**Study title: Observational cohort study of treatment outcomes in human Monkeypox virus disease**

**Short title: Monkeypox observational cohort**

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**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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# Synopsis

|  |  |
| --- | --- |
| **Scientific Title** | Observational cohort study of treatment outcomes in human monkeypox virus disease |
| **Short title** | Monkeypox treatment cohort |
| **Design** | Observational cohort study |
| **Objectives** | To describe clinical and virological outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat (or other antiviral drugs).To describe safety outcomes in patients with monkeypox virus disease treated with tecovirimat (or other antiviral drugs). |
| **Participants** | Male and female patients, with:1. Laboratory confirmed monkeypox virus disease
2. Laboratory confirmation pending, but who are being managed as a presumptive case.
 |
| **Planned Sample Size** | Up to 500 patients |
| **Follow up duration** | 180 Days |
|  | **Objectives** | **Outcome Measures** |
| **Primary** | To describe clinical outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat (or other antiviral drugs). | 1. Time to lesion resolution, defined as the first day on which all lesions are scabbed or desquamated, and absence of any serious complications, up to 14 days post treatment.
 |
| **Secondary** | To describe other clinical outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat (or other antiviral drugs). | 1. Clinical status on day 14 and day 28 according to a four-point ordinal scale (all lesions resolved and no serious complications, active lesions and no serious complications, hospitalised because of a serious complication of monkeypox, and death).
2. Evidence of recrudescence or relapse at D60 and D180
 |
| To describe virological outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat (or other antiviral drugs). | 1. Change from baseline in Monkeypox virus DNA levels in throat swabs on days 4, 8, 14 and 28.
2. Change from baseline in Monkeypox virus DNA levels in blood on days 4, 8, 14 and 28 (hospitalised patients only).
3. Presence of Monkeypox virus DNA in lesion swabs on days 4, 8, 14 and 28.
 |
| **Safety** | To describe safety outcomes in patients with monkeypox virus disease treated with tecovirimat (or other antiviral drugs). | 1. Number of SAEs, SARS & SUSARS within 28 days of enrolment, with descriptive statistics of the main causes.
2. Outcome of pregnancy in women who are pregnant.
 |

# Lay Summary

Monkeypox is a viral disease that causes a fever and a rash, and can be more severe in some people. Usually, it is more common in Africa, but this year there have been a growing number of cases in Europe and other regions, where it has continued to spread from person to person.

At the moment, most patients with monkeypox are treated only for their symptoms, such as pain and itch. However, there are also several specific treatments that have been developed to treat monkeypox and similar viruses. The most widely used at present is tecovirimat. It has been shown to be effective against monkeypox in animal testing, and safe in human testing in patients without the disease. This drug is approved by the European Medicines Agency (EMA) for the treatment of smallpox (a related virus), cowpox and monkeypox under exceptional circumstances.

In this protocol we describe a study to enrol patients with monkeypox disease to monitor the time it takes to recover from infection. We plan to enrol adults and children who have tested positive for monkeypox and who agree to being involved in the study after we have explained the benefits and potential risks. In the study we will not be providing any additional treatments, or changing the care that patients are receiving through their medical team. We will be monitoring patients to understand more about their disease, and their signs and symptoms if they do receive treatments like tecovirimat. Patients are free to leave the study at any time if they wish.

To check how quickly patients recover from monkeypox we will monitor signs and symptoms via an electronic form that patients fill in each day, and also check how quickly patients clear the virus (through blood tests in patients who are in hospital and by throat swabs and lesion swabs in all patients) We will also be monitoring for potential side effects and adverse reactions to treatments. We will review patients when they are enrolled and after 2 weeks, and 1,2, and 6 months, or if they are in hospital. We expect to enrol around 500 patients.

This study is led by researchers from the University of Oxford and includes experts in infectious diseases from around Europe. When the study is complete, we will publish the anonymised results in a scientific journal so the results can be used by others.

# Abbreviations

|  |  |
| --- | --- |
| **AE** | Adverse Event |
| **eCRF** | Electronic Case Report Form |
| **EMA** | European Medicines Agency |
| **FDA** | United States Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **HRA** | Health Research Authority |
| **ICF** | Informed Consent Form |
| **MPXV** | Monkeypox virus |
| **NHS** | National Health Service |
| **PI** | Principal Investigator |
| **PIL** | Participant/ Patient Information Leaflet |
| **R&D** | NHS Trust R&D Department |
| **REC** | Research Ethics Committee |
| **RGEA** | Research Governance, Ethics and Assurance, University of Oxford |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SOP** | Standard Operating Procedure |
| **SSAR** | Suspected Serious Adverse Reaction |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TPOXX** | Tecovirimat (brand name) |
| **WHO** | World Health Organisation |

# Background and rationale

## Disease or Condition for Treatment Use

Monkeypox is an acute febrile rash illness caused by the monkeypox virus (MPXV). The clinical features of human monkeypox closely resemble those of smallpox. Although monkeypox is typically milder than smallpox, it can be fatal. Monkeypox cases have been increasing markedly in Central and West Africa, possibly due to waning of population immunity derived from the smallpox eradication program [1-3]. Historically, there have been sporadic imported cases to other parts of the world with limited onward transmission.

Following notification from the United Kingdom to WHO on the 15th of May 2022, of two confirmed and one probable case, there is evidence of a growing number of monkeypox cases in Europe without a travel history, indicating community transmission of monkeypox virus in this region.

## Purpose for Treatment Use

Two distinct clades of MPXV have been characterized: Congo Basin (CB) and West African (WA). A prospective cohort of 216 patients with CB clade disease estimated mortality at approximately 1 %. [4] After a 5 - 21-day incubation period, a prodromal illness with fever, malaise, and swollen lymph nodes is observed in most patients. The prodromal period generally lasts 1–3 days before the occurrence of the typical vesiculo-pustular rash, which lasts 2 to 4 weeks. Other common symptoms include malaise (97% of cases), sore throat (78% of cases), and lymphadenopathy (57% of cases). [5] In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12%), ocular complications (4%–5%), and encephalitis (<1%) can be observed in patients infected with MPXV. Death, when it occurs, generally occurs during the second week of the lesional stage of the disease.

## Description of current therapies

*A number of antivirals have been proposed for use for MPXV. The list of antivirals that are to be used in Europe may expand during the timeframe of this study*

## Tecovirimat (TPOXX)

Tecovirimat (TPOXX) is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein. Tecovirimat is US Food and Drug Administration (FDA) approved since July 2018 for the treatment of smallpox in adults and paediatric patients weighing ≥13 kg under the so-called ‘animal rule’.[6] This allows registration of drugs for conditions for which it is either not possible (e.g. rare diseases) or ethical to conduct a clinical trial. “In these cases, FDA may grant approval based on well-controlled animal studies, when the results of those studies establish that the drug or biologic product is reasonably likely to produce clinical benefit in humans. The product sponsor must still demonstrate the product’s safety in humans.” On the basis of these animal data, in January 2022, the European Commission (EU), following positive evaluation by the European Medicines Agency (EMA) also granted marketing authorisation under exceptional circumstances for tecovirimat for the treatment of monkeypox and other orthopoxvirus diseases including vaccinia complications in adults and children of at least 13kg body weight. [7]

Tecovirimat specifically inhibits all orthopoxviruses tested, including the human pathogenic viruses, variola, vaccinia, cowpox virus and, importantly for this protocol, MPXV[8]. The effectiveness of tecovirimat for treatment of smallpox disease has not been determined in humans as it would be neither feasible nor ethical to conduct such trials. SIGA Technologies Netherlands (SIGA), the applicant of the FDA and EMA approvals, have conducted twelve clinical trials evaluating the safety and pharmacokinetics of tecovirimat; ten Phase 1 studies, one Phase II study and one Phase III study.

In addition, an Expanded Use Access programme has been established in the Central African Republic (CAR), under a tripartite agreement between the Ministry of Health, Institut Pasteur Bangui, University of Oxford – which acts as the sponsor for the embedded research (OxTREC reference: 1-20). The programme is underway and has recruited so far 14 patients.

Tecovirimat is generally well tolerated.[9] The approved human dose of 600 mg twice daily results in exposures that clearly exceed efficacious exposures in the monkeypox/non-human primate models. [9] At the approved dose, the incidence of adverse events (AEs) was similar to the incidence of AEs among subjects receiving placebo in human trials. Most AEs were mild or moderate and resolved without sequelae. [9]

There are no known instances of naturally occurring tecovirimat resistant orthopoxviruses, although tecovirimat resistance may develop under drug selection. Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37 protein can confer large reductions in tecovirimat antiviral activity.

No adequate and well-controlled studies in pregnant women have been conducted; therefore, there are no human data to establish the presence or absence of tecovirimat associated risk in pregnancy. In animal reproduction studies, no embryofetal developmental toxicity was observed. [9]

# Study rationale

Tecovirimat was licensed in the EU on the basis of efficacy data in non-human primate studies, and safety data in human trials. [7] Because there has not previously been a substantive number of monkeypox cases in Europe ascertainment of efficacy in humans was not possible. The aim of this study is to improve our understanding of clinical and virological outcomes in patients with monkeypox virus disease treated or not treated with tecovirimat (or other antiviral drugs), given the small number of patients with the disease in whom have been used in. We will include patients who are being treated for their disease, as well as patients who are eligible for, but not receiving treatment due to logistical reasons, patient choice, or safety reasons, as this group may provide useful comparison data.

Inclusion is independent of whether a patient is considered for, or receives treatment with an antiviral or not.

# Study objectives and outcome measures

As a relatively rare human infection, precise clinical criteria to define cure/resolution of monkeypox are presently lacking. We anticipate that improved natural history data will become available in the coming months, and outcomes will be refined in light of this emerging evidence if required.

Primary outcome

Clinical status defined by

1. Time to lesion(s) resolution, defined
	1. From a start point of date that positive test is collected
	2. Until an endpoint of up to 14 days since commencement of treatment.
	3. Where lesion resolution is the first day on which all lesions are resorbed, scabbed or desquamated and mucosal ulcers healed.
	4. And the absence of any serious complications

Secondary outcomes

Clinical status defined by

1. Clinical status on day 14 and day 28 according to an ordinal scale assessed by a physician or a study nurse. The ordinal scale is a) all lesions resolved and no serious complications, b) active lesions and no serious complications, c) hospitalised because of a serious complication of monkeypox, or d) death.
2. Evidence of recrudescence or relapse at day 60 and day 180

A "serious complication" is one that: results in a complication that is life-threatening, or results in a hospitalisation or prolongation of existing hospitalisation, or results in a disability or incapacity, or results in congenital anomaly, or results in any other complication that is considered medically significant.

Virological status defined by

1. Change from baseline in Monkeypox virus DNA levels in throat swabs on days 4, 8, 14 and 28.
2. Change from baseline in Monkeypox virus DNA levels in blood on days 4, 8, 14 and 28.
3. Presence of Monkeypox virus DNA in lesion swabs on days 4, 8, 14 and 28.

An additional test will take place at day 21 for patients who are still positive at day 14.

Patient self-collection of throat and lesion swabs will only occur in countries where these can be collected or posted in a way that is compliant to national regulations.

Blood samples will only be collected in patients who are reviewed in person (either hospitalised or clinic visit). In patients under the age of 12, blood samples will only be taken if they are also being taken for clinical reasons, or the patient has suitable existing intravenous access

Safety assessment

 (In cohort receiving tecovirimat (or other antivirals)): Number and type of Serious Adverse Events (SAEs), Suspected Adverse Reactions (SARS) and Suspected Unexpected Serious Adverse Reactions, (SUSARs) within 28 days of enrolment. We will assess outcome of pregnancy in women who are pregnant.

Exploratory outcomes

The following may be added in some countries. If these are to be included, they will be detailed in further protocol submissions with information on sampling, and an updated patient schedule and statistical analysis.

* Virus culture: to discriminate between live and residual virus.
* Additional virological analyses including the slope of viral clearance and Area Under the Curve (AUC).
* Serology: To quantify antibody responses, blood samples will be collected at baseline and then on days TD4, 8, 14 and 28 (or equivalent days for patients who are not receiving the drug).
* Resistance: A further optional component may occur at some sites where a subset of samples will be tested for the emergence of resistance mutations in the gene encoding VP37 protein.

# Study design

This a multi-centre, multi-country prospective observational cohort study enrolling patients with laboratory confirmed monkeypox. Patients who are being managed as a presumptive case can also be enrolled while laboratory confirmation is pending. A patient who is a presumptive case and subsequently tests negative for MPXV will exit the study.

Participants will be enrolled in hospitals in the UK and Europe (mainly through Eu-Response network in the European Union and under the Ecraid umbrella) and may be managed as either inpatients or as outpatients.

Participation in the study will last for a maximum of 6 months (180 days) from the commencement of treatment. Pregnant women will be followed up at the completion of pregnancy.

Data will be collected directly from participants in the form of an online self-completion survey and from their direct care team on an eCRF.

Blood samples will be collected from participants at the point of enrolment if they are present in a hospital. Blood samples will continue to be collected from inpatients on Days 4, 8, 14 and 28. Outpatients will give blood samples only if they attend an inpatient visit on Day 14 and 28.

Lesion and throat swab samples will be collected from all participants at enrolment and Days 4, 8, 14, and 28.

# Participant pathway

Exit study immediately

Exit follow up at treatment day (TD180)

Commence follow up at day 1 (D1)

Commence follow up at treatment day 1 (TD1)

Baseline assessments

1. Patient with laboratory diagnosis of Monkeypox
2. Patient with presumptive monkeypox awaiting laboratory diagnosis
3. Consents to inclusion in study

Enrolment

Prescribed tecovirimat

No tecovirimat treatment

Initial therapy

Progress

Drug subsequently prescribed

No drug treatment

Does not have laboratory confirmed monkeypox

Exit follow up at day 180 (D180)

Exit study immediately

Does not have laboratory confirmed monkeypox

Drug treatment

Progress

Diagram 1 – Participant pathway

# Study Participants

Participants with laboratory confirmed monkeypox.

## Inclusion criteria

1. Male and female patients, with:
	1. Laboratory confirmed monkeypox virus disease
	2. Laboratory confirmation pending, but who are being managed as a presumptive case
2. Informed consent provided for participation in the study

A presumptive case is defined as a patient who is managed as a case of monkeypox due to high clinical suspicion of disease (according to the prevailing WHO case definition) or high risk of serious disease (such as immunosuppression). A patient who is a presumptive case and subsequently tests negative for MPXV will exit the study.

Inclusion is independent of whether a patient is considered for, or receives antiviral treatment or not.

We will seek consent from patients to be enrolled in the study under the circumstances where they have already been managed as a monkeypox case at a study site, but prior to launch of that study site. Once study sites are launched, all enrolment will be prospective.

## Exclusion criteria

Presumptive cases with subsequent negative test for MPXV will be excluded from the study.

# Study procedures

## Recruitment

Participants will be identified and approached to participate in this study by their direct care team at a participating site.

Potential participants will be given the study participant information sheet and adequate time to consider the implications of their participation in the study.

Participation will be entirely voluntary, and potential participants will not be coerced to participate against their will. It will be made clear that participants will be free to withdraw from the study at any time without impact on their care.

## Eligibility assessment

No exemptions will be made regarding eligibility. Each participant must satisfy all the approved inclusion criteria.

## Informed consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. Verbal consent will not be used for this study. Patients who cannot write will be asked to annotate written consent.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their doctor or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

This study is not a clinical trial but the study will monitor patients who will be prescribed tecovirimat or other antiviral medications (or are eligible for but not receiving treatment for various reasons including availability, contraindications or unwillingness to receive treatment). Consent to receive treatment will be undertaken by the patient’s treating clinician and does not constitute a component of the consent for this study.

## Children

Participants of any age can be enrolled in the study providing a parent or legally designated representative gives consent and the child provides assent.

The participant information sheet should be given to the child’s parent or legally designated representative and an age appropriate information sheet should be given to the child.

Parents or legally designated representative will be asked to sign the consent form and children will be asked to complete an assent form, where they are of an appropriate age to do so.

Participants above the age of 16 can sign the consent form themselves in countries where legally applicable.

If during the study the minor reaches the age of legal competence to give informed by consent ias defined by law in the country concerned, their express informed consent shall be obtained.

## Participants who do not have capacity to consent for themselves or who lose capacity following consent

In severe cases of monkeypox, it is possible that participants approached about the study do not have capacity to decide whether to take part. It is also possible that participants may lose capacity following consent.

The inclusion and continued participation of participants who do not have capacity to consent for themselves or who lose capacity will be managed according to local regulatory requirements.

In the UK, in order to comply with the Mental Capacity Act 2005, the study will consider that:

* a person must be assumed to have capacity unless established otherwise
* individuals should be helped to make their own decisions as far as practicable
* a person is not to be treated as unable to make a decision merely because he makes an unwise decision
* all decisions and actions must be in the best interests of the person lacking capacity
* all decisions and actions must be the least restrictive of the person’s rights and freedom of action.

If potential participants are considered not to have sufficient capacity to consent to the study, a personal consultee (or legally designated representative depending on the jurisdiction) will be sought to advise on what the participant’s wishes and feelings would be about taking part.

A personal consultee (or legally designated representative depending on the jurisdiction) will also be sought if a participant in the study loses capacity following consent to advise on whether the participant would wish to continue in the study or be withdrawn.

The consultee (or legally designated representative depending on the jurisdiction) will be provided with written information about the study. They will be given sufficient time to consider the study and the opportunity to ask questions to the patient's direct care team.

The advice of the consultee (or legally designated representative depending on the jurisdiction) will be respected by the study team and documented on a record of consultation form to confirm that they have received this information and had the opportunity to ask any questions and give advice.

If no consultee (or legally designated representative depending on the jurisdiction) can be identified a third party unconnected with the research who is willing to act as a nominated consultee will be nominated by the potential participant's direct care team.

The personal consultee (or legally designated representative depending on the jurisdiction) will be kept fully informed throughout the study and will be asked to attend any research procedures, including sampling and clinical reviews, to provide support to the participant.

If the personal consultee (or legally designated representative depending on the jurisdiction) becomes unavailable during the course of the study, the participant's direct care team will either find an alternative or appoint a nominated consultee.

Nothing will be done to which the participant appears to object, including but not limited to sample taking.

If a participant who was considered not to have capacity at enrolment and was included in the study based on the advice of a personal consultee (or legally designated representative depending on the jurisdiction) subsequently regains capacity (or becomes of an age where they can legally consent), they will be provided with the study information sheet and asked to consider whether they wish to continue taking part. Unless they give consent to retain and analyse any data and samples collected so far, these will be destroyed. They will have the same opportunity to consider the study and ask questions to their direct care team as other participants. If they do not wish to continue participating, they will be withdrawn from the study.

## Enrolment

This is a non-randomised study.

Participants will be enrolled in the study after written informed consent has been entered and their details have been registered on the eCRF.

## Blinding and code-breaking

This is not a blinded study and therefore no-code breaking procedures will apply.

## Description of study interventions, comparators and study procedures

This is an observational cohort study and there are no study interventions or comparators. Treatment should be given according to national prescribing guidelines.

## Schedule of procedures (diagram 2)

Demographics and medical history: Data relating to the participant’s demographics and medical history will be collected at baseline.

Clinical review: There will be face-to-face (including by video link) clinical assessments undertaken at baseline, and treatment day or observation day 14, day 28, day 60, and day 180. Patients who are in hospital for monkeypox (or a related condition) will have a clinical assessment daily while they are in hospital until the point of discharge.

Follow up will occur at two and six months can be undertaken face to face, or by video link, or by phone. Patients who are pregnant will be followed up until the completion of their pregnancy.

Self-monitoring: Patients will collect daily symptom data via a secure online form, or assisted by study staff if available and required for accessibility or other reasons.

Biologic sampling: Outpatients will self-collect swabs (where these can be transported under local regulations) and hospitalised patients will have blood tests taken according to the schedule below. Blood tests at day 14 and day 28 will be performed in outpatients having a clinical visit.

*A note on study days (D) and treatment days (TD) (diagram 3)*

Some patients will never receive treatment (because the drugs are not available, contraindicated, or they do not consent). Other patients will receive the drugs immediately. We anticipate that there also may be some cases where patients begin observation but then receive the drug at a later date.

When a patient starts treatment, they follow procedures from treatment day (TD) 1 and continue. This overrides any previous study day and will therefore extend the study participation period by the number of days between enrolment and treatment initiation.

Diagram 2: Schedule of procedures

|  | **Ba** | **D1****&****TD1** | **D2****&****TD2** | **D3****&****TD3** | **D4****&****TD4** | **D5****&****TD5** | **D6****&****TD6** | **D7****&****TD7** | **D8****&****TD8** | **D9****&****TD9** | **D10****&****TD10** | **D11****&****TD11** | **D12****&****TD12** | **D13****&****TD13** | **D14****&****TD14** | **D21****&****TD21** | **D28****&****TD28** | **D60****&****TD60** | **D180****&****TD180** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Consent** | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Demographics** | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Comorbidities** | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Pregnancy testb** | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **HIV testb** | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Clinical review** | X |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  | X | X | X |
| **Patient self assessment (including SAE and SSAR)** | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Hospital assessmentc** |  | X | X | X | X | X | X | X | X | X | X | X | X | X | Xd |  |  |  |  |
| **Lesion swab** | X |  |  |  | X |  |  |  | X |  |  |  |  |  | X | Xe | X |  |  |
| **Throat swab** | X |  |  |  | X |  |  |  | X |  |  |  |  |  | X | Xe | X |  |  |
| **Blood sample collectionc** | X |  |  |  | X |  |  |  | X |  |  |  |  |  | X | Xe | X |  |  |

a Baseline

b These tests will be voluntary if not already undertaken in routine clinical care

c Whilst hospitalised only or if inpatient visit

 d Will continue daily until point of discharge.

e if positive at day 14

Diagram 3: Study day and treatment day

****

## Baseline assessments

## Pregnancy test

All female subjects of childbearing age will be offered a urine pregnancy test. If participants receive a positive pregnancy test they will be followed in the study until their pregnancy outcome is known. Information on pregnancy outcome will be captured as part of the study.

Pregnant patients will be eligible for enrolment.

## HIV test

Tecovirimat efficacy may be reduced in immunocompromised patients based on studies demonstrating reduced efficacy in immunocompromised animal models. In humans, more severe monkeypox disease has been observed in HIV-positive subjects (8). Therefore, all subjects will be offered a voluntary test for HIV. Results will be returned to the treating site. Subjects found to be HIV-positive will be referred to the HIV service offered by the local health care system Both HIV positive and HIV negative subjects are eligible in the study.

Both the course of infection and treatment outcomes may be influenced by the patient HIV status and so this information, if available, will influence analysis

## Subsequent visits

There will be face-to-face (including by video link) clinical assessments undertaken at baseline, and treatment day or observation day 14 and day 28, Month 2 and Month 6.

## Sampling

Blood samples (estimated 0.5ml - 5ml depending on local specimen collection protocols) will be collected from participants who are enrolled in-person at a participating site. Blood samples will also be collected from in-patients on Days 4, 8, 14 and 28. If there is ongoing evidence of infection at Day 14, a blood sample will also be collected on Day 21. For outpatients attending an in-patient visit, blood sample will be collected at Day 14 and 28.

Throat and lesion swabs will be collected from participants in both in-patient and out-patient settings at baseline and Days 4, 8, 14 and 28. If there is ongoing evidence of infection at Day 14, throat and lesion samples will also be collected on Day 21. Where practical under national laws and guidelines, out-patients will be sent sample kits to their home with instructions on how to obtain a sample and shipping.

Sample handling in hospital will be according to routine hospital practices, including processing and storage. The duration of storage will be dependent on national regulations on the storage of study samples.

## Early discontinuation and withdrawal of participants

During the course of the study a participant may choose to withdraw early from the study at any time. This may happen for several reasons, including but not limited to:

* A presumptive case enrolled in the study will be withdrawn if they subsequently test negative for MPXV
* The occurrence of what the participant perceives as an intolerable AE
* Inability to comply with study procedures
* Participant decision
* Clinician decision

Participants may choose to stop the self-completed questionnaire assessments and sampling but may wish to remain on study follow-up through their direct care team.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

According to the design of the study, participants may have the following three options for withdrawal;

1) Participants may withdraw from active follow-up and further communication but allow their direct care team acting for the study to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care and would be relevant to data collection on the eCRF.

2) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

3) Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

# Definition of end of study

The end of the study will be defined as the date of the last visit (Month 6 or pregnancy outcome) of the last participant and all samples have been analysed.

There are jurisdictional differences in reporting end of study data. In the EU, a summary of study results will be submitted within one year of the last patient visit an will not be postponed for secondary sample analysis. These information will be provided without delay when they are available.

# Safety reporting

There may be country specific additions to safety reporting depending on regulatory requirements, in particular, the additional requirements for the EU/EEA are found in the appendix “safety reporting for EU/EEA sites” annexe that will supersede sections 14.1 and 14.2 for sites who participate under this umbrella

The study procedures carry minimal risk and therefore adverse events related to the study procedures are not anticipated.

However, as part of the secondary outcome measures defined above, the study will collect information on SAEs, SARS & SUSARS within 28 days of enrolment that occur in patients receiving tecovirimat or any other anti-viral medication as prescribed under usual care by their treating clinician. Participants who experience an SAR or SUSAR (an event considered to be related to treatment) will be followed-up until the resolution of the event. All SUSARs should be reported to the sponsor within 24 hours who will report to the EMA within 15 days.”

## Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

* results in death
* is life-threatening
* requires inpatient hospitalisation or prolongation of existing hospitalisation
* results in persistent or significant disability/incapacity
* consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

All serious adverse events (SAEs) will be documented and their causal relationship to tecovirimat (or other antivirals) will be assessed. Any Serious Adverse Event that is believed with a reasonable probability to be due to tecovirimat (or other antiviral) will be considered a Suspected Serious Adverse Reaction (SSAR).

Clinicians at the Oxford University will review reports of SSARs received. Additional information (including the reason for considering it both serious and related, and relevant medical and medication history) will be sought.

Expectedness of a SSAR will be assessed by the Central Coordinating Office taking into account what is expected considering section 4.8 of the EMA SPC (reference safety information) of tecovirimat and the reference safety information (in the SPC) of any other antiviral if applicable. SARS considered to be unexpected (SUSAR) will be reported by the sponsor to Eudravigilance within legal timelines (i.e. 15 calendar days or 7 if related to dead or life-threatening).

## Reporting Procedures for Serious Adverse Events

As this is an observational study, in which treatment decisions are not made for participants and SAEs are collected for study purposes only, information on serious adverse events will be collected via the eCRF.

It is the responsibility of the treating clinician to report (serious) adverse events directly to national and regional regulatory bodies according to applicable national and regional legislation.

# Statistical analysis

## Statistical analysis plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time that the first participant is recruited. The SAP will be finalised before any analysis takes place.

The SAP will be developed by the investigators and published whilst still blind to any analyses of aggregated data on study outcomes by treatment status.

## Description of statistical methods

This is an observational study and so there is no sample size calculation to establish a treatment effect. Since this is an observational cohort and since the availability of treatments and prescription rules will differ in time and across countries all analyses will account for confounding effects when estimating the efficacy of the active treatment. It will be specified in the SAP which causal inference model will be used, how patients will be grouped (e.g. not treated as no drug available, not treated as non-eligible for treatment, treated since D1, delayed treatment) and which groups will be compared.

## Sample size determination

This study is being conducted in the context of an outbreak, in which the study aims to generate as much information as possible about a disease that has previously been poorly characterised, particularly in patients presenting in a non-endemic region who are being treated with a drug under emergency use which has not been widely used for monkeypox.

The number of patients specified in the sample size has been selected as it can be feasibly achieved. It also represents the maximum number of patients that the study would enrol in order to generate conclusions on the primary and secondary outcome measures.

## Analysis populations

All eligible participants will be included in the final analysis.

## Subgroup analysis

Some countries may change to a seven-day treatment course of tecovirimat (for some patients). We will plan to incorporate a subgroup analysis if this occurs.

## Outcomes analysis

Descriptive statistics will be performed in the various groups defined in the SAP.

For time-to-event analyses, Kaplan-Meier estimates will be plotted and used to estimate median time of resolution and/or proportion of resolution at D14.

For clinical status, counts and percentages will be presented together with their confidence interval.

Medians and interquartile ranges of monkeypox virus levels, quantified in Cycle threshold (Ct) values, will be presented for days 4, 8, 14 and 28. These data will also be used to define viral clearance, as a binary variable, in each of the three tissues that will be sampled (blood, skin lesions and throat). Frequency of viral clearance will be presented by day of follow-up and treatment groups.

# Data management

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

## Source data

Source documents are where data are first recorded, and from which participants’ eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data).

In this study, primary data are collected from two main sources: (i) electronic case report forms completed by study staff in participating sites at enrolment, scheduled study visits, daily for in-patients, and when lab results are available; and (ii) an online questionnaire, completed daily by the participant, during the first 14 days of the study (or as long as they are in hospital), at D21, D28, M2 and M6.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

The electronic case record forms will be hosted on a secure, web-based REDCap instance, hosted by University of Oxford.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will be retained only be the site staff on the consent form, the clinical records, and on a contact sheet for the purpose of sending of the self-assessment questionnaires via email or text.

Access to the study database will require unique usernames and passwords, issued to trained study staff approved by the site investigator. All data entries and edits will be fully auditable. The online participant questionnaire will be hosted on a separate, web-based REDCap instance, hosted by the University of Oxford. Participants will be issued a link to access the questionnaire, enter their participant ID and complete the Participant Self-Assessment.  Data from the electronic case record form and the online questionnaire will be downloaded to University of Oxford servers using HTTPS. Participant IDs will be used to link data from the Participant Self-Assessment with data from the case record forms.

Data security will be managed by the University of Oxford according to the ISARIC Data Platform Data Security Model (supplementary material to the protocol).

# Quality assurance procedures

## Risk assessment

As this study carries minimal risk, no risk assessment will be undertaken before the study opens. However, the requirement for a formal risk assessment will be regularly reviewed by the Sponsor after study activation. There is no risk to clinical staff beyond that incurred through routine clinical management of patients.

## Data quality

Data quality checks that alert the user during data entry, will be programmed into the REDCap systems to minimise missed, inconsistent or erroneous data. Study sites will be responsible to review data entered into the case record form for participants at their sites. The study team at the University of Oxford will review the REDCap audit trail and all study data, and trigger queries to be resolved by the sites where issues are found. Issues identified in data from the Participant Self-Assessment will be informed to the study site to communicate with the participant if required.  The sponsors and regulatory agencies will have the right to conduct confidential audits of study records in the recruiting sites and the central coordinating office.

## Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol and the applicable regulatory requirements.

Centralised monitoring will be performed by the University of Oxford on all data collected as part of this study according to the Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy as these are defined in the study specific Monitoring Plan.

On-site monitoring may be required in the event that serious or repeated non-compliance with the protocol is identified via centralised monitoring. This will be carried out by the local/regional coordinating centres.

## Study Committees

## Steering Committee

The role of the Study Steering Committee is to provide overall supervision for the study on behalf of the Sponsor and to ensure that the study is conducted according to the protocol and all relevant regulations and local policies.

## Operations Committee

The role of the Operations Committee is to oversee the day-to-day management, conduct and progress of the study. Any issues identified by the Operations Committee will be reported to the Steering Committee.

## Protocol deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

Details on how to report protocol deviations and their onward management will be described in a SOP.

## Serious breach

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

1. the safety or physical or mental integrity of the study subjects; or
2. the scientific value of the research

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Sponsor P.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

## Ethical and regulatory considerations

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

## Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet and any patient-facing materials material will be submitted to an appropriate Research Ethics Committee (REC) for each jurisdiction, and HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Sites in the EU will comply with the General data protection Regulation (EU) 2016/679 and complementary national data protection legislation in the participating member states.

## Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee for each jurisdiction, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

## Participant confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants’ personal data.

All documents and samples will be labelled with a pseudonymised subject ID code. Identifying information collected as a part of this protocol will remain confidential.

Patients’ names, telephone numbers and email addresses will be recorded at the time of consent to allow for the self-assessment questionnaire to be sent each day and their identification at follow-up visits. Identifiable information will be linked to stored data or samples only by a protected master list. This list will not be shared outside the clinical site staff and no identifying information will be transferred between study sites. However, the participant name, phone number and email address will be transferred to the Sponsor and local/regional coordinating centre so that patients can be sent the self-assessment questionnaire and be assisted in collecting data. A member of the Coordinating Centre (UK participants) or jurisdictional Coordinating Centre (non-UK participants) may contact the participant in the event that the diary is not completed or if the participant requests assistance completing their diary. After the last diary entry has been completed, the participant’s name, email address and phone number will be permanently deleted from the electronic system on which it was held.

All CRF forms and samples will be labelled only with a subject identification number and stored in suitable secure locations. Only persons who have undertaken the locally appropriate data protection training will have access to the password-protected computer where entered data is stored.

Source documents for the study constitute the records held in the study main database. These will be retained for at least 25 years from the completion of the study. Identifiable data will be retained only for so long as it is required. The data will be made available to the manufacturer of the drug, to regulators for licensing decisions, and anonymised data may be shared with other research groups. Informed consent forms will be retained securely by the recruiting sites depending on their jurisdictional requirements.

## Expenses and benefits

There will be no costs to the participants and no payment will be given for participation in the study. Patients will not be reimbursed for incidental expenses related to enrolment.

# Finance and insurance

## Funding

Funding for this study is provided by Wellcome and the Bill and Melinda Gates Foundation. In the EU, additional funding is provided by EU-Response and ECRAID.

Other sources of funding may be determined as the study progresses.

## Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd’s of London). NHS indemnity (or local arrangements for European sites) operates in respect of the clinical treatment that is provided.

# Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

# Publication policy

The patient-anonymised outcomes of this study are expected to be published in the peer-reviewed literature.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Wellcome. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

A summary of the results will be made available in the EU public CTIS within one year following the last visit of the last patient in the last participating EU country.

# Development of a new product/ process or the generation of intellectual property

Not applicable

# References

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8. Grosenbach DW, Honeychurch K, Rose EA, Chinsangaram J, Frimm A, Maiti B, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med. 2018;379(1):44-53. Epub 2018/07/05. doi: 10.1056/NEJMoa1705688. PubMed PMID: 29972742; PubMed Central PMCID: PMCPMC6086581.

9. SIGA Technologies I. TPOXX® (tecovirimat) Investigator’s Brochure 2021.

# Appendix A. Amendment History

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
| - | 1.0 | 7 June | Rojek, Bourner | - |

**Appendix B – Country-specific safety reporting requirements**

**For the UK:**

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA [report of serious adverse event](http://www.nres.npsa.nhs.uk/docs/forms/Safety_Report_Form_%28non-CTIMPs%29.doc) form (see HRA website).

**For EU/EEA member states:**

The complete safety data circuit and safety working instruction is available in a Standard Operating Procedure (SOP) related to the study

**1. Définitions**

|  |  |
| --- | --- |
| **TERM** | **DEFINITION** |
| **Adverse Event (AE)\*** | Any untoward medical occurrence in a patient or clinical trial participant, which does not necessarily have a causal relationship with the research procedures or the investigational medicinal product (IMP). |
| **Adverse Reaction (AR)** | Any untoward and unintended responses to an investigational medicinal product related to any dose administered. |
| **Serious Adverse Event or Reaction (SAE/SAR)** | Any AE/AR that, at any dose, results in:* death;
* a life-threatening AE\*\*;
* hospitalization or prolongation of existing hospitalization\*\*\*;
* a persistent or significant disability or incapacity;
* a congenital anomaly/birth defect;
* a grade 3 or 4 clinical or biological AE;
* an important medical event\*\*\*\*;
* an adverse event of special interest" (AESI)
 |
| **Adverse Event of Special Interest (AESI)** | An AE/AR that are considered as SAE/SAR and require an immediate notification to the sponsor (SAE Form must be used). In this trial, AESI include:* a grade 4 clinical or biological AE;
* any event leading to permanent or temporary discontinuation of the investigational medicinal product;
* the adverse events of special interest are summarised in the protocol (nausea and headache)
*
 |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | An unexpected adverse reaction is an AR of which the nature, the outcome, the frequency or severity is not consistent with the applicable Reference Safety Information (RSI): reference document summary of product characteristics (see below). https://www.ema.europa.eu/en/documents/product-information/tecovirimat-siga-epar-product-information\_en.pdf  |
| **New fact** | Any safety data that could modify significantly the evaluation of the benefit/risk ratio of the IMP or the clinical trial, likely to affect the safety of participants or that could modify the study drug administration, the trial documentation or the conduct of the trial, or to suspend or interrupt or modify the protocol or similar trials.*Example: a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial, a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease, recommendations of the DSMB, if any, where relevant for the safety of subjects*. |

\* An adverse event include:

• Any increase in frequency or intensity of an event or pre-existing condition

• Any condition (even if it was present before the start of the trial) detected after administration of the investigational medicinal product)

An adverse event does not include:

• A medical or surgical procedure (only the condition that led to such a procedure is an adverse event)

• A pre-existing pathology or detected before the first intake of the IMP and which does not worsen

• An event related to the disease studied (such as symptom progression)

\*\*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

\*\*\*Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation.

**EXCEPTIONS:** the following events are not considered as SAE requiring immediate reporting to the sponsor:

- Hospitalisation for a pre-existing condition that has not worsened, scheduled before inclusion in the trial

- Hospitalisation without harmful or unwanted manifestation (hospitalisation for administrative or social reasons, elective hospitalisation for medical or surgical treatment, hospitalisation predefined by the protocol, etc.)

\*\*\*\* Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

**2. Responsibilities of the investigator**

**2.1** **AE/AR and SAE/SAR reporting**

The investigator should:

* Report any non-serious AE **in the corresponding eCRF AE form**.

* Report any SAE and AESI as a detailed, written report, using "SAE initial notification form" **in the corresponding eCRF SAE form**, immediately and no later than 24h after being made aware of it. Once the eCRF SAE notification form is completed, dated and signed by the investigator, an automatic email is sent immediately to the sponsor (pharmacovigilance department).

* Send to the sponsor all relevant documentation related to reported SAE (e.g. hospitalization report, laboratories results…), without omitting to make it anonymous and note the identification number of the participant in the trial and send to the sponsor (pharmacovigilance department) by email: pharmacovigilance@anrs.fr

* Follow any SAE until participant’s clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilized (even if the participant left the trial, when the SAE is possibly related to the IMP).

* Report all new relevant information on SAE or AESI using "SAE complementary notification form" **in the corresponding eCRF SAE form**.

* The sponsor will notify SIGA of any SAE or SUSAR within 15 days.

Any AE/SAE must be reported, if it occurs for a participant, throughout the duration of the research, therefore from the time the subject signed the informed consent and until the end of the follow-up of the participant.

SAE occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them, especially if the SAE is possibly related to the IMP. The investigator does not need to actively monitor subjects for adverse events once the trial has ended, unless provided otherwise in the protocol.

*Back-up circuit when eCRF is unavailable:*

The investigator must report all SAE/SAR using the CRF SAE printed form, dated and signed by email to the study email site.

Then the site will send, within one business day, the CRF SAE printed form to the sponsor (pharmacovigilance department), by fax: 01 53 94 60 02 or by email: pharmacovigilance@anrs.fr

If a SAE is declared by the back-up (paper) circuit, it is the responsibility of the site to re-enter the form in the eCRF as soon as possible.

**2.2** **AE assessment**

*2.2.1* *Seriousness*

For any adverse event, the investigator must determine whether the event meets one or more of the seriousness criteria described above.

*2.2.2* *Severity (grading)*

For any adverse event, the investigator must assess the severity (i.e. intensity) using the table below and reported in the corresponding form of the CRF.

|  |  |  |
| --- | --- | --- |
| **Grade 1** | **Mild** | Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required. |
| **Grade 2** | **Moderate** | Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required. |
| **Grade 3** | **Severe** | Marked limitation of normal daily activities; medical intervention and corrective treatment required possible hospitalization. |
| **Grade 4** | **Life-threatening** | Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting. |

*2.2.3* *Causality*

The investigator must assess the causality of all AEs/SAEs in relation to study drug or research procedures using the following guidelines.

**]**

|  |  |  |
| --- | --- | --- |
| **Relationship** | **Description** | **AE Type** |
| Unrelated | There is no evidence of any causal relationship | Unrelated AE |
| Unlikely | There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient’s clinical condition, other concomitant treatment). | Unrelated AE |
| Possibly | There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient’s clinical condition, other concomitant treatments). | AR |
| Probably | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. | AR |
| Definitely | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. | AR |
| Unable to assess | The causal relationship between the event and study drug cannot be assessed | Unknown |

All AEs/SAEs for which the investigator or the sponsor considers a causal relationship to be a reasonable possibility are considered suspected ARs/SARs.

**2.3** **Pregnancy reporting**

The investigator should:

* Report any pregnancy and its outcome, concerning either the enrolled woman as a detailed, written report, using the "Initial pregnancy notification form" **in the corresponding eCRF Pregnancy form**, immediately and no later than 48 hours after being made aware of it. Once the eCRF Pregnancy notification form is completed, dated and signed by the investigator, an automatic email is sent immediately to the sponsor (pharmacovigilance department).

* Follow the participant until the end of the pregnancy or its interruption and to notify the outcome to the sponsor using the “Final pregnancy notification form” **in the corresponding eCRF Pregnancy form.**

**Warning:**

If the pregnancy outcome fulfilled a seriousness criteria (eg: **anomaly or birth defect, fetal death, voluntary or therapeutic interruption of pregnancy, miscarriage needed a hospitalisation**), the investigator has to notify it to the sponsor as an SAE.

**3. Responsibilities of the sponsor**

* The sponsor is responsible for assessing the causality and expectedness (using the applicable Reference Safety Information) of all SAE reports received, in relation to the IMP, research procedures and concomitant medication (e.g. drug-drug interactions).

* All **Suspected Unexpected Adverse Reactions** (SUSARs) have to be reported, within the legal timeframe, by the sponsor’s representative to the European Medicine Agency (EudraVigilance, EMA) and the National Competent Authorities of the Member State concerned according to local requirements.

All SUSARs will be sent to the independent monitor for information. An extraordinary meeting can be organized in regard of safety concerns.

* The national principal investigator will immediately inform the National Competent Authorities of their member state and concerned Ethics Committees of safety data or safety issues that might alter the current benefit-risk assessment of the trial and may be relevant in terms of subject safety.

* Once a year, the national principal investigator will submit to the National Competent Authorities and the Ethics Committees of each Member State a Development Safety Update Report (DSUR), according to applicable laws and regulations.