

Safety Assessments: Adverse Events and Serious Adverse Events

Adverse Event:

An AE is defined as any untoward medical occurrence in a clinical study participant that **administered an investigational product (IP)**, and which does not necessarily have a causal relationship with that treatment.

The definition of an AE includes:

- **Worsening** (in severity and frequency) of **pre-existing conditions** ("medical history") after trial drug administration and,
- **abnormalities of procedures** (i.e., ECG, X-ray...) or **laboratory results** which are assessed as "clinically significant".

Laboratory/Processing Abnormalities considered as AEs

All Laboratory abnormalities (haematology or blood chemistry) must be assessed as **“clinically significant”** and should be reported as an AE if they meet AT LEAST ONE of the following criteria, in accordance with the protocol:

- ❖ The abnormality suggests a disease and/or organ toxicity AND this abnormality was not present at the screening visit or is assessed as having evolved since the screening visit.
- ❖ The abnormality results in discontinuation of the IP
- ❖ The abnormality requires medical intervention or concomitant therapy
- ❖ The abnormality is associated with clinical signs and symptoms

When reporting an abnormal laboratory/procedure result, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (*for example, "anaemia" rather than "decreased red blood cell count"*).

→ *If there is an abnormal laboratory finding, **the lab test will be repeated** and if the abnormality, is still present, will be assessed further for clinical significance.*

What is not an AE?

- ❖ Medical conditions present at the initial study visit that **do not** worsen in severity or frequency during the study are NOT considered as AEs.
- ❖ Symptoms, exacerbation or worsening of COVID-19 will **NOT be considered as AE** and will not be captured in the AE page of the eCRF if consistent with the anticipated natural progression of the disease (overall and for this given participant).
- ❖ Lack of efficacy of the trial treatment is **NOT considered as AE**.

AE Assessments:

Each AE is to be classified by the Investigator and information must be evaluated by a physician:

- ❖ as serious or non-serious. (as per regulatory definitions)
- ❖ for severity (= intensity; as per clinical definition)
- ❖ for causality (relationship with each study treatment administered)

Serious Adverse Event:

An AE becomes a Serious AE if it:

- ❖ **results in death:** i.e. it causes or contributes to the death.
- ❖ **is life-threatening:** i.e. in this context refers to an AE in which the subject was at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if more severe.
 - **requires in-patient hospitalisation or prolongation of existing hospitalisation:** i.e. the AE requires at least an overnight admission (24 hours) or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons (i.e. social distancing), for any elective surgery (i.e. plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion (i.e. if the protocol or the standard management of the disease under study requires planned hospitalisation). **Hospitalisation in Intensive Care Unit (ICU) and/or start of mechanical ventilation MUST be considered as serious and reported as a SAE.**
- ❖ **results in persistent or significant disability or incapacity:** i.e. the AE resulted in a substantial disruption of the subject's ability to conduct normal activities.
- ❖ **consists of a congenital anomaly/birth defect:** i.e. an AE outcome in a child or foetus of a subject exposed to the IP/trial treatment before conception or during pregnancy.
- ❖ **is an important medical event,** i.e. is medically significant: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events/reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Also, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event/reaction.

SAE onset/start date:

Start date of SAE or date when the AE becomes serious

SAE end/stop date:

SAE end date is the date of AE recovery.

What is NOT an SAE?

Hospital admissions planned for:

- ❖ Any intervention or surgery planned before study entry or for social reasons,
 - ❖ Any elective surgery (i.e. plastic surgery).
 - ❖ respite care in the absence of any deterioration in the subject's general condition and
 - ❖ for normal disease management (including treatment adjustment)
- are NOT to be considered as SAE (i.e. if the protocol requires planned hospitalization).

SAE Reporting

Any new SAE report or follow-up information occurring since the ICF signature, are to be reported by investigators:

- **Immediately OR within 24 hours of awareness**
- Using: SAE form (dated, signed, scanned)
- To: Sponsors, national regulatory body and IRB, as applicable.
- Similarly Follow-Up information: Immediately or within 2 – 5 Working days.

Alternatively, SAEs could be first preliminary notified with key information* by telephone to Clinical team (conversation to be transcribed in an email or phone report by the recipient)

***Key information** (at least 4 minimum criteria that are mandatory for considering a notification as a valid one):

- Identification of the **PATIENT** (trial code number, initials, etc. without name)*
- **REPORTER** identification (trial site number, name...)*
- Suspected **IP** (trial number, start date of study drug administration)* - **study treatment** and information from which study treatment can be identified **remains blinded** in the SAE form
- Diagnosis or very short description of the **EVENT** *

Causality assessment to study drug is necessary for ICSR reportability assessment to external bodies (Health Authorities / Ethics Committees / DSMB / other bodies as applicable)

SAEs must also be recorded in the AE section of the eCRF in addition to SAE form. **The information recorded in the SAE reporting form and in the AE section of the eCRF must be consistent.**

Severity/Grading of an AE/SAE

Severity is a clinical determination of the intensity of each AE to describe its maximum severity. The severity of AEs will be graded using the standardised terminology mild, moderate or severe. The terms are defined as follows:

- ✓ **Mild:** the patient is aware of the event or symptom, but the event or symptom is easily tolerated, and no reduction in daily activities is required;
- ✓ **Moderate:** the patient experiences sufficient discomfort to interfere with or reduces his or her usual level of activity;
- ✓ **Severe:** significant impairment of functioning: the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

Note: A Severe AE is not necessarily a Serious AE

Causality Assessments

The Investigator is required to assess the possible causal relationship between each IP and the event to determine whether there is a reasonable possibility or evidence to suggest a causal relationship that study IP caused or contributed to the event.

Causality will be assessed using the following terms:

- ✓ **Definitely Related:** IP administration and onset of the AE are related in time and a direct association can be demonstrated.
- ✓ **Probably Related:** IP administration and onset of the AE are reasonably related in time and the IP provides a more likely explanation of the AE than other causes.
- ✓ **Possibly Related:** IP administration and onset of the AE are reasonably related in time and causes other than the IP could equally well provide an explanation for the AE.
- ✓ **Probably not Related:** A potential relationship between the IP and the AE could exist, i.e., the possibility cannot be excluded, however causes other than the IP provide a more likely explanation for the AE.
- ✓ **Not Related:** The AE is clearly explained by another cause not related to the IP.

AE/SAE Reporting Period:

- ❖ The AE reporting period begins upon signature of the informed consent form (ICF) and ends at the end-of-study visit on Day 21 or the early withdrawal visit.
- ❖ All AEs that occur during the AE reporting period **must be reported** to the **Sponsor**, whether or not the AE is considered treatment related.
- ❖ In addition, any **AE** that occurs **after the AE reporting period** and until Data Base Lock that the *Investigator considers to be **possibly related to the IP*** should also be reported as an **AE**.
- ❖ Any SAE considered as possibly related to the IP that occurs after the reporting period should also be reported as an SAE.

Important Note: All AEs/SAEs should be followed **until complete resolution** or until the Investigator declares them to be “**chronic**” or “**stable**” or **until the patient’s participation in the study ends** (=final study report is validated and signed/last contact with the patient)

Reference:

ANTICOV_01 COV_Master Protocol: please always refer to the most recent version