on this dose is 0.587 mcg/mL The CV for tecovirimat AUC, Cmax, and Cmin are reported to be between ~30-40% thus the 10^{th} percentile for Cave in adults is ~0.9 mcg/mL.

FDA-approved tecovirimat doses in adults are well above the concentrations needed to prevent smallpox infection in the non-human primate model [Leeds, 2013]. The 3 mg/kg/daily NHP dose was identified as the lowest efficacious dose using both Kaplan Meier and ROC analysis. This dose results in a steady-date $AUC_{0\text{-}24}$ of ~3-4 mcg*h/mL (Cave=~0.15 mcg/mL). Thus, the adult human tecovirimat dose provides Cave exposures approximately ~10 times higher and uniformly greater than the average NHP exposure from the efficacious NHP dose of 3 mg/kg.

The pediatric dosing regimens proposed are predicted to maintain Cave of 1-2 mcg/mL after the first week of life. These concentrations are several times above those shown to be effective for pox infection in primates, but safe in adults. Proposed doses include age and weight considerations for neonates to account for immature UGT1 metabolism.

11.1 Pharmacology Objectives

11.1.1 To define the pharmacokinetic (PK) profile and PK-pharmacodynamic (PD) associations for tecovirimat in HMPXV.

11.1.2 To assess the potential for drug interactions between tecovirimat and antiretrovirals among PWH.

11.1.3 To determine the steady-state tecovirimat AUC_{tau} and C_{tau} in children.

11.1.4 To describe PK of tecovirimat in pregnant persons.

11.1.5 To describe the PK of tecovirimat in persons receiving potent inducers rifampin, rifapentine, rifabutin, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir.

11.2 Pharmacology Study Design

Participants will undergo PK testing per section 6.3.7.

Non-Compartmental Tecovirimat PK Analysis of Intensive PK Data

Intensive PK sampling will be performed in select participants (see section 6.3.7). From intensive PK samples, the following PK parameters will be observed or calculated via non-compartmental analysis:

- C_{max} is defined as the maximum concentration observed during the dosing interval.
- T_{max} is defined as the time at which C_{max} occurs.
- AUC_{tau}, the area under the concentration-time curve over the dosing interval, will be calculated either using the linear or log-linear trapezoidal rule.
- $AUC_{0\text{-}inf}$, the area under the concentration-time curve from time 0 extrapolated to infinite time, will be calculated either using the linear or log-linear trapezoidal rule.
- Apparent clearance (CL/F) will be calculated as dose divided by $AUC_{0\text{-}inf}$.
- Apparent terminal elimination half-life ($t_{1/2}$) can be estimated using $\ln(2)/k_e$, where k_e is the first-order rate constant and is obtained from the lambda z parameter calculated by standard pharmacokinetic software packages.
- C_{tau} is defined as the concentration at the end of the dosing interval.

Tecovirimat Population PK Modeling

The tecovirimat PK parameter estimates derived from non-compartmental analysis will be used as prior initial estimates when constructing a population pharmacokinetic model of tecovirimat via nonlinear mixed effects modeling. Both sparse and intensive PK sampling data will be leveraged for model development. Several covariates will be evaluated in the model including disease severity, renal function, hepatic function, age, weight, sex, race (black vs. Non-black), pregnancy (yes/no), and inducing medications (yes/no). Phoenix (Certara) will be used for noncompartmental and population PK analysis.

Tecovirimat PK/PD Analysis

To examine the association of tecovirimat exposure with clinical outcomes, participant-specific estimates (from the population PK models) of tecovirimat clearance (or another PK parameter) will be used as independent variables in models of clinical outcomes as the dependent variable. Drug exposure parameter estimates may also be used as independent variables in models for the occurrence of selected toxicities. Further details will be provided in the PK SAP.

Adherence may be used as predictor variable(s) in evaluations of associations with treatment response.

PK in Pregnant Participants

Tecovirimat PK in the pregnant participants will be determined using non-compartmental methods and summarized using descriptive statistics. The AUC_{tau} and C_{tau} in pregnant women will be compared to these values in non-pregnant participants undergoing intensive PK in Arms A/B and historical data.

PK in Children

Geometric mean AUC_{tau} and C_{tau} in each weight band will be compared to these values in participants undergoing intensive PK in Arms A/B and historical data. The relationship between tecovirimat AUC_{tau} and C_{tau} quartiles and tecovirimat safety and efficacy will be examined in the first 8 children in each weight band. If the protocol team determines dose adjustments are needed, additional intensive PK may be performed on the adjusted doses. Initial tecovirimat doses for neonates are based on experience with raltegravir, another antiviral drug primarily metabolized by uridine glucuronosyltransferase enzymes. Initial tecovirimat starting doses for neonates are shown in Table 5.1-2. PK for each neonate will be used to inform dosing of subsequent neonates enrolled.

ARV PK

ARV PK will be compared within person with (**D**ay 8 and 15) v**ersus** without tecovirimat (**E**ntry). ARV will also be compared in persons on tecovirimat vs. Placebo. If there are insufficient numbers of participants on **a** particular ARV, we will evaluate classes of ARV in the population PK model covariates. If the ARV class reduces the objective function by 3.84, this is analogous to a $p<0.05$ in a Chi square test.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity [FDA 2021]. The site must make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. The Data Management Center will configure Medidata Remove Source Review (RSR) and make it available to all sites. We encourage sites to use the DMC provided Medidata RSR platform but other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, and direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendices I-IV) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, U.S., and international regulatory entities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other country-specific government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

The U.S. government does not consider the West African clade of monkeypox virus as meeting the definition of Category A infectious substance under the Hazardous Materials Regulations (HMR). Therefore, specimens and material suspected or confirmed to contain the West African clade of monkeypox virus can be shipped as UN 3373 Biological Substance, Category B [CDC 2022].

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: INFORMED CONSENT AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR ADULTS AND PARTICIPANTS REACHING AGE OF MAJORITY (AOM) **WHO ARE ENROLLED/FOLLOWED IN PERSON**

Sponsor / Study Title:	National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"
Protocol Number:	A5418
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Address:	«PiLocations»

SUMMARY

PURPOSE

This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate how well tecovirimat works for the treatment of human monkeypox virus infection and if the study drug is safe in people. The study will also help us understand more about how human monkeypox causes disease and how the body fights off infection.

STUDY DRUG

Study drug will be either tecovirimat or placebo for tecovirimat. A placebo looks like a "real" drug but does not have any active drug in it. Twice as many people will receive the active drug in this study, so you are more likely to receive the active study drug. Tecovirimat or placebo for tecovirimat will be taken two or three times a day for 14 days.

NUMBER OF PARTICIPANTS

530 people will participate in this study and receive active study drug or placebo. Children, people who are pregnant, people with severe disease or severe skin conditions, people taking certain medications that may lower tecovirimat levels in the blood, and people whose immune systems are weakened will be in a separate group that receives tecovirimat with no possibility of receiving placebo – there is no limit to how many people will be assigned to this group.

LENGTH OF STUDY

Your participation in this study will last about 2 months. If you are pregnant, we will contact you periodically to see how your pregnancy

goes and to know the health of your child. We would also like you to bring your baby in for a study visit about 4 weeks after they are born so we can examine the baby.

REQUIRED ACTIVITIES

If you participate in this study, the following study procedures are required:

- You will have physical exams
- You will record your symptoms daily
- You will provide blood and urine samples
- You will provide (or a study team member will obtain) swabs of the sores on your skin, mouth, vagina, and rectum,
- You will complete questionnaires about your symptoms

RISKS

The most common side effects people receiving tecovirimat have noticed are:

- Headache
- Nausea (feeling like you want to vomit)
- Vomiting
- Stomach pain

BENEFITS

We do not know if you will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat your infection and prevent it from getting worse, but we cannot make any guarantee.

OTHER CHOICES

There is no proven way to treat human monkeypox virus. You may benefit from supportive therapy (such as intravenous [IV] fluids, or medicine to control fever or pain) and antibiotics for any bacterial infections you may have. There may be other medications that your study doctor may consider using to treat your infection. Tecovirimat may be available outside this study. There may also be research studies looking at other new treatments for poxviruses.

INTRODUCTION

You are being asked to take part in this research study because:

- You are known to have monkeypox virus or your healthcare providers suspect you have monkeypox virus
- You have had symptoms for fewer than 14 days
- You have at least one active, not yet scabbed lesion, or proctitis (inflammation of the lining of the rectum) or mouth sores

This study is sponsored by the National Institutes of Health (NIH). The study doctor is in charge of this study at this site. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Monkeypox is caused by a virus. This virus is most often spread by close contact with someone who has monkeypox. Illness caused by monkeypox virus infection usually starts with a fever and feeling poorly before a rash begins. The rash looks like raised bumps and pus-filled blisters (called lesions). The lesions then crust, scab, and fall off after about 2-4 weeks, sometimes leaving a scar.

Since Spring 2022, monkeypox has rapidly spread throughout the world, with more than **70,000** cases in **107** countries and more than **26,000** cases in the United States reported as of **September** 2022.

Tecovirimat is a drug that may help to treat infections caused by pox viruses. Tecovirimat is approved by the Food and Drug Administration (FDA) to treat smallpox in adults and children, but its use in this study is considered investigational. An investigational use is one that has not been approved by the FDA. Tecovirimat has been approved based only on data from animals. We don't know for sure if it works to treat any infections in people. The FDA has reviewed information on tecovirimat and determined that tecovirimat may help treat infection, including serious or potentially life-threatening disease, from poxviruses.

Tecovirimat has been given safely to some people with monkeypox in the recent outbreak and is currently being studied in several ongoing studies outside of the U.S., but none of the studies have shown whether or not this study drug works to treat monkeypox. The safety of tecovirimat has been evaluated in a study with adult participants without monkeypox. Tecovirimat was generally safe and well tolerated – the risks are noted below.

We are doing this study to see if tecovirimat is safe and whether it helps treat monkeypox in people. The study will also help us understand more about how human monkeypox causes disease and how the body fights off infection with monkeypox.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

<u>Screening/Entry Visit</u>
If you would like to be in this study, after you have read and signed this consent form, you will have a visit to make sure you meet the requirements for joining the study.

We will collect some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count and viral load if you

are living with HIV) information. We will collect this information even if you do not start study drug.

At this visit:

- You will have a physical exam and answer questions about your medical history and any medications you have taken recently.
- You will have an exam of your skin to identify where you have monkeypox lesions. You will have to remove your clothes and wear a robe for this exam. Site staff will **ask to** take pictures of your skin lesions. **You do not have to agree to have these pictures taken. You can participate in this study regardless of what you decide about having pictures taken. If you agree, t**hese pictures will be used so that the study staff can follow how well your lesions are healing. These pictures will not be used for any other purpose without your written permission. If you have lesions on your face, it is possible that you will be able to be identified in these pictures. **These pictures may be stored in your electronic medical record. If** these pictures are stored **in a study database**, they will be stored securely with a code instead of your name. **Please discuss how pictures are stored at your clinical research site.**
- If you can become pregnant (and you are not already pregnant), you will give a blood sample or urine sample for a pregnancy test.
- Study staff will collect the following swabs:
  - Swabs from your skin, mouth/throat, and rectum if you do not have a lab diagnosis of monkeypox. The study doctor may be required by law to report the result of this test to the local health authorities.
  - Swabs of any lesions you have that may be caused by herpes
- You will answer questionnaires about any pain your lesions may be causing you

If you qualify for the study, you will have some more tests:

- You will have blood drawn for the following tests:
  - HIV-1 testing. The study doctor may be required by law to report the result of this test to the local health authorities.
  - CD4 count (if you are living with HIV)
  - HIV viral load (if you are living with HIV)
  - Liver and kidney tests and blood counts
  - Tests for Hepatitis C, Hepatitis B (unless this information is in your medical records), and syphilis. The study doctor may be required by law to report the results of these tests to the local health authorities.
  - A test to measure concentrations of medicines used to treat or prevent HIV (if you are living with HIV or taking medications to prevent HIV infection)
  - Tests to see the levels of monkeypox virus in your blood
  - Stored blood for future study-required testing
- You will be asked to give a urine sample for the following tests:
  - Tests for sexually transmitted infections. If you have a positive test for a sexually transmitted infection, you will be referred to your regular doctor for evaluation and treatment. You can join this study if you have a sexually transmitted infection. The study doctor may be required by law to report the result of these tests to the local health authority.

- If you are breastfeeding, we will ask you for a sample of your breastmilk
- You will answer questionnaires about others who live in your home and whether they have monkeypox and how you are feeling
- If you have eye disease from monkeypox or eye symptoms, study staff will place a strip of paper inside your lower eyelid to collect tears from you. You may also be given eyedrops to help treat eye disease. Please talk to the study staff, your primary care provider, or your eye doctor about this. These eyedrops are not provided by the study.
- Study staff will take swabs for the following tests. The study doctor may be required by law to report the results of these tests to the local health authorities:
  - Swabs from the back of your throat and your rectum to test for gonorrhea and chlamydia
  - Swabs of from your skin, mouth and throat, rectum, and vagina (you will collect this swab yourself and give it to the study staff) for monkeypox testing
- You will answer questionnaires about any recent sexual activity that you have had and any anal/rectal symptoms you may be having
- If you qualify for the study, you will receive a study kit that includes:
  - Your study drugs. Tecovirimat or placebo for tecovirimat will be taken two or three times a day for 14 days.
  - Instructions on how to complete the study diary that you will complete at home to record how your skin lesions are doing, any symptoms that you are experiencing, and any pain that you are experiencing. We will also ask you to write down the date and time that you take your study drug.
  - Containers for any sample collections that you will do at home.

Most people will be randomly assigned (like flipping a coin or rolling dice) to a study group. You and the study staff will not be able to choose which study treatment group you are in. You and the study staff will not know whether you are receiving active study drug or placebo. Twice as many people will receive active study drug as receive placebo in this study, so you are twice as likely to receive “real” study drug.

Some people will be assigned to receive tecovirimat instead of being randomly assigned to a study group. If you belong to one of the groups below, you will receive tecovirimat – there is no chance you will receive placebo.

- Participants under 18
- People who are pregnant or breastfeeding
- People with severe skin disease
- People with a severely suppressed immune system
- People with monkeypox disease in their eye or on their face (cheeks, nose, eyelid)
- People with severe monkeypox lesions that have to be treated surgically
- People who have to be hospitalized due to their monkeypox infection
- People taking medicines that may reduce tecovirimat levels including rifampin, rifapentine, rifabutin, St. John’s Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir

If you join the study at an in-person visit, you should continue to be seen in person if possible, however visits may occur through telemedicine if needed.

Study Visit on Day 6
At this visit:

- The study staff will contact you by phone or via telemedicine to ask about any symptoms you are experiencing and any pain that you might be experiencing.
- Study staff will ask if you are taking your study drugs as directed.
- You will answer questionnaires about your anal/rectal health.

Study Visits on Days 8, 15, 22, 29, 57
At these visits:

- You will have a brief physical exam and answer questions about any medications you are taking.
- You will have an exam of your skin to identify where you have monkeypox lesions. Study staff will take pictures of your skin lesions.
- You will answer questionnaires about recent sex you may have had (day 29) and whether people in your household have monkeypox (day 29 and 57), your quality of life (days 8, 15, and 29), and anal/rectal health (days 15 and 57).
- Study staff will collect the following swabs:
  - Swabs of your skin, mouth and throat, rectum, and vagina (you will collect this swab yourself and give it to the study staff) for monkeypox testing
  - If the study staff thinks you have monkeypox in your eye or you have eye symptoms, a small strip of paper will be placed in your lower eyelid to collect tear fluid.
- If you are breastfeeding, we will collect a sample of your breastmilk
- You will have blood drawn for the following tests:
  - Routine safety tests (liver and kidney tests and blood counts) (day 8)
  - Blood tests to see the levels of monkeypox virus in your blood
  - Blood tests to see how your body processes the study drugs and other medications you take that may interact with study drug (these tests are called pharmacokinetic [PK] tests (days 8 and 15)
  - A test to measure concentrations of medicines used to treat or prevent HIV (if you are living with HIV or taking medications to prevent HIV infection) (days 8 and 15)
    Stored blood for future study-required testing (days 8, 15, 29, and 57)
- You may have a series of blood draws to see how your body processes the study drugs (these tests are called intensive PK tests) (day 8). These tests are required for some participants. The study staff at your site can tell you if you will have to have these tests. If you have these tests, you will be asked to have nothing to eat or drink except for water for 8 hours before your visit. You will be arrive at the facility in the morning and will remain there for 8-12 hours, depending on how often you take your study drug. You will have a blood sample drawn, eat a standardized meal provided by the site, and then you will take your study drug. Additional blood samples will be obtained at 1, 2, 3, 4, 6-, 8-, and 10-hours after your dose of study drug. On the day of the visit, we will place a small plastic tube (like a “drip”) in your arm. The tube is attached to a plastic needle. The tube will stay in your arm until all the blood draws are done. We use the tube so we do not have to stick you with a needle each time blood is drawn.

Study Evaluations to Complete at Home
In addition to study visits at the clinic, you will have to complete some study evaluations at home:

- Complete your study diary and pain rating every day on days 1-29
- If you are able to **and you agree**, you will take a photograph of your lesions on days 1-29 so you can show them to the study staff to track how your lesions are healing
- If you agree to provide a semen sample, you will receive specimen containers for this purpose. You will masturbate into the container on the morning of your day 1, day 15, and day 57 study visits and bring the sample with you to your study visit.

Additional Study Visits
You will have extra study visits if your monkeypox disease gets worse or if your lesions heal up. If you need to report to the site that your lesions have healed, this visit may be done remotely (over the phone or via telemedicine systems approved for use at your site).

Early Discontinuation
If at any point in the study you want to stop participating in the study, you must contact the site immediately. If you choose to withdraw consent, no additional samples will be collected and no new information will be collected. Any samples that have not been analyzed prior to your withdrawal of consent will be destroyed, but any information from any samples already analyzed will still be used.

ARE THERE ANY TESTS THAT ARE OPTIONAL?

Some people in this study are required to have the intensive PK tests described above. Even if you are not required to, you may be asked to have the intensive PK tests.

____ (initials) I understand and I agree to participate in this procedure

OR

____ (initials) I understand but I do not agree to participate in this procedure

QUICK SUMMARY OF EVALUATIONS

	Screening/ Day 1	Day 6	Day 8	Day 15	Day 22	Day 29	Day 57	Lesion Resolution	Disease Progression
Physical Exam	X		X	X	X	X	X	X	X
Telephone Check		X							
Blood Drawn	X		X	X	X	X	X		X
Urine Collected	X								
Intensive PK			X						
Swabs Collected	X		X	X	X	X	X		X
Questionnaires	X	X	X	X		X	X		X
Semen Sample (optional)	X			X			X		X
Study Diary/Self Assessments	Days 1-29								

WHAT IF I AM IN PAIN OR MY MONKEYPOX VIRUS GETS WORSE?

If you become more ill from monkeypox or you develop new skin lesions on your face, please contact the study staff. You may be able to start tecovirimat without the possibility of placebo. You may also be able to start tecovirimat without the possibility of placebo if you have severe pain for 5 days after starting the study.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

You will receive the results of routine lab tests (for example, blood counts, liver and kidney tests, pregnancy test, testing for sexually transmitted diseases and HIV, HIV viral load, CD4 count) that are performed at the study visits. You will be told of the monkeypox results from swabs taken from skin lesions, rectal swab, and mouth swab.

Some of the blood that is collected from you will be stored and tested later. Some of these tests may be done after you are done with the study, and other tests are not yet approved by the FDA and are still considered “research” tests. For these reasons, you will not receive the results of:

- Monkeypox testing from areas other than skin lesions, mouth, and rectum
- Monkeypox testing after entry
- Tests of your immune response to monkeypox
- Tests of blood concentrations of tecovirimat or other medicines

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required pharmacologic, immunologic, and virologic testing.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Please refer to Attachment A to consent for use of your samples in other studies.

COMMERCIAL PROFIT

Your biospecimens collected during this study may be used for commercial profit (even if identifiers are removed) and you will not share in this profit.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

530 people will participate in this study and receive active study drug or placebo.

There is a third group of people (including participants under 18, people who are pregnant or breastfeeding, people with severe disease, people taking certain medicines that may interact with tecovirimat, and people whose immune systems are weakened by other infections) who will be assigned to active study drug with no possibility of receiving placebo – there is no limit to how many people will be assigned to this group.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about two months (60 days).

WHY WOULD THE STUDY DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- The study is stopped or cancelled
- Your primary care doctor thinks that this study is no longer in your best interest and they request that you stop participating

The study doctor may also need to take you off the study drug(s) without your permission if:
- Continuing the study drug may be harmful to you

- You need a treatment that you may not take while on the study
- You are not able to take the study drug as required by the study

WHAT HAPPENS WHEN I FINISH THE STUDY?

After you have completed your study participation, the study will not be able to continue to provide you with the study drug you received on the study. If continuing to take this or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this study drug. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the study staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or study nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or study nurse before enrolling in any other clinical trials while on this study.

The risks of tecovirimat in people with smallpox or other poxviruses are not known. Tecovirimat has not been studied in people with weak immune systems, the elderly, or children. Tecovirimat 600 mg capsules were tested in 359 healthy adults, including 336 healthy adults who received tecovirimat capsules twice a day for 14 days. Tecovirimat for injection was also tested in 26 healthy adults. No serious problems occurred in any of the participants in these studies.

During the 2022 monkeypox outbreak in the U.S., tecovirimat capsules have also been given to more than 230 people with poxvirus infection, including people with monkeypox, as of July 2022; side effects are being monitored but no serious problems with tecovirimat have been reported so far. Still, tecovirimat may cause some adverse events (side effects). There also may be other adverse events that we cannot predict. The most common adverse events in people who have taken tecovirimat were:

- Headache
- Nausea
- Vomiting
- Stomach pain

As with any medication, there is a potential risk of an allergic reaction. An allergic reaction after receiving tecovirimat could include:

- Rash
- Difficulty breathing
- Wheezing
- Sudden drop in blood pressure causing dizziness or fainting
- Swelling (around the mouth, throat, or eyes)
- Fast pulse
- Sweating

Risks of Drug Interactions
There are drug interactions with tecovirimat. Tecovirimat can lower or raise the concentrations of other medicines in your blood. When the blood concentrations of other medicines are lower, the other medicines may not work as well. When the blood concentrations of other medicines are raised, the other medicines may cause more side effects. Other medicines may also lower or raise the tecovirimat concentrations in the blood. To minimize the risk for drug interactions, it is important to review all of your prescription and over-the- counter medicines and dietary and herbal supplements with study personnel. It is also important to notify study personnel before you start any new prescription or over-the-counter medicines and dietary and herbal supplements while taking the study drug.

Risks of Blood Draw
Having blood drawn may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, and in rare cases it may result in fainting. There is a small risk of infection.

Risks of Anal Swabs, Mouth Swabs, Skin Swabs, and Vaginal Swabs
These can be uncomfortable and occasionally there can be some bleeding. If you are having pain in the rectum, there may be significant pain with the anal swab.

Questionnaires
You may be embarrassed by the detailed questions about sex and your anal health.

Loss of Privacy - Photographs of Participant's Face
You may have photographs of your face **or areas of your skin that have distinctive markings such as tattoos** taken for this study. It is possible that **these photographs** may be recognizable and your identity may be known. All photographs taken during the study **will be stored in your electronic medical record or** will be stored with a code instead of your name.

Risks of Starting the Study Before Your Monkeypox Virus is Confirmed by a Lab
There are other things that can cause lesions on your skin, but we want you to start the study as soon as possible, so we will let you begin study drug even if your skin lesions have not been tested by a lab and confirmed to be monkeypox. There is a chance that your lab tests will show that you do not have monkeypox, so there is a risk that you will have taken study drug and participated in study tests when you do not have monkeypox.

The study doctors at your site will use their best judgement to make sure that this does not happen, but if it does happen you will stop taking the study drug and **the study staff at your**

study site will check on you in 7 days to make sure that you do not have any side effects before you leave the study.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Tecovirimat has not been studied in pregnant or nursing people. It is not known if giving tecovirimat to a pregnant person would hurt the unborn child. Tecovirimat has been tested on pregnant mice and rabbits. There were no serious problems in the unborn animals. Poxviruses during pregnancy can cause serious harm to the pregnant person and unborn baby.

In animal studies, tecovirimat was present in animal milk. When a drug is present in animal milk it is likely to be present in human milk. Because of the potential for virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended while the nursing individual has active lesions. A lactating person should consider pausing breastfeeding and consider pumping and discarding breast milk during the study.

If you can get pregnant but are not pregnant when you join the study and you are engaging in sexual activity that could lead to pregnancy, you must agree to use at least one effective method of contraception from the time you join the study until you are finished with the study. Effective methods of contraception are hormonal contraceptives (injected or in pills), male or female condoms, diaphragm or cervical cap with a spermicide, or an intrauterine device (an IUD). Abstinence (agreeing not to have sex) is also allowed as a way to prevent pregnancy.

If at any point during the study you think you may be pregnant, you should let the study staff at your site know so that a pregnancy test can be done.

If you are pregnant or become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). We would also like you to bring your baby in for a study visit about 4 weeks after they are born so we can examine the baby.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

We do not know for certain if you will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat your infection and prevent it from getting worse, but we cannot make any guarantee.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

There is no proven way to treat poxviruses, but research is ongoing. You may benefit from supportive therapy (such as IV fluids, or medicine to control fever or pain) and antibiotics for any bacterial infections you may have. There may be other medications that your study doctor

may consider using to treat your infection. Tecovirimat may be available outside this study. There may also be research studies looking at other new treatments for poxviruses.

Please talk to your study doctor about these and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the AIDS Clinical Trials Group (ACTG), the U.S. Office for Human Research Protections (OHRP), or other local, U.S., and international regulatory entities as part of their duties, Advarra Institutional Review Board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

Also, any publication of this study will not use your name or identify you personally.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

The study will pay for research-related tests and assessments. Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

«Compensation»

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ *["following each completed visit", "monthly", "quarterly", "at the end of your participation in the research study", "following each completed visit or at the end of your participation in the research study, whichever you prefer"]*.

If you have any questions regarding your compensation for participation, please contact the study staff.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. There is no program for compensation through the NIH. The cost for this treatment will be charged to you or your insurance company.
You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in

other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a research participant;
- Eligibility to participate in the study;
- The study doctor's or study site's decision to withdraw you from participation;
- Results of tests and/or procedures;

Please contact the study doctor at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call toll free: 877-992-4724
- or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00065749.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Signature and Date
Study Staff Conducting Consent Discussion (print)	Signature and Date
Witness's Name (print) (As appropriate)	Signature and Date

FOR CHILDREN WHO BECOME ADULTS

I have been told that my parents/legal guardian agreed for me to participate in this research study as a minor. I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to continue to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing and dating this consent document. I will receive a copy of this signed and dated consent document.

Participant's Name (print)	Signature and Date

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of University of California, Los Angeles (UCLA) and National Institute of Allergy and Infectious Diseases (NIAID).
- Representatives of ACTG.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other U.S. federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this study, if applicable.
- A data safety monitoring board which oversees this study, if applicable.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study drug works and is safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____ _____
Participant's Name (print) Signature and Date

_____ _____
Witness's Name (print) Signature and Date

FOR CHILDREN WHO BECOME ADULTS

I have been told that my parents/legal guardian agreed to the use and disclosure of my Protected Health Information as outlined in this document. I have read and understand the information in this authorization. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I continue to authorize the use and disclosure of my Protected Health Information. I will receive a copy of this signed and dated authorization.

_____
Participant's Printed Name

_____ _____
Participant's Signature Date

APPENDIX II: INFORMED CONSENT AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR ADULTS AND PARTICIPANTS REACHING AGE OF MAJORITY (AOM) WHO ARE ENROLLED/FOLLOWED REMOTELY

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"**
Protocol Number:	**A5418**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

SUMMARY

PURPOSE	**This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate how well tecovirimat works for the treatment of human monkeypox virus infection and if the study drug is safe in people. The study will also help us understand more about how human monkeypox causes disease and how the body fights off infection.**
STUDY DRUG	**Study drug will be either tecovirimat or placebo for tecovirimat. A placebo looks like a "real" drug but does not have any active drug in it. Twice as many people will receive the active drug in this study, so you are more likely to receive the active study drug. Tecovirimat or placebo for tecovirimat will be taken two or three times a day for 14 days.**
NUMBER OF PARTICIPANTS	**530 people will participate in this study and receive active study drug or placebo. Children, people who are pregnant, people with severe disease or severe skin conditions, people taking certain medications that may lower tecovirimat levels in the blood, and people whose immune systems are weakened will be in a separate group that receives tecovirimat with no possibility of receiving placebo – there is no limit to how many people will be assigned to this group.**

LENGTH OF STUDY **Your participation in this study will last about 2 months. If you are pregnant, we will contact you periodically to see how your pregnancy goes and to know the health of your child.**

REQUIRED ACTIVITIES **If you participate in this study, the following study procedures are required:**

- **You will record your symptoms daily**
- **You will provide swabs of the sores on your skin**
- **You will complete questionnaires about your symptoms**

RISKS **The most common side effects people receiving tecovirimat have noticed are:**

- **Headache**
- **Nausea (feeling like you want to vomit)**
- **Vomiting**
- **Stomach pain**

BENEFITS **We do not know if you will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat your infection and prevent it from getting worse, but we cannot make any guarantee.**

OTHER CHOICES **There is no proven way to treat human monkeypox virus. You may benefit from supportive therapy (such as intravenous [IV] fluids, or medicine to control fever or pain) and antibiotics for any bacterial infections you may have. There may be other medications that your study doctor may consider using to treat your infection. Tecovirimat may be available outside this study. There may also be research studies looking at other new treatments for poxviruses.**

INTRODUCTION

You are being asked to take part in this research study because:

- **You are known to have monkeypox virus or your healthcare providers suspect you have monkeypox virus**
- **You have had symptoms for fewer than 14 days**
- **You have at least one active, not yet scabbed lesion, or proctitis (inflammation of the lining of the rectum) or mouth sores**

This study is sponsored by the National Institutes of Health (NIH). The study doctor is in charge of this study at this site. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Monkeypox is caused by a virus. This virus is most often spread by close contact with someone who has monkeypox. Illness caused by monkeypox virus infection usually starts with a fever and feeling poorly before a rash begins. The rash looks like raised bumps and pus-filled blisters (called lesions). The lesions then crust, scab, and fall off after about 2-4 weeks, sometimes leaving a scar.

Since Spring 2022, monkeypox has rapidly spread throughout the world, with more than 70,000 cases in 107 countries and more than 26,000 cases in the United States reported as of September 2022.

Tecovirimat is a drug that may help to treat infections caused by pox viruses. Tecovirimat is approved by the Food and Drug Administration (FDA) to treat smallpox in adults and children, but its use in this study is considered investigational. An investigational use is one that has not been approved by the FDA. Tecovirimat has been approved based only on data from animals. We don't know for sure if it works to treat any infections in people. The FDA has reviewed information on tecovirimat and determined that tecovirimat may help treat infection, including serious or potentially life-threatening disease, from poxviruses.

Tecovirimat has been given safely to some people with monkeypox in the recent outbreak and is currently being studied in several ongoing studies outside of the U.S., but none of the studies have shown whether or not this study drug works to treat monkeypox. The safety of tecovirimat has been evaluated in a study with adult participants without monkeypox. Tecovirimat was generally safe and well tolerated – the risks are noted below.

We are doing this study to see if tecovirimat is safe and whether it helps treat monkeypox in people. The study will also help us understand more about how human monkeypox causes disease and how the body fights off infection with monkeypox.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

<u>Screening/Entry Visit</u>
If you would like to be in this study, after you have read and signed this consent form, you will have a visit to make sure you meet the requirements for joining the study. This visit will be done via telemedicine.

We will collect some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count and viral load if you are living with HIV) information. We will collect this information even if you do not start study drug.

At this visit:

- **You will answer questions about your medical history and any medications you have taken recently.**
- **You will have an exam of your skin to identify where you have monkeypox lesions. You may have to remove some of your clothes for this exam. Site staff will ask to take pictures of your skin lesions. You do not have to agree to have these pictures taken. You can participate in this study regardless of what you decide about having pictures taken. If you agree, these pictures will be used so that the study staff can follow how well your lesions are healing. These pictures will not be used for any other purpose without your written permission. If you have lesions on your face, it is possible that you will be able to be identified in these pictures. These pictures may be stored in your electronic medical record. If these pictures are stored in a study database, they will be stored securely with a code instead of your name. Please discuss how pictures are stored at your clinical research site.**
- **You will answer questionnaires about any pain your lesions may be causing you**
- **If it is available in your medical records, we will record the results from your latest physical exam, any recent testing you have had for herpes virus, and results from any recent pregnancy test.**

If you qualify for the study, you will have some more tests:

- **You will be advised to obtain testing for sexually transmitted infections outside of the study as indicated. If you are found to have an STI or HIV, you will be referred for treatment or study staff will provide appropriate treatment.**
- **You will answer questionnaires about others who live in your home and whether they have monkeypox and how you are feeling**
- **If you have eye disease from monkeypox or eye symptoms, study staff will ask you to be seen by an eye doctor outside of the study**
- **You will answer questionnaires about any recent monkeypox exposure, any recent sexual activity that you have had, and any anal/rectal symptoms you may be having**
- **If they are available in your medical records, we will record the results from recent bloodwork you had, recent testing for sexually transmitted infections, recent testing for hepatitis, recent testing for HIV, and recent CD4 and viral load testing (if you are living with HIV)**
- **If you qualify for the study, a study kit will be delivered to you that includes:**
  - **Your study drugs. Tecovirimat or placebo for tecovirimat will be taken two or three times a day for 14 days. The study drugs may arrive in a separate shipment.**
  - **Instructions on how to complete the study diary that you will complete at home to record how your skin lesions are doing, any symptoms that you are experiencing, and any pain that you are experiencing. We will also ask you to write down the date and time that you take your study drug.**

- **Containers for any sample collections that you will do at home.**

Most people will be randomly assigned (like flipping a coin or rolling dice) to a study group. You and the study staff will not be able to choose which study treatment group you are in. You and the study staff will not know whether you are receiving active study drug or placebo. Twice as many people will receive active study drug as receive placebo in this study, so you are twice as likely to receive "real" study drug.

Some people will be assigned to receive tecovirimat instead of being randomly assigned to a study group. If you belong to one of the groups below, you will receive tecovirimat – there is no chance you will receive placebo.

- **Participants under 18**
- **People who are pregnant or breastfeeding**
- **People with severe skin disease**
- **People with a severely suppressed immune system**
- **People with monkeypox disease in their eye or on their face (cheeks, nose, eyelid)**
- **People with severe monkeypox lesions that have to be treated surgically**
- **People who have to be hospitalized due to their monkeypox infection**
- **People taking medicines that may reduce tecovirimat levels including rifampin, rifapentine, rifabutin, St. John's Wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir**

If you join the study remotely, we expect that all of your visits will be done remotely, but you may elect to have follow up visits in person. In this event, you would sign the consent form for in person follow up.

<u>Study Visit on Day 6</u>
At this visit:

- **The study staff will contact you by phone or via telemedicine to ask about any symptoms you are experiencing and any pain that you might be experiencing.**
- **Study staff will ask if you are taking your study drugs as directed.**
- **You will answer questionnaires about your anal/rectal health.**

<u>Study Visits on Days 8, 15, 22, 29, 57</u>
These visits will be conducted via telemedicine. At these visits:

- **You will answer questions about any medications you are taking.**
- **You will have an exam of your skin to identify where you have monkeypox lesions. Study staff will ask you take pictures of your skin lesions or they will take pictures via telemedicine.**
- **You will answer questionnaires about recent sex you may have had (day 29) and whether people in your household have monkeypox (day 29 and 57), your quality of life (days 8, 15, and 29), and anal/rectal health (days 15 and 57).**

Study Evaluations to Complete at Home

In addition to the telemedicine visits, you will have to complete additional study evaluations at home:

- **Complete your study diary and pain rating every day on days 1-29**
- **If you are able to and you agree, you will take photographs of your skin lesions at least twice a week so you can show them to the study staff to track how your lesions are healing**
- **On the day you start the study and again on Day 8 you will be asked to take swabs of your skin for monkeypox testing. You will return these samples to the testing lab via mail or courier service. These samples may be omitted if testing/shipping kits are not available or if health laws where you live do not allow you to ship the samples.**
- **If a new lesion appears on your skin on or after day 6, you will be asked to take a swab of the new lesion for monkeypox testing. You will send the swab to the testing laboratory.**

Additional Study Visits

You will have extra telemedicine visits if your monkeypox disease gets worse or if your lesions heal up. If your monkeypox disease gets worse you may also choose to come into the site to see the site staff in person if you would prefer.

Early Discontinuation

If at any point in the study you want to stop participating in the study, you must contact the site immediately. If you choose to withdraw consent, no additional samples will be collected and no new information will be collected. Any samples that have not been analyzed prior to your withdrawal of consent will be destroyed, but any information from any samples already analyzed will still be used.

QUICK SUMMARY OF EVALUATIONS

	Screening/ Day 1	Day 6	Day 8	Day 15	Day 22	Day 29	Day 57	Lesion Resolution	Disease Progression
Skin Exam via Telemedicine	X		X	X	X	X	X	X	X
Swabs Collected	X		X						
Questionnaires	X	X	X	X		X	X		X
Study Diary/Self Assessments	Days 1-29								

WHAT IF I AM IN PAIN OR MY MONKEYPOX VIRUS GETS WORSE?

If you become more ill from monkeypox or you develop new skin lesions on your face, please contact the study staff. You may be able to start tecovirimat without the

possibility of placebo. You may also be able to start tecovirimat without the possibility of placebo if you have severe pain for 5 days after starting the study.

WILL I RECEIVE THE RESULTS OF ANY TESTS?

Testing of the swabs that you collect may be done after you are done with the study. For this reason, you will not receive these results.
You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your care, you will be provided with those results.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Please refer to Attachment A to consent for use of your samples in other studies.

COMMERCIAL PROFIT

Your biospecimens collected during this study may be used for commercial profit (even if identifiers are removed) and you will not share in this profit.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

530 people will participate in this study and receive active study drug or placebo.

There is a third group of people (including participants under 18, people who are pregnant or breastfeeding, people with severe disease, people taking certain medicines that may interact with tecovirimat, and people whose immune systems are weakened by other infections) who will be assigned to active study drug with no possibility of receiving placebo – there is no limit to how many people will be assigned to this group.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about two months (60 days).

WHY WOULD THE STUDY DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- **The study is stopped or cancelled**
- **Your primary care doctor thinks that this study is no longer in your best interest and they request that you stop participating**

The study doctor may also need to take you off the study drug(s) without your permission if:

- **Continuing the study drug may be harmful to you**
- **You need a treatment that you may not take while on the study**
- **You are not able to take the study drug as required by the study**

WHAT HAPPENS WHEN I FINISH THE STUDY?

After you have completed your study participation, the study will not be able to continue to provide you with the study drug you received on the study. If continuing to take this or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this study drug. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the study staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or study nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or study nurse before enrolling in any other clinical trials while on this study.

The risks of tecovirimat in people with smallpox or other poxviruses are not known. Tecovirimat has not been studied in people with weak immune systems, the elderly, or children. Tecovirimat 600 mg capsules were tested in 359 healthy adults, including 336 healthy adults who received tecovirimat capsules twice a day for 14 days. Tecovirimat for injection was also tested in 26 healthy adults. No serious problems occurred in any of the participants in these studies.

During the 2022 monkeypox outbreak in the U.S., tecovirimat capsules have also been given to more than 230 people with poxvirus infection, including people with monkeypox, as of July 2022; side effects are being monitored but no serious problems with tecovirimat have been reported so far. Still, tecovirimat may cause some adverse events (side effects). There also may be other adverse events that we

cannot predict. The most common adverse events in people who have taken tecovirimat were:

- **Headache**
- **Nausea**
- **Vomiting**
- **Stomach pain**

As with any medication, there is a potential risk of an allergic reaction. An allergic reaction after receiving tecovirimat could include:

- **Rash**
- **Difficulty breathing**
- **Wheezing**
- **Sudden drop in blood pressure causing dizziness or fainting**
- **Swelling (around the mouth, throat, or eyes)**
- **Fast pulse**
- **Sweating**

Risks of Drug Interactions

There are drug interactions with tecovirimat. Tecovirimat can lower or raise the concentrations of other medicines in your blood. When the blood concentrations of other medicines are lower, the other medicines may not work as well. When the blood concentrations of other medicines are raised, the other medicines may cause more side effects. Other medicines may also lower or raise the tecovirimat concentrations in the blood. To minimize the risk for drug interactions, it is important to review all of your prescription and over-the- counter medicines and dietary and herbal supplements with study personnel. It is also important to notify study personnel before you start any new prescription or over-the- counter medicines and dietary and herbal supplements while taking the study drug.

Risks of Skin Swabs

These can be uncomfortable and occasionally there can be some bleeding.

Questionnaires

You may be embarrassed by the detailed questions about sex and your anal health.

Loss of Privacy - Photographs of Participant's Face

You may have photographs taken for this study of your face or areas of your skin that have distinctive markings such as tattoos. It is possible that these photographs may be recognizable and your identity may be known. All photographs taken during the study will be stored in your electronic medical record or will be stored with a code instead of your name.

Risks of Starting the Study Before Your Monkeypox Virus is Confirmed by a Lab

There are other things that can cause lesions on your skin, but we want you to start the study as soon as possible, so we will let you begin study drug even if your skin lesions have not been tested by a lab and confirmed to be monkeypox. There is a chance that

your lab tests will show that you do not have monkeypox, so there is a risk that you will have taken study drug and participated in study tests when you do not have monkeypox.

The study doctors at your site will use their best judgement to make sure that this does not happen, but if it does happen you will stop taking the study drug and the study staff at your study site will check on you in 7 days to make sure that you do not have any side effects before you leave the study.

Risks of Participating in the Study through Telemedicine
Study providers are not able to fully examine you through telemedicine. It is possible that their assessment is not complete or not as accurate as an in-person visit. You are encouraged to see local providers in person if you have concerns about your health.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Tecovirimat has not been studied in pregnant or nursing people. It is not known if giving tecovirimat to a pregnant person would hurt the unborn child. Tecovirimat has been tested on pregnant mice and rabbits. There were no serious problems in the unborn animals. Poxviruses during pregnancy can cause serious harm to the pregnant person and unborn baby.

In animal studies, tecovirimat was present in animal milk. When a drug is present in animal milk it is likely to be present in human milk. Because of the potential for virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended while the nursing individual has active lesions. A lactating person should consider pausing breastfeeding and consider pumping and discarding breast milk during the study.

If you can get pregnant but are not pregnant when you join the study and you are engaging in sexual activity that could lead to pregnancy, you must agree to use at least one effective method of contraception from the time you join the study until you are finished with the study. Effective methods of contraception are hormonal contraceptives (injected or in pills), male or female condoms, diaphragm or cervical cap with a spermicide, or an intrauterine device (an IUD). Abstinence (agreeing not to have sex) is also allowed as a way to prevent pregnancy.

If at any point during the study you think you may be pregnant, you should let the study staff at your site know. You are encouraged to obtain pregnancy testing if you believe you may be pregnant.

If you are pregnant or become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends).

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

We do not know for certain if you will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat your infection and prevent it from getting worse, but we cannot make any guarantee.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

There is no proven way to treat poxviruses, but research is ongoing. You may benefit from supportive therapy (such as IV fluids, or medicine to control fever or pain) and antibiotics for any bacterial infections you may have. There may be other medications that your study doctor may consider using to treat your infection. Tecovirimat may be available outside this study. There may also be research studies looking at other new treatments for poxviruses.

Please talk to your study doctor about these and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the AIDS Clinical Trials Group (ACTG), the U.S. Office for Human Research Protections (OHRP), or other local, U.S., and international regulatory entities as part of their duties, Advarra Institutional Review Board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

Also, any publication of this study will not use your name or identify you personally.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

The study will pay for research-related tests and assessments. Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. If you go to a clinic other than your site clinic for STI testing, pregnancy testing, or other testing, the study will not pay for this testing.

WILL I RECEIVE ANY PAYMENT?

«Compensation»

You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ *["following each completed visit", "monthly", "quarterly",*

***"at the end of your participation in the research study", "following each completed visit or at the end of your participation in the research study, whichever you prefer"]*.**

If you have any questions regarding your compensation for participation, please contact the study staff.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. There is no program for compensation through the NIH. The cost for this treatment will be charged to you or your insurance company.

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study such as:

- **Whom to contact in the case of a research-related injury or illness;**
- **Payment or compensation for being in the study, if any;**
- **Your responsibilities as a research participant;**
- **Eligibility to participate in the study;**
- **The study doctor's or study site's decision to withdraw you from participation;**
- **Results of tests and/or procedures;**

<u>Please contact the study doctor at the telephone number listed on the first page of this consent document</u>.

If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help

protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- **By mail:**
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- **or call toll free: 877-992-4724**
- **or by email: adviser@advarra.com**

Please reference the following number when contacting the Study Subject Adviser: Pro00065749.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	**Signature and Date**
Study Staff Conducting Consent Discussion (print)	**Signature and Date**
Witness's Name (print) (As appropriate)	**Signature and Date**

FOR CHILDREN WHO BECOME ADULTS

I have been told that my parents/legal guardian agreed for me to participate in this research study as a minor. I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to continue to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing and dating this consent document. I will receive a copy of this signed and dated consent document.

Participant's Name (print)	**Signature and Date**

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- **Your name.**
- **Address.**
- **Phone number.**
- **Date of birth.**
- **Medical history.**
- **Information from your study visits, including all test results.**

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- **Representatives of University of California, Los Angeles (UCLA) and National Institute of Allergy and Infectious Diseases (NIAID).**
- **Representatives of ACTG.**
- **Representatives of Advarra IRB (an Institutional Review Board that reviews this study).**
- **The Food and Drug Administration (FDA) and other U.S. federal and state agencies.**
- **Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.**
- **Governmental agencies of other countries.**
- **Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.**
- **Other research doctors and medical centers participating in this study, if applicable.**
- **A data safety monitoring board which oversees this study, if applicable.**

Your health data will be used to conduct and oversee the research, including for instance:

- **To see if the study drug works and is safe.**
- **To compare the study drug to other drugs.**
- **For other research activities related to the study drug.**

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form.

If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____ _____
Participant's Name (print) **Signature and Date**

_____ _____
Witness's Name (print) **Signature and Date**

FOR CHILDREN WHO BECOME ADULTS

I have been told that my parents/legal guardian agreed to the use and disclosure of my Protected Health Information as outlined in this document. I have read and understand the information in this authorization. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I continue to authorize the use and disclosure of my Protected Health Information. I will receive a copy of this signed and dated authorization.

_____
Participant's Printed Name

_____ _____
Participant's Signature **Date**

ATTACHMENT A: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES **FOR ADULTS AND PARTICIPANTS REACHING AGE OF MAJORITY (AOM)**

Everything in the main study consent form you signed before still applies to your participation in this study unless otherwise noted in this form.

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called “extra samples.” The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored.

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the study team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the study staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples

Research with Human Genetic Testing
The ACTG has two studies that collect samples for genetic testing.

If you live in the U.S., this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials for Currently Unspecified Analyses.

If you live outside of the U.S., this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like to participate in this study if it is being done where you live. If you would like to participate, you will sign and date a separate consent form.

Your extra samples will not be used for human genetic testing unless you sign and date a consent form for A5128 **or A5243**.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

Participant's Name (print)	Signature and Date
Study Staff Conducting Consent Discussion (print)	Signature and Date
Witness's Name (print)	Signature and Date

FOR CHILDREN WHO BECOME ADULTS

I have been told that my parents/legal guardian agreed for me to participate in this research study as a minor. I have read and understand the information in this informed consent document. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I voluntarily agree to continue to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing and dating this consent document. I will receive a copy of this signed and dated consent document.

Participant's Name (print)	Signature and Date

APPENDIX III: INFORMED CONSENT TO PARTICIPATE IN ADDITIONAL SAMPLING **FOR ADULT PARTICIPANTS WHO ARE ENROLLED/FOLLOWED IN PERSON**

Sponsor / Study Title:	National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"
Protocol Number:	A5418
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Address:	«PiLocations»

The optional procedures and sample collections described below will advance the scientific goals of this study but will offer no direct benefit to participants. Neither you nor your primary care doctor will receive any results from these procedures because these tests are for research purposes only. You can still be in this study even if you choose not to participate in the optional procedures. Even if you choose to participate in the optional procedures at this time, you may withdraw your consent at any time during the study.

WHAT DO I HAVE TO DO IF I PARTICIPATE IN THE ADDITIONAL SAMPLING?

If you agree, you will have the evaluations described below in addition to the evaluations that were described in the previous consent form. Everything in the main study consent form you signed before still applies to your participation in this study unless otherwise noted in this form.

Screening/Entry Visit

- You will provide a urine sample
- Study staff will teach you how to collect oral swabs, anogenital swabs (the area around your anus and genitals), and swabs of monkeypox lesions on your skin

Study Evaluations to Complete at Home

- On days 2, 5, 11, 18, and 25 you will collect swabs from the back of the throat, rectum, vagina, and skin lesions

Day 3
This is an extra visit that you will have only if you are in the additional sampling group. At this visit:

- You will provide a urine sample
- You will have blood drawn
- You will return the swabs you have taken at home
- You will have swabs from the back of the throat, skin lesions, rectum and vagina (you will collect this swab yourself and give it to the study staff)

Days 8, 15, 22, 29

- You will return the swabs you have taken at home
- You will provide a urine sample (days 8, 15, and 29)

ARE THERE ANY PROCEDURES THAT ARE OPTIONAL?

If you agree, you will have an **extra blood drawn** on the day you enter the study and on days 15 and 57. **This blood will be used to collect a type of cells called peripheral blood mononuclear cells (PBMCs).**

You can still be a part of the additional sampling group even if you do not agree to **provide PBMCs.**

____ (initials) I understand and I agree to **provide PBMCs.**

OR

____ (initials) I understand but I do not agree to **provide PBMCs.**

QUICK SUMMARY OF ADDITIONAL SAMPLING

Remember that you will have these additional sampling procedures done in addition to the procedures described in the main consent form that you signed.

	Screening / **Day 1**	Day 2	Day 3	Day 5	Day 8	Day 11	Day 15	Day 18	Day 22	Day 25	Day 29	Day 57
Blood Drawn			X									
Urine Collected	X		X		X		X				X	
Stored PBMCs (optional)	X						X					X
Self Collected Swabs		X		X		X		X		X		
Return Swabs		X			X		X		X		X	

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Signature and Date

APPENDIX IV: INFORMED CONSENT AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR PARENTS/LEGAL GUARDIANS OF CHILDREN **WHO ARE ENROLLED/FOLLOWED IN PERSON**

Sponsor / Study Title:	National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"
Protocol Number:	A5418
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Address:	«PiLocations»

SUMMARY

PURPOSE

This is a research study and your child's participation in this study is voluntary. The purpose of this study is to evaluate how well tecovirimat works for the treatment of human monkeypox virus infection and if the study drug is safe in people. The study will also help us understand more about how human monkeypox causes disease, how the body fights off infection, and how to dose tecovirimat in children.

STUDY GROUPS

There are different groups in this study. Arm A will take the tecovirimat study drug, Arm B will take a placebo. A placebo looks like a "real" drug but does not have any active drug in it. Participants will be randomly assigned to Arm A or Arm B (like flipping a coin or rolling dice).

All participants in Arm C will take tecovirimat, without any chance of getting the placebo. Children under 18 years of age will be in Arm C and receive tecovirimat.

STUDY DRUG

The study drug will be tecovirimat. **Tecovirimat will be taken two or three times a day for 14 days.**

NUMBER OF PARTICIPANTS

There is no limit to how many children will enroll in this study.

LENGTH OF STUDY

Your child's participation in this study will last about 2 months. If they become pregnant, we will contact you periodically to see how their pregnancy goes and to know the health of their child. We would also like them to bring their baby in for a study visit about 4 weeks after they are born so we can examine the baby.

REQUIRED ACTIVITIES

If your child is in this study, the following study procedures are required

- They will have physical exams
- You or your child will record their symptoms daily
- They will provide blood and urine samples
- A study team member will obtain swabs of the sores on their skin and a swab of their throat
- You or your child will complete questionnaires **about their symptoms**

RISKS

The most common side effects people receiving tecovirimat have noticed are:

- Headache
- Nausea (feeling like you want to vomit)
- Vomiting
- Stomach pain

BENEFITS

We do not know if your child will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat their infection and prevent it from getting worse, but we cannot make any guarantee.

OTHER CHOICES

There is no proven way to treat human monkeypox virus. Your child may benefit from supportive therapy (such as intravenous [IV] fluids, or medicine to control fever or pain) and antibiotics for any bacterial infections they may have. There may be other medications that your child's study doctor may consider using to treat their infection. Tecovirimat may be available outside this study. There may also be research studies looking at other new treatments for poxviruses.

INTRODUCTION

This form is for the parent or legal guardian of a child or adolescent who is being asked to participate in this research study. In this form, participants are referred to as "children" even though they may be older teenagers.

You are being asked for your child to take part in this research study because they:

- Have confirmed or suspected monkeypox virus
- They have had symptoms for fewer than 14 days

- They have at least one active, not yet scabbed lesion in the skin, a sore in the mouth or proctitis (inflammation of the lining of the rectum)

This study is sponsored by the National Institutes of Health (NIH). The study doctor is in charge of this study at this site. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree for your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Monkeypox is caused by a virus. This virus is most often spread by close contact with someone who has monkeypox. Illness caused by monkeypox virus infection usually starts with a fever and feeling poorly before a rash begins. However, the rash may begin without other symptoms. The rash looks like raised bumps and pus-filled blisters (called lesions). They usually crust, scab, and fall off after about 2-4 weeks, sometimes leaving a scar.

Since Spring 2022, monkeypox has rapidly spread throughout the world, with more than **70,000** cases in **107** countries and more than **26,000** cases in the United States reported as of **September** 2022.

Tecovirimat is a drug that may help to treat infections caused by pox viruses. Tecovirimat is approved by the Food and Drug Administration (FDA) to treat smallpox in adults and children, but its use in this study is considered investigational. An investigational use is one that has not been approved by the FDA. Tecovirimat has been approved based only on data from animals. We don't know for sure if it works to treat any infections in people. The FDA has reviewed information on tecovirimat and determined that tecovirimat may help treat infection, including serious or potentially life-threatening disease, from poxviruses.

Tecovirimat has been given safely to some people with monkeypox in the recent outbreak and is currently being studied in several ongoing studies outside of the U.S., but none of the studies have shown whether or not this study drug works to treat monkeypox. The safety of tecovirimat has been evaluated in a study with adult participants without monkeypox. Tecovirimat was generally safe and well tolerated – the risks are noted below.

We are doing this study to see if tecovirimat is safe and whether it helps treat monkeypox in people. The study will also help us understand more about how human monkeypox causes disease and how the body fights off infection. This study will help us understand how much tecovirimat to give children to treat monkeypox.

WHAT DOES MY CHILD HAVE TO DO IF THEY ARE IN THIS STUDY?

Screening/Day 1 Visit
If you would like your child to be in this study, after you have read and signed this consent form, your child will have a screening visit to make sure they meet the requirements for joining the study.

We will collect some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count and viral load if your child is living with HIV) information. We will collect this information even if your child does not join this study.

At this visit:
- Your child will have a physical exam and answer questions about their medical history and any medications they have taken recently.
- Your child will have an exam of their skin to identify where they have monkeypox lesions. Your child will have to remove their clothes and wear a robe for this exam. Site staff will **ask to** take pictures of your child's skin lesions. **Your child does not have to agree to have these pictures taken. Your child can participate in this study regardless of what they decide about having pictures taken. If your child agrees, t**hese pictures will be used so that the study staff can follow how well their lesions are healing. These pictures will not be used for any other purpose without your child's written permission. If your child has lesions on their face, it is possible that they will be able to be identified in these pictures. **These pictures may be stored in your child's electronic medical record. If** these pictures are stored **in a study database**, they will be stored securely with a code instead of your child's name. **Please discuss how pictures are stored at your child's clinical research site.**
- Study staff will collect the following swabs:
  - Swabs from your child's skin and mouth/throat if they do not have a lab diagnosis of monkeypox. The study doctor may be required by law to report the result of this test to the local health authorities.
- Your child will answer questionnaires about any pain their lesions may be causing.
- **Your child may have blood drawn 2-4 hours after their first dose of study drug to test the levels of drug in their blood. This test is required for some participants. The study staff at your site can tell your child if they will have to have this test.**

There are some tests that we will only do at this study visit if your child is sexually active:
- If your child can become pregnant (and is not already pregnant), they will give a blood sample or urine sample for a pregnancy test
- Study staff will take swabs for the following tests:
  - Swabs of any lesions your child has that may be caused by herpes

If your child qualifies for the study, they will have some more tests:
- Your child will have blood drawn for the following tests:
  - Liver and kidney tests and blood counts
  - A test to measure concentrations of medicines used to treat or prevent HIV (if they are living with HIV or taking medications to prevent HIV infection)
  - CD4 count (if they are living with HIV)

  - HIV viral load (if they are living with HIV)
  - Tests for syphilis. The study doctor may be required by law to report the result of these tests to the local health authorities
  - Tests to see the levels of monkeypox virus in their blood
  - Stored blood for future study-required testing
- Your child will answer questionnaires about others who live in their home and whether these household members have monkeypox
- Study staff will take swabs for the following tests:
  - Swabs of your child's skin, mouth, and throat for monkeypox testing
- If your child has eye disease from monkeypox or eye symptoms, study staff will place a strip of paper inside their lower eyelid to collect tears. Your child may also be given eyedrops to help treat eye disease. Please talk to the study staff, your child's primary care provider, or your child's eye doctor about this. These eyedrops are not provided by the study.
- If your child qualifies for the study, they will receive a study kit that includes:
  - Their study drugs. **Tecovirimat or placebo for tecovirimat will be taken two or three times a day for 14 days**.. If you child spits out a dose of study drug or vomits within 15 minutes after taking their study drug, they should take a replacement dose. If your child spits up or vomits more than 15 minutes after taking their study drug, a replacement dose should not be given (the next dose should be taken as scheduled).
  - Instructions on how to complete the study diary that they will complete at home to record how their skin lesions are doing, any symptoms that they are experiencing, and any pain that they are experiencing. We will also ask your child to write down the date and time that they take their study drug.

There are some tests that will only be done at this study visit if your child qualifies for the study and is sexually active:

- Your child will have blood drawn for the following tests. The study doctor may be required by law to report the result of these tests to the local health authorities
  - Tests for Hepatitis C
  - Tests for Hepatitis B (unless this information is in their medical records)
  - HIV-1 testing
- Your child will be asked to give a urine sample for the following tests:
  - Tests for sexually transmitted infections. If your child has a positive test for a sexually transmitted infection, they will be referred to their regular doctor for evaluation and treatment. Your child can join this study if they have a sexually transmitted infection. The study doctor may be required by law to report the result of these tests to the local health authorities.
- Study staff will take swabs for the following tests. The study doctor may be required by law to report the result of these tests to the local health authorities.
  - Swabs from the back of your child's throat to test for gonorrhea and chlamydia.

If your child joins the study at an in-person visit, they should continue to be seen in person if possible, however visits may occur through telemedicine if needed.

Study Visit on Day 6
At this visit:
- The study staff will contact your child by phone or via telemedicine to ask about any symptoms they are experiencing and any pain that they might be experiencing.
- Study staff will ask your child if they are taking their study drugs as directed.

Study Visits on Days 8, 15, 22, 29, 57
At these visits:
- Your child will have a brief physical exam and answer questions about any medications they are taking.
- Your child will have an exam of their skin to identify where they have monkeypox lesions. Study staff will take pictures of their skin lesions.
- Your child will answer questionnaires about whether people in their household have monkeypox (day 29 and 57).
- Study staff will collect the following swabs:
  - Swabs of your child's skin, mouth, and throat for monkeypox testing
- If the study staff thinks your child has monkeypox in their eye or they have eye symptoms, a small strip of paper will be placed in their lower eyelid to collect tears.
- Your child will have blood drawn for the following tests:
  - Routine safety tests (liver and kidney tests and blood counts) (day 8)
  - Blood tests to see the levels of monkeypox virus in their blood
  - Blood tests to see how their body processes the study drugs and other medications they take that may interact with study drug (these tests are called pharmacokinetic [PK] tests (days 8 and 15)
  - A test to measure concentrations of medicines used to treat or prevent HIV (if they are living with HIV or taking medications to prevent HIV infection) (day 8 and 15)
  - Stored blood for future study-required testing (day 15)
- Your child may have a series of blood draws to see how their body processes the study drugs (these tests are called intensive PK tests) (day 8). These tests are required for some participants. The study staff at your site can tell your child if they will have to have these tests. If your child has these tests, they will be asked to have nothing to eat or drink except for water for 2-8 hours before their visit. They will arrive at the facility in the morning and will remain there for 8-12 hours, depending on how often they take their study drug. They will have a blood sample drawn, eat a meal appropriate to their age and size, and then they will take their study drug. Additional blood samples will be obtained at 1, 2, 3, 4, 6-, 8-, and 10-hours after their dose of study drug. On the day of the visit, we will place a small plastic tube (like a "drip") in your child's arm. The tube is attached to a plastic needle. The tube will stay in your child's arm until all the blood draws are done. We use the tube so we do not have to stick your child with a needle each time blood is drawn.

Study Evaluations to Complete at Home
In addition to study visits at the clinic, your child will have to complete some study evaluations at home:
- Complete their study diary and pain rating every day on days 1-29
- If you are able to **and you agree**, you will take a photograph of your child's lesions on days 1-29 so you can show them to the study staff to track how your child's lesions are healing.

Additional Study Visits
Your child will have extra study visits if their monkeypox disease gets worse or if their lesions heal up. If you need to report to the site that your child's lesions have healed, this visit may be done remotely (over the phone or via telemedicine systems approved for use at your site).

Early Discontinuation
If at any point in the study you or your child want your child to stop participating in the study, you must contact the site immediately. If you choose to withdraw consent, no additional samples will be collected and no new information will be collected. Any samples that have not been analyzed prior to your withdrawal of consent will be destroyed, but any information from any samples already analyzed will still be used.

QUICK SUMMARY OF EVALUATIONS

	Screening/ Day 1	Day 6	Day 8	Day 15	Day 22	Day 29	Day 57	Lesion Resolution	Disease Progression
Physical Exam	X		X	X	X	X	X	X	X
Telephone Check		X							
Blood Drawn	X		X	X	X	X	X		X
Urine Collected	X								
Intensive PK			X						
Swabs Collected	X		X	X	X	X	X		X
Questionnaires	X	X	X	X		X	X		X
Study Diary/Self Assessments	Days 1-29								

WILL MY CHILD RECEIVE THE RESULTS OF ANY TESTS?

You and your child will receive the results of routine lab tests (for example, blood counts, liver and kidney tests, pregnancy test (if your child is sexually active), testing for sexually transmitted diseases (if your child is sexually active), HIV viral load and CD4 count (if your child is living with HIV) that are performed at the study visits. You will be told of the monkeypox results from swabs taken from skin lesions.

Some of the blood that is collected from your child will be stored and tested later. Some of these tests may be done after you child is done with the study, and other tests are not yet approved by the FDA and are still considered "research" tests. For these reasons, you and your child will not receive the results of: monkeypox testing from areas other than skin lesions, immune response to monkeypox, or blood concentrations of tecovirimat.

You and your child will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study,

you and your child will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your child's care, you and your child will be provided with those results.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY CHILD'S SAMPLES AND INFORMATION ARE USED FOR?

Some of your child's blood will be stored and used for study-required tests that measure the amount of tecovirimat in the blood, how your child's immune system is fighting off monkeypox and how long monkeypox lasts in your child.

Identifiers will be removed from your child's samples and from any private information that has been collected about your child. This means that no one looking at the labels or at other information will be able to know that the samples or information came from your child.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not give permission for your child join this study.

Please refer to Attachment B to consent for use of your child's samples in other studies.

COMMERCIAL PROFIT

Your child's biospecimens collected during this study may be used for commercial profit (even if identifiers are removed) and your child will not share in this profit.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There is no limit to how many children will be in Arm C.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for about two months (60 days).

WHY WOULD THE STUDY DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take your child off the study early without your permission if:

- The study is stopped or cancelled
- Your child's primary care doctor thinks that this study is no longer in your child's best interest and they request that your child stop participating

The study doctor may also need to take your child off the study drug(s) without your permission if:
- Continuing the study drug may be harmful to your child
- Your child needs a treatment that they may not take while on the study
- Your child is not able to take the study drug as required by the study

WHAT HAPPENS WHEN MY CHILD FINISHES THE STUDY?

After your child has completed the study, the study will not be able to continue to provide your child with the study drug they received on the study. If continuing to take this or similar drugs would be of benefit to your child, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this study drug. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the study staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your child's safety, you and your child must tell the study doctor or study nurse about all medications your child is taking before they start the study and also before starting any new medications while on the study. Also, you and your child must tell the study doctor or study nurse before enrolling in any other clinical trials while on this study.

The risks of tecovirimat in people with smallpox or other poxviruses are not known. Tecovirimat has not been studied in people with weak immune systems, the elderly, or children and unanticipated side effects may occur. Tecovirimat 600 mg capsules were tested in 359 healthy adults, including 336 healthy adults who received tecovirimat capsules twice a day for 14 days. Tecovirimat for injection was also tested in 26 healthy adults. No serious problems occurred in any of the participants in these studies.

During the 2022 monkeypox outbreak in the U.S., tecovirimat capsules have also been given to more than 230 people with poxvirus infection, including people with monkeypox, as of July 2022; side effects are being monitored but no serious problems with tecovirimat have been reported so far. Still, tecovirimat may cause some adverse events (side effects). There also may be other adverse events that we cannot predict. The most common adverse events in people who have taken tecovirimat were:
- Headache
- Nausea
- Vomiting
- Stomach pain

As with any medication, there is a potential risk of an allergic reaction. An allergic reaction after receiving tecovirimat could include:

- Rash
- Difficulty breathing
- Wheezing
- Sudden drop in blood pressure causing dizziness or fainting
- Swelling (around the mouth, throat, or eyes)
- Fast pulse
- Sweating.

Risks of Drug Interactions

There are drug interactions with tecovirimat. Tecovirimat can lower or raise the concentrations of other medicines in your blood. When the blood concentrations of other medicines are lower, the other medicines may not work as well. When the blood concentrations of other medicines are raised, the other medicines may cause more side effects. Other medicines may also lower or raise the tecovirimat concentrations in the blood. To minimize the risk for drug interactions, it is important to review all of your child's prescription and over-the- counter medicines and dietary and herbal supplements with study personnel. It is also important to notify study personnel before your child starts any new prescription or over-the-counter medicines and dietary and herbal supplements while taking the study drug.

Risks of Blood Draw

Having blood drawn may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, and in rare cases it may result in fainting. There is a small risk of infection.

Risks of Mouth and Skin Swabs

These can be uncomfortable and occasionally there can be some bleeding.

Questionnaires

You or your child may be embarrassed by the questions about sex.

Loss of Privacy - Photographs of Participant's Face

You**r child** may have photographs taken for this study of **their** face **or areas of their skin that have distinctive markings such as tattoos**. It is possible that **these photographs** may be recognizable and **their** identity may be known. All photographs taken during the study **will be stored in your child's electronic medical record or will be stored** with a code instead of **their** name.

Risks of Your Child Starting the Study Before Their Monkeypox Virus is Confirmed by a Lab

There are other things that can cause lesions on your child's skin, but we want your child to start the study as soon as possible, so we will let them begin study drug even if their skin lesions have not been tested by a lab and confirmed to be monkeypox. There is a chance that your child's lab tests will show that they do not have monkeypox, so there is a risk that they will have taken study drug and participated in study tests when they do not have monkeypox.

The study doctors at your child's site will use their best judgement to make sure that this does not happen, but if it does happen your child will stop taking the study drug and **the study staff at your study site will check on your child in 7 days** to make sure that they do not have any side effects before they leave the study.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Tecovirimat has not been studied in pregnant or nursing people. It is not known if giving tecovirimat to a pregnant person would hurt the unborn child. Tecovirimat has been tested on pregnant mice and rabbits. There were no serious problems in the unborn animals. Poxviruses during pregnancy can cause serious harm to the pregnant person and unborn baby.

In animal studies, tecovirimat was present in animal milk. When a drug is present in animal milk it is likely to be present in human milk. Because of the potential for virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended while the nursing individual has active lesions. A lactating person should consider pausing breastfeeding and consider pumping and discarding breast milk during study treatment.

If your child can get pregnant but is not pregnant when they join the study and they are engaging in sexual activity that could lead to pregnancy, they must agree to use at least one effective method of contraception from the time they join the study until they are finished with the study. Effective methods of contraception are hormonal contraceptives (injected or in pills), male or female condoms, diaphragm or cervical cap with a spermicide, or an intrauterine device (an IUD). Abstinence (agreeing not to have sex) is also allowed as a way to prevent pregnancy.

If at any point during the study you think your child may be pregnant, you should let the study staff at your site know so that a pregnancy test can be done.

If your child is pregnant or they become pregnant while on study, the study staff would like to obtain information from your child about the outcome of the pregnancy (even if it is after their participation in the study ends). We would also like them to bring the baby in for a study visit about 4 weeks after they are born so we can examine the baby.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

We do not know for certain if your child will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat their infection and prevent it from getting worse, but we cannot make any guarantee.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

There is no proven way to treat poxviruses, but research is ongoing. Your child may benefit from supportive therapy (such as IV fluids, or medicine to control fever or pain) and antibiotics

for any bacterial infections they may have. There may be other medications that your child's study doctor may consider using to treat their infection. There may also be research studies looking at other new treatments for poxviruses.

Please talk to your study doctor about these and other choices available to your child. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your child's privacy. In addition to the efforts of the study staff to help keep your child's personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your child's participation. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify your child in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (see below); if you have consented to the disclosure, including for your child's medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about your child or your child's involvement in this research. If you want your child's research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Having a Certificate of Confidentiality does not prevent you or your child from releasing information about your child and your child's participation in the study. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

Your child's records may be reviewed by the U.S. Food and Drug Administration (FDA), the AIDS Clinical Trials Group (ACTG), the U.S. Office for Human Research Protections (OHRP), or other local, U.S., and international regulatory entities as part of their duties, Advarra Institutional Review Board (IRB) (a committee that protects the rights and safety of participants in research),

National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

Also, any publication of this study will not use your child's name or identify them personally.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO MY CHILD?

The study will pay for research-related tests and assessments. Taking part in this study may lead to added costs to your child and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your child is taking part in a research study.

WILL MY CHILD RECEIVE ANY PAYMENT?

Compensation

You child will be paid up to a total of $xx.xx if they complete this study. You child will be paid for the visits they complete according to the following schedule:
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.

If your child does not complete the study, for any reason, they will be paid for each study visit they do complete.

Your child will be paid _____ *["following each completed visit", "monthly", "quarterly", "at the end of their participation in the research study", "following each completed visit or at the end of their participation in the research study, whichever you prefer"]*.

If you have any questions regarding your child's compensation for participation, please contact the study staff.

WHAT HAPPENS IF MY CHILD IS INJURED?

If your child is injured as a result of being in this study, they will be given immediate treatment for their injuries. There is no program for compensation through the NIH. The cost for this treatment will be charged to you or your insurance company.

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You or your child may choose not to take part in this study or leave this study at any time. You or your child's decision will not have any impact on your or your child's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you or your child are otherwise entitled.

We will tell you about new information from this or other studies that may affect your child's health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if your child experiences any medical problems, suffers a research-related injury, or has questions, concerns or complaints about the study such as:

- Whom to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Their responsibilities as a research participant;
- Eligibility to participate in the study;
- The study doctor's or study site's decision to withdraw your child from participation;
- Results of tests and/or procedures;

Please contact the study doctor at the telephone number listed on the first page of this consent document.

If you seek emergency care, or hospitalization is required, alert the treating physician that your child is participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your child's rights as a research participant, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call toll free: 877-992-4724
- or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00065749.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree for your child to take part in this study, please sign your name below.

Name of Child or Adolescent (print)		
Name of Parent or Legal Guardian (print)	Parent or Legal Guardian Signature	Date
Name of Witness (if applicable, print)	Witness Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide for your child to be in this study, the study doctor and study staff will use and share health data about your child to conduct the study. Health data may include:

- Your child's name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your child's study visits, including all test results.

Health data may come from your child's study records or from existing records kept by your child's doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of University of California, Los Angeles (UCLA) and National Institute of Allergy and Infectious Diseases (NIAID).
- Representatives of ACTG.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other U.S. federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this study, if applicable.
- A data safety monitoring board which oversees this study, if applicable.

Your child's health data will be used to conduct and oversee the research, including for instance:

- To see if the study drug works and is safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your child's health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about your child will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about your child at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, your child will not be able to stay in this study. No new health data that identifies your

child will be gathered after your written request is received. However, health data about your child that has already been gathered may still be used and given to others as described in this form.

Your right to access your child's health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your child's study health data.

If you decide not to sign and date this form, your child will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my child's health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my or my child's legal rights by signing and dating this form.

_____
Name of Child or Adolescent (print)

_____	_____
Name of Parent of Legal Guardian (print)	Parent of Legal Guardian Signature and Date
_____	_____
Name of Witness (if applicable) (print)	Witness Signature and Date

APPENDIX V: INFORMED CONSENT AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR PARENTS/LEGAL GUARDIANS OF CHILDREN WHO ARE ENROLLED/FOLLOWED REMOTELY

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"**
Protocol Number:	**A5418**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

SUMMARY

PURPOSE **This is a research study and your child's participation in this study is voluntary. The purpose of this study is to evaluate how well tecovirimat works for the treatment of human monkeypox virus infection and if the study drug is safe in people. The study will also help us understand more about how human monkeypox causes disease, how the body fights off infection, and how to dose tecovirimat in children.**

STUDY GROUPS **There are different groups in this study. Arm A will take the tecovirimat study drug, Arm B will take a placebo. A placebo looks like a "real" drug but does not have any active drug in it. Participants will be randomly assigned to Arm A or Arm B (like flipping a coin or rolling dice).**

All participants in Arm C will take tecovirimat, without any chance of getting the placebo. Children under 18 years of age will be in Arm C and receive tecovirimat.

STUDY DRUG **The study drug will be tecovirimat. Tecovirimat will be taken two or three times a day for 14 days..**

NUMBER OF PARTICIPANTS **There is no limit to how many children will enroll in this study.**

LENGTH OF STUDY **Your child's participation in this study will last about 2 months. If they become pregnant, we will contact you periodically to see how their pregnancy goes and to know the health of their child.**

REQUIRED ACTIVITIES **If your child is in this study, the following study procedures are required**

- **You or your child will record their symptoms daily**
- **They will provide swabs of the sores on their skin**
- **You or your child will complete questionnaires about their symptoms**

RISKS **The most common side effects people receiving tecovirimat have noticed are:**

- **Headache**
- **Nausea (feeling like you want to vomit)**
- **Vomiting**
- **Stomach pain**

BENEFITS **We do not know if your child will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat their infection and prevent it from getting worse, but we cannot make any guarantee.**

OTHER CHOICES **There is no proven way to treat human monkeypox virus. Your child may benefit from supportive therapy (such as intravenous [IV] fluids, or medicine to control fever or pain) and antibiotics for any bacterial infections they may have. There may be other medications that your child's study doctor may consider using to treat their infection. Tecovirimat may be available outside this study. There may also be research studies looking at other new treatments for poxviruses.**

INTRODUCTION

This form is for the parent or legal guardian of a child or adolescent who is being asked to participate in this research study. In this form, participants are referred to as "children" even though they may be older teenagers.

You are being asked for your child to take part in this research study because they:

- **Have confirmed or suspected monkeypox virus**

- **They have had symptoms for fewer than 14 days**
- **They have at least one active, not yet scabbed lesion in the skin, a sore in the mouth or proctitis (inflammation of the lining of the rectum)**

This study is sponsored by the National Institutes of Health (NIH). The study doctor is in charge of this study at this site. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree for your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Monkeypox is caused by a virus. This virus is most often spread by close contact with someone who has monkeypox. Illness caused by monkeypox virus infection usually starts with a fever and feeling poorly before a rash begins. However, the rash may begin without other symptoms. The rash looks like raised bumps and pus-filled blisters (called lesions). They usually crust, scab, and fall off after about 2-4 weeks, sometimes leaving a scar.

Since Spring 2022, monkeypox has rapidly spread throughout the world, with more than 70,000 cases in 107 countries and more than 26,000 cases in the United States reported as of September 2022.

Tecovirimat is a drug that may help to treat infections caused by pox viruses. Tecovirimat is approved by the Food and Drug Administration (FDA) to treat smallpox in adults and children, but its use in this study is considered investigational. An investigational use is one that has not been approved by the FDA. Tecovirimat has been approved based only on data from animals. We don't know for sure if it works to treat any infections in people. The FDA has reviewed information on tecovirimat and determined that tecovirimat may help treat infection, including serious or potentially life-threatening disease, from poxviruses.

Tecovirimat has been given safely to some people with monkeypox in the recent outbreak and is currently being studied in several ongoing studies outside of the U.S., but none of the studies have shown whether or not this study drug works to treat monkeypox. The safety of tecovirimat has been evaluated in a study with adult participants without monkeypox. Tecovirimat was generally safe and well tolerated – the risks are noted below.

We are doing this study to see if tecovirimat is safe and whether it helps treat monkeypox in people. The study will also help us understand more about how human monkeypox causes disease and how the body fights off infection. This

study will help us understand how much tecovirimat to give children to treat monkeypox.

WHAT DOES MY CHILD HAVE TO DO IF THEY ARE IN THIS STUDY?

<u>Screening/Day 1 Visit</u>
If you would like your child to be in this study, after you have read and signed this consent form, your child will have a screening visit to make sure they meet the requirements for joining the study. This visit will be done via telemedicine.

We will collect some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count and viral load if your child is living with HIV) information. We will collect this information even if your child does not join this study.

At this visit:
- **Your child will answer questions about their medical history and any medications they have taken recently.**
- **Your child will have an exam of their skin to identify where they have monkeypox lesions. Your child will may have to remove some of their clothes for this exam. Site staff will ask to take pictures of your child's skin lesions. Your child does not have to agree to have these pictures taken. Your child can participate in this study regardless of what they decide about having pictures taken. If your child agrees, these pictures will be used so that the study staff can follow how well their lesions are healing. These pictures will not be used for any other purpose without your child's written permission. If your child has lesions on their face, it is possible that they will be able to be identified in these pictures. These pictures may be stored in your child's electronic medical record. If these pictures are stored in a study database, they will be stored securely with a code instead of your child's name. Please discuss how pictures are stored at your child's clinical research site.**
- **Your child will answer questionnaires about any pain their lesions may be causing.**
- **If your child has eye disease from monkeypox or eye symptoms, study staff will ask you to have your child be seen by an eye doctor outside of the study.**
- **If they are available in their medical records, we will record the results from your child's latest physical exam and results from any recent pregnancy test.**

There are some tests that we will only request at this study visit if your child is sexually active:
- **Your child will be advised to obtain testing for sexually transmitted infections outside of the study as indicated. If your child is found to have an STI or HIV, they will be referred for treatment or study staff will provide appropriate treatment.**

There are some tests that will only be done at this study visit if your child qualifies for the study:

- **Your child will answer questionnaires about others who live in their home and whether these household members have monkeypox.**
- **If they are available in your medical records, we will record the results from recent blood tests your child had.**
- **If your child qualifies for the study, a study kit will be delivered to them that includes:**
  - **Their study drugs. Tecovirimat will be taken two or three times a day for 14 days. If you child spits out a dose of study drug or vomits within 15 minutes after taking their study drug, they should take a replacement dose. If your child spits up or vomits more than 15 minutes after taking their study drug, a replacement dose should not be given (the next dose should be taken as scheduled).**
  - **Instructions on how to complete the study diary that they will complete at home to record how their skin lesions are doing, any symptoms that they are experiencing, and any pain that they are experiencing. We will also ask your child to write down the date and time that they take their study drug.**
  - **Containers for any sample collections that your child will do at home.**

If your child joins the study remotely, we expect that all of their visits will be done remotely, but they may elect to have follow up visits in person. In this event, they would sign the consent form for in person follow up.

<u>Study Visit on Day 6</u>
At this visit:

- **The study staff will contact your child by phone or via telemedicine to ask about any symptoms they are experiencing and any pain that they might be experiencing.**
- **Study staff will ask your child if they are taking their study drugs as directed.**

<u>Study Visits on Days 8, 15, 22, 29, 57</u>
These visits will be conducted via telemedicine. At these visits:

- **Your child will answer questions about any medications they are taking.**
- **Your child will have an exam of their skin to identify where they have monkeypox lesions. Study staff will ask you to take pictures of their skin lesions or they will take pictures via telemedicine.**
- **Your child will answer questionnaires about whether people in their household have monkeypox (day 29 and 57).**

<u>Study Evaluations to Complete at Home</u>
In addition to the telemedicine visits, your child will have to complete additional study evaluations at home:

- **Complete their study diary and pain rating every day on days 1-29**
- **If you are able to and you and your child agree, you will take photographs of your child's lesions at least twice a week so you can show them to the study staff to track how your child's lesions are healing.**
- **On the day that they enter the study and again on day 8 your child will be asked to take swabs of their skin for monkeypox testing. You will return these samples to the**

testing lab via mail or courier service. These samples may be omitted if testing/shipping kits are not available or if health laws where you live do not allow you to ship the samples. If a new lesion appears on your child's skin on or after day 6, they will be asked to take a swab of the new lesion for monkeypox testing. You will send the swab to the testing laboratory.

Additional Study Visits

Your child will have extra telemedicine visits if their monkeypox disease gets worse or if their lesions heal up. If you need to report to the site that your child's lesions have healed, this visit may be done remotely (over the phone or via telemedicine systems approved for use at your site). If your child's monkeypox disease gets worse they may also choose to come into the site to see the site staff in person if they would prefer.

Early Discontinuation

If at any point in the study you or your child want your child to stop participating in the study, you must contact the site immediately. If you choose to withdraw consent, no additional samples will be collected and no new information will be collected. Any samples that have not been analyzed prior to your withdrawal of consent will be destroyed, but any information from any samples already analyzed will still be used.

QUICK SUMMARY OF EVALUATIONS

	Screening/ Day 1	Day 6	Day 8	Day 15	Day 22	Day 29	Day 57	Lesion Resolution	Disease Progression
Skin Exam via Telemedicine	X		X	X	X	X	X	X	X
Swabs Collected	X		X						
Questionnaires	X	X	X	X		X	X		X
Study Diary/Self Assessments	Days 1-29								

WILL MY CHILD RECEIVE THE RESULTS OF ANY TESTS?

Testing of the swabs that you collect may be done after you are done with the study. For this reason, you will not receive these results.

You and your child will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you and your child will be told when study results may be available and how to learn about them. As with all studies, if we find out important information that may affect your child's care, you and your child will be provided with those results.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY CHILD'S SAMPLES AND INFORMATION ARE USED FOR?

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not give permission for your child join this study.

Please refer to Attachment B to consent for use of your child's samples in other studies.

COMMERCIAL PROFIT

Your child's biospecimens collected during this study may be used for commercial profit (even if identifiers are removed) and your child will not share in this profit.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There is no limit to how many children will be in Arm C.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for about two months (60 days).

WHY WOULD THE STUDY DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take your child off the study early without your permission if:

- **The study is stopped or cancelled**
- **Your child's primary care doctor thinks that this study is no longer in your child's best interest and they request that your child stop participating**

The study doctor may also need to take your child off the study drug(s) without your permission if:

- **Continuing the study drug may be harmful to your child**
- **Your child needs a treatment that they may not take while on the study**
- **Your child is not able to take the study drug as required by the study**

WHAT HAPPENS WHEN MY CHILD FINISHES THE STUDY?

After your child has completed the study, the study will not be able to continue to provide your child with the study drug they received on the study. If continuing to take this or

similar drugs would be of benefit to your child, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drug used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with this study drug. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the study staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your child's safety, you and your child must tell the study doctor or study nurse about all medications your child is taking before they start the study and also before starting any new medications while on the study. Also, you and your child must tell the study doctor or study nurse before enrolling in any other clinical trials while on this study.

The risks of tecovirimat in people with smallpox or other poxviruses are not known. Tecovirimat has not been studied in people with weak immune systems, the elderly, or children and unanticipated side effects may occur. Tecovirimat 600 mg capsules were tested in 359 healthy adults, including 336 healthy adults who received tecovirimat capsules twice a day for 14 days. Tecovirimat for injection was also tested in 26 healthy adults. No serious problems occurred in any of the participants in these studies.

During the 2022 monkeypox outbreak in the U.S., tecovirimat capsules have also been given to more than 230 people with poxvirus infection, including people with monkeypox, as of July 2022; side effects are being monitored but no serious problems with tecovirimat have been reported so far. Still, tecovirimat may cause some adverse events (side effects). There also may be other adverse events that we cannot predict. The most common adverse events in people who have taken tecovirimat were:

- **Headache**
- **Nausea**
- **Vomiting**
- **Stomach pain**

As with any medication, there is a potential risk of an allergic reaction. An allergic reaction after receiving tecovirimat could include:

- **Rash**
- **Difficulty breathing**
- **Wheezing**
- **Sudden drop in blood pressure causing dizziness or fainting**
- **Swelling (around the mouth, throat, or eyes)**

- **Fast pulse**
- **Sweating.**

Risks of Drug Interactions
There are drug interactions with tecovirimat. Tecovirimat can lower or raise the concentrations of other medicines in your blood. When the blood concentrations of other medicines are lower, the other medicines may not work as well. When the blood concentrations of other medicines are raised, the other medicines may cause more side effects. Other medicines may also lower or raise the tecovirimat concentrations in the blood. To minimize the risk for drug interactions, it is important to review all of your child's prescription and over-the- counter medicines and dietary and herbal supplements with study personnel. It is also important to notify study personnel before your child starts any new prescription or over-the-counter medicines and dietary and herbal supplements while taking the study drug.

Risks of Skin Swabs
These can be uncomfortable and occasionally there can be some bleeding.

Questionnaires
You or your child may be embarrassed by the questions about sex.

Loss of Privacy - Photographs of Participant's Face
Your child may have photographs taken for this study of their face or areas of their skin that have distinctive markings such as tattoos. It is possible that these photographs may be recognizable and their identity may be known. All photographs taken during the study will be stored in your child's electronic medical record or will be stored with a code instead of their name.

Risks of Your Child Starting the Study Before Their Monkeypox Virus is Confirmed by a Lab
There are other things that can cause lesions on your child's skin, but we want your child to start the study as soon as possible, so we will let them begin study drug even if their skin lesions have not been tested by a lab and confirmed to be monkeypox. There is a chance that your child's lab tests will show that they do not have monkeypox, so there is a risk that they will have taken study drug and participated in study tests when they do not have monkeypox.

The study doctors at your child's site will use their best judgement to make sure that this does not happen, but if it does happen your child will stop taking the study drug and the study staff at your study site will check on your child in 7 days to make sure that they do not have any side effects before they leave the study.

Risks of Participating in the Study through Telemedicine
Study providers are not able to fully examine your child through telemedicine. It is possible that their assessment is not complete or not as accurate as an in-person visit.

You are encouraged to see local providers in person if you or your child have concerns about their health.

ARE THERE RISKS RELATED TO PREGNANCY AND BREASTFEEDING?

Tecovirimat has not been studied in pregnant or nursing people. It is not known if giving tecovirimat to a pregnant person would hurt the unborn child. Tecovirimat has been tested on pregnant mice and rabbits. There were no serious problems in the unborn animals. Poxviruses during pregnancy can cause serious harm to the pregnant person and unborn baby.

In animal studies, tecovirimat was present in animal milk. When a drug is present in animal milk it is likely to be present in human milk. Because of the potential for virus transmission through direct contact with the breastfed infant, breastfeeding is not recommended while the nursing individual has active lesions. A lactating person should consider pausing breastfeeding and consider pumping and discarding breast milk during study treatment.

If your child can get pregnant but is not pregnant when they join the study and they are engaging in sexual activity that could lead to pregnancy, they must agree to use at least one effective method of contraception from the time they join the study until they are finished with the study. Effective methods of contraception are hormonal contraceptives (injected or in pills), male or female condoms, diaphragm or cervical cap with a spermicide, or an intrauterine device (an IUD). Abstinence (agreeing not to have sex) is also allowed as a way to prevent pregnancy.

If at any point during the study you think your child may be pregnant, you should let the study staff at your site know. Your child is encouraged to obtain pregnancy testing if they believe they may be pregnant.

If your child is pregnant or they become pregnant while on study, the study staff would like to obtain information from your child about the outcome of the pregnancy (even if it is after their participation in the study ends).

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

We do not know for certain if your child will benefit from tecovirimat. Based on what we know about tecovirimat, the study drug may help to treat their infection and prevent it from getting worse, but we cannot make any guarantee.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

There is no proven way to treat poxviruses, but research is ongoing. Your child may benefit from supportive therapy (such as IV fluids, or medicine to control fever or pain)

and antibiotics for any bacterial infections they may have. There may be other medications that your child's study doctor may consider using to treat their infection. There may also be research studies looking at other new treatments for poxviruses.

Please talk to your study doctor about these and other choices available to your child. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your child's privacy. In addition to the efforts of the study staff to help keep your child's personal information private, we have gotten a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your child's participation. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify your child in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (see below); if you have consented to the disclosure, including for your child's medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about your child or your child's involvement in this research. If you want your child's research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

Having a Certificate of Confidentiality does not prevent you or your child from releasing information about your child and your child's participation in the study. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

Your child's records may be reviewed by the U.S. Food and Drug Administration (FDA), the AIDS Clinical Trials Group (ACTG), the U.S. Office for Human Research Protections

(OHRP), or other local, U.S., and international regulatory entities as part of their duties, Advarra Institutional Review Board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

Also, any publication of this study will not use your child's name or identify them personally.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO MY CHILD?

The study will pay for research-related tests and assessments. Taking part in this study may lead to added costs to your child and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because your child is taking part in a research study. If your child goes to a clinic other than their site clinic for STI testing, pregnancy testing, or other testing, the study will not pay for this testing.

WILL MY CHILD RECEIVE ANY PAYMENT?

«Compensation»

You child will be paid up to a total of $xx.xx if they complete this study. You child will be paid for the visits they complete according to the following schedule:
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.
$xx.xx for Visits xxx.

If your child does not complete the study, for any reason, they will be paid for each study visit they do complete.

Your child will be paid _____ *["following each completed visit", "monthly", "quarterly", "at the end of their participation in the research study", "following each completed visit or at the end of their participation in the research study, whichever you prefer"]*.

If you have any questions regarding your child's compensation for participation, please contact the study staff.

WHAT HAPPENS IF MY CHILD IS INJURED?

If your child is injured as a result of being in this study, they will be given immediate treatment for their injuries. There is no program for compensation through the NIH. The cost for this treatment will be charged to you or your insurance company.

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You or your child may choose not to take part in this study or leave this study at any time. You or your child's decision will not have any impact on your or your child's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you or your child are otherwise entitled.

We will tell you about new information from this or other studies that may affect your child's health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if your child experiences any medical problems, suffers a research-related injury, or has questions, concerns or complaints about the study such as:

- **Whom to contact in the case of a research-related injury or illness;**
- **Payment or compensation for being in the study, if any;**
- **Their responsibilities as a research participant;**
- **Eligibility to participate in the study;**
- **The study doctor's or study site's decision to withdraw your child from participation;**
- **Results of tests and/or procedures;**

<u>Please contact the study doctor at the telephone number listed on the first page of this consent document</u>.

If you seek emergency care, or hospitalization is required, alert the treating physician that your child is participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your child's rights as a research participant, contact:

- **By <u>mail</u>:**
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600

Columbia, MD 21044

- **or call <u>toll free</u>: 877-992-4724**
- **or by email: <u>adviser@advarra.com</u>**

Please reference the following number when contacting the Study Subject Adviser: <u>Pro00065749</u>.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree for your child to take part in this study, please sign your name below.

Name of Child or Adolescent (print)		
Name of Parent or Legal Guardian (print)	**Parent or Legal Guardian Signature**	**Date**
Name of Witness (if applicable, print)	**Witness Signature**	**Date**
Study Staff Conducting Consent Process Name (print)	**Study Staff Signature**	**Date**

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide for your child to be in this study, the study doctor and study staff will use and share health data about your child to conduct the study. Health data may include:

- **Your child's name.**
- **Address.**
- **Phone number.**
- **Date of birth.**
- **Medical history.**
- **Information from your child's study visits, including all test results.**

Health data may come from your child's study records or from existing records kept by your child's doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- **Representatives of University of California, Los Angeles (UCLA) and National Institute of Allergy and Infectious Diseases (NIAID).**
- **Representatives of ACTG.**
- **Representatives of Advarra IRB (an Institutional Review Board that reviews this study).**
- **The Food and Drug Administration (FDA) and other U.S. federal and state agencies.**
- **Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.**
- **Governmental agencies of other countries.**
- **Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.**
- **Other research doctors and medical centers participating in this study, if applicable.**
- **A data safety monitoring board which oversees this study, if applicable.**

Your child's health data will be used to conduct and oversee the research, including for instance:

- **To see if the study drug works and is safe.**
- **To compare the study drug to other drugs.**
- **For other research activities related to the study drug.**

Once your child's health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about your child will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about your child at any time by writing to the study doctor at the address listed on the first page of

this form. If you do this, your child will not be able to stay in this study. No new health data that identifies your child will be gathered after your written request is received. However, health data about your child that has already been gathered may still be used and given to others as described in this form.

Your right to access your child's health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your child's study health data.

If you decide not to sign and date this form, your child will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my child's health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my or my child's legal rights by signing and dating this form.

Name of Child or Adolescent (print)		
Name of Parent or Legal Guardian (print)	Parent or Legal Guardian Signature	Date
Name of Witness (if applicable, print)	Witness Signature	Date

ATTACHMENT B: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES **FOR PARENTS/LEGAL GUARDIANS OF CHILDREN**

Everything in the main study consent form you signed before still applies to your child's participation in this study unless otherwise noted in this form.

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples". The ACTG will only allow your child's extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your child's samples and from any private information that has been collected about your child. This means that no one looking at the labels or at other information will know that the samples or information came from your child.

Extra samples are stored in a secure central place called a repository. Your child's samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your child's extra samples will be stored.

When a researcher wants to use your child's samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your child's samples to the researcher's location. This means that researchers who are not part of the study team may use your child's samples without asking you again for your consent.

Your child will not be paid for their samples. Also, a researcher may make a new scientific discovery or product based on the use of your child's samples. If this happens, there is no plan to share any money with your child.

You may withdraw your consent for research on your child's extra samples at any time and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the study staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your child's extra samples may be stored (with usual protection of their identity) and used for ACTG-approved research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my child's samples

OR
____ (initials) I understand but I do not agree to this storage and possible use of my child's samples

Research with Human Genetic Testing
The ACTG has two studies that collect samples for genetic testing.

If you live in the U.S., this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials for Currently Unspecified Analyses.

If you live outside of the U.S., this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like for your child to participate in this study if it is being done where your child lives. If you would like your child to participate, you will sign and date a separate consent form.

Your child's extra samples will not be used for human genetic testing unless you sign and date a consent form for A5128 **or A5243**.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree for your child to take part in this study, please sign your name below.

Name of Child or Adolescent (print)		
Name of Parent or Legal Guardian (print)	Parent or Legal Guardian Signature	Date
Name of Witness (if applicable, print)	Witness Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date

APPENDIX VI: PARTICIPANT ASSENT FORM FOR STUDY PARTICIPATION FOR PARTICIPANTS AGED 7 TO AGE OF MAJORITY (AOM) **WHO ARE ENROLLED/FOLLOWED IN PERSON**

Sponsor / Study Title:	National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"
Protocol Number:	A5418
Principal Investigator: (Study Doctor)	«PiFullName»
Telephone:	«IcfPhoneNumber»
Address:	«PiLocations»

INTRODUCTION

You are being asked to take part in a research study. In order for you to take part, you must give your permission. Your parent/lega**l** guardian must also give permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we talk with you about this, if you decide to take part in the study, you will write your decisions at the end of this form. You will be offered a copy to keep.

ABOUT THE STUDY

The study is testing a drug called, tecovirimat, which is being tested to see if it works to treat human monkeypox virus infection and if the study drug is safe in people.

Participants in the study will take the tablets **two or three times** every day for two weeks and be checked by study nurses and study doctors to see if the tablets cause bad effects. Participants will have blood drawn to test for bad effects. Tests will also check the amount of study drug that can be found in the blood.

YOUR RIGHTS

It is up to you and your parent/legal guardian to decide if you will take part in this study. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on your medical care.

You do not need to join this study to receive medical care but right now, there is no proven way to treat human monkeypox virus. There may be other treatments to help you feel better and you can receive that treatment outside the study. The study drug may be available outside this study. You may also qualify for other studies. Please ask any questions you may have about these options.

WHAT HAPPENS IN THE STUDY?

If you decide to take part in the study, we will first examine you (check your body), draw blood, and do some tests to see if you qualify to be in the study. You may also have to give a urine sample.

If you are having sex, you will have a test for HIV. The study doctor may be required by law to report the result of this test to the local health authority.

If you are living with HIV, you will have a test to see how much HIV virus is in your blood and how many immune cells you have in your blood (immune cells help fight infection). You will receive the results of these tests.

While in the study, you will take the tablets being tested. We will remind you and your parent/legal guardian that you should take the tablets two **or three** times **e**very day, for two weeks.

You will come to this clinic for at least 6 visits.

At these visits, we will ask you and your parent/legal guardian about your health, and the medicines you take. We will ask questions about the tablets being tested. We will examine you and draw blood for tests. We will collect swabs for monkeypox testing from your mouth, any lesions you have on your skin, and possibly your eyes (if you have infection in your eyes).

If you are having sex, we will do tests at your first visit to see if you have any infections that people sometimes get from sex. You will receive the results of these tests. The study doctor may be required by law to report any positive test results to the local health authority.

Besides coming in for these visits, we will also ask you to collect information at home. For example, you and your parent/legal guardian will be asked to fill out a study diary.

We will tell you as much information as you want about the tablets being tested and what will happen when you come here for visits. Please ask any questions you may have. Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 2 months.

EXTRA BLOOD DRAWS

You may have to have some extra blood tests done to measure the amount of study drug in your blood very closely. Whether you have to have these tests depends on how many kids have already joined the study who are about the same weight as you are. The study staff at your site will tell you if you have to have these tests.

If you have to have these tests, we will ask that you have nothing to eat or drink except for water for **2-**8 hours before your visit. You will arrive at the facility in the morning. You will have blood taken, eat a meal, and then take your study tablets. Additional blood samples will be taken 7 more times that day. You will have to stay at the facility for up to 12 hours on the day of this visit. On the day of the visit, we will place a small plastic tube (like a “drip”) in your arm. The tube is attached to a plastic needle. The tube will stay in your arm until all the blood draws are done. We use the tube so we do not have to stick you with a needle each time blood is drawn.

LEFTOVER BLOOD SAMPLES

After your blood is tested for the study, some samples may be left over. We call these extra samples. We would like to keep these extra samples and use them for other research in the future. You and your parent/legal guardian can decide whether to allow your extra samples to be kept and used for future research. You are free to say yes or no, and to change your mind at any time. Your decision will have no effect on your being in the study.

If you say no, all extra samples will be destroyed.

If you say yes, there is no limit on how long extra samples will be kept or when they will be used.

The results of research done with your extra samples will not be given to you or your parent/legal guardian.

WHAT GOOD AND BAD EFFECTS COULD HAPPEN?

By taking part in this study, you will be helping test a new drug that may benefit (have good effects for) people with monkeypox virus. You may also have good effects from the tablets being tested. For example, the tablets could work well for you and help you get healthy. However, we do not know this for sure.

The study drugs may not work well for you. They could cause bad effects. For example, they could make you feel sick, by causing a headache, make you **throw up** or feel like you need to **throw up**, or have stomach pain. We will ask you to tell your parent/legal guardian any time you do not feel well. You and your parent/legal guardian should also tell us if you do not feel well. We will ask you to come here so we can check on you and try to make you feel better.

Having your blood drawn may cause fainting, pain, bleeding, bruising, swelling, or infection where the needle goes in your arm. You may feel nervous or embarrassed when answering questions for the study.

Another possible risk is to your privacy. For example, **if you agree,** you may have photographs of your face taken for this study. It is possible that your face may be recognizable and your identity may be known. All photographs taken during the study will be stored with a code instead of your name. **You do not have to agree to have photos taken to be in this study.** Other people could find out that you are in the study or learn other information about you. We will make every effort to avoid this. For example, most of the records we keep here for the study will be labeled with a code number (not your name). We will share information about you, including information that you tell us, with your parent/legal guardian. We will not share your information with other people unless you or your parent/legal guardian ask us to.

You may be embarrassed by some of the questions we ask you about your health and your sexual activity (if you have sex). You may be embarrassed or upset about sharing information with parents/legal guardians, especially information about sexual activity (if you have sex).

Other people may review the records from your study visits, including people who work at your study clinic, people from the government agencies that are overseeing this study, and people who work for the company that make the study tablets that you will take. These records will not include your name. Your records will have a series of numbers that are used instead of your name.

If we learn of new information while you are on the study that may make you change your mind about being in the study, we will tell you this information.

GIRLS SHOULD KNOW

The study drugs used in this study might hurt you or hurt a baby if you get pregnant. You will be asked questions to see if you can get pregnant. If you can get pregnant and you are having sex, you will have a pregnancy test. If you can get pregnant, you must use birth control while you are participating in this study.

You should not get pregnant while you are in this study. If you are doing things that might get you pregnant, you have to take care to keep from getting pregnant to be in this study. The study doctor and your parents or legal guardian will explain what you need to do. If you think you might be pregnant, you must tell the study doctor or the study staff right away.

WILL I GET PAID FOR BEING IN THIS STUDY?

You will get paid a small amount for study visits and study tests. The study staff at your site can tell you more about how much you will get paid.

WHOM TO CONTACT ABOUT THIS STUDY?

You and your parent/legal guardian can contact us at any time. Please talk to your parent/legal guardian and to us about any questions or problems you may have.

For questions about this study or a research-related injury, contact the study doctor or other study staff at the telephone number on the first page of this assent document.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call toll free: 877-992-4724
- or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00065749.

SIGNATURES

Before deciding whether to take part in this study, make sure you have read this form or had it read to you. Make sure all your questions have been answered.

If you decide to join this study, please sign or make your mark below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print	Study Staff's Signature and Date

If you have decided to join this study, please write your initials or make your mark below to show your choices for your leftover samples:

_____ I allow my leftover samples to be kept and used for future research

_____ I do <u>not</u> allow my leftover samples to be used for any future research.

APPENDIX VII: PARTICIPANT ASSENT FORM FOR STUDY PARTICIPATION FOR PARTICIPANTS AGED 7 TO AGE OF MAJORITY (AOM) WHO ARE ENROLLED/FOLLOWED REMOTELY

Sponsor / Study Title:	**National Institute of Allergy and Infectious Diseases (NIAID)/ "A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Monkeypox Virus Disease"**
Protocol Number:	**A5418**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

INTRODUCTION

You are being asked to take part in a research study. In order for you to take part, you must give your permission. Your parent/legal guardian must also give permission.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we talk with you about this, if you decide to take part in the study, you will write your decisions at the end of this form. You will be offered a copy to keep.

ABOUT THE STUDY

The study is testing a drug called, tecovirimat, which is being tested to see if it works to treat human monkeypox virus infection and if the study drug is safe in people.

Participants in the study will take the tablets two or three times every day for two weeks and be checked by study nurses and study doctors to see if the tablets cause bad effects.

YOUR RIGHTS

It is up to you and your parent/legal guardian to decide if you will take part in this study. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on your medical care.

You do not need to join this study to receive medical care but right now, there is no proven way to treat human monkeypox virus. There may be other treatments to help you feel better and you can receive that treatment outside the study. The study drug may be available outside this study. You may also qualify for other studies. Please ask any questions you may have about these options.

WHAT HAPPENS IN THE STUDY?

If you decide to take part in the study, we will first do an assessment to see if you qualify to be in the study.

While in the study, you will take the tablets being tested. We will remind you and your parent/legal guardian that you should take the tablets two or three times every day, for two weeks.

You will have at least 6 study visits. These visits will take place via telemedicine (a system where you and the study doctors can see and hear each other over video).

At these visits, we will ask you and your parent/legal guardian about your health, and the medicines you take. We will ask questions about the tablets being tested. We will examine your skin.

Besides these visits, we will also ask you to collect information at home. For example, you and your parent/legal guardian will be asked to fill out a study diary. You will also be asked to take swabs from the monkeypox sores that you have and mail them to the testing laboratory.

We will tell you as much information as you want about the tablets being tested and what will happen when you come here for visits. Please ask any questions you may have. Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 2 months.

WHAT GOOD AND BAD EFFECTS COULD HAPPEN?

By taking part in this study, you will be helping test a new drug that may benefit (have good effects for) people with monkeypox virus. You may also have good effects from the tablets being tested. For example, the tablets could work well for you and help you get healthy. However, we do not know this for sure.

The study drugs may not work well for you. They could cause bad effects. For example, they could make you feel sick, by causing a headache, make you throw up or feel like you need to throw up, or have stomach pain. We will ask you to tell your parent/legal guardian any time you do not feel well. You and your parent/legal guardian should also tell us if you do not feel well. We will talk to you on the phone or by telemedicine so we can check on you and try to make you feel better.

Another possible risk is to your privacy. For example, if you agree, you may have photographs of your face taken for this study. It is possible that your face may be recognizable and your identity may be known. All photographs taken during the study will be stored with a code instead of your name. You do not have to agree to have photos taken to be in this study. Other people could find out that you are in the study or learn other information about you. We will make every effort to avoid this. For example, most of the records we keep here for the study will be labeled with a code number (not your name). We will share information about you, including information that you tell us, with your parent/legal guardian. We will not share your information with other people unless you or your parent/legal guardian ask us to.

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  Columbia, MD 21044
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If you decide to join this study, please sign or make your mark below.

Participant's Name (print)	**Participant's Signature and Date**
Study Staff Conducting Consent Discussion (print	**Study Staff's Signature and Date**

If you have decided to join this study, please write your initials or make your mark below to show your choices for your leftover samples:

_____ I allow my leftover samples to be kept and used for future research

_____ I do <u>not</u> allow my leftover samples to be used for any future research.