Definition of Serious Adverse Event

A SAE is any untoward medical occurrence that, at any dose:

a. Results in death
   
   **NOTE:** Death due to disease under study is to be recorded in the Death eCRF and does not need to be reported as an SAE.

b. Is life-threatening
   
   **NOTE:** The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.

c. Requires hospitalization or prolongation of existing hospitalization
   
   **NOTE:** In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or
   
   **NOTE:** The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

   Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
g. All events of possible treatment-induced liver injury with hyperbilirubinemia defined as:

- ALT ≥5 times ULN and bilirubin ≥3 times ULN (>35% direct) or ALT ≥5 times ULN and INR >1.5, if INR is measured, with no existing liver disease

OR

- ALT ≥8 times ULN and bilirubin ≥5 times ULN (>35% direct) or INR >1.5, if INR is measured, with pre-existing liver disease

**NOTE:** INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

**NOTE:** Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥3 times ULN, if no existing liver disease or ≥3 times ULN if pre-existing liver disease; the event is still reported as an SAE. If INR is obtained, include values on the SAE form. Elevations in INR >1.5 suggest severe liver injury.

h. Protocol-specific SAEs:

- cuSCC (Section 8.2.2.1), new primary melanomas (Section 8.2.2.2) and non-cutaneous malignancies (Section 8.2.2.3) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.

- LVEF that meets the dose interruption criteria (Section 8.1.1.2): absolute LVEF decreases of >10% from baseline (not relative decrease) and below the LLN

- Liver chemistry events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible ‘Hy’s Law’) (Section 8.1.3.1)

- RPED also referred to as central serous retinopathy (CSR) or RVO (Section 8.2.7)

- Pyrexia accompanied by hypotension or dehydration requiring IV fluids or renal insufficiency or severe rigors/chills in the absence of an obvious infectious cause (Section 8.2.3).

11.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.
In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment(s), dose reduction, and/or dose interruption/delay. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject’s condition, are not to be reported as AEs or SAEs.

11.4 Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within 1 week of when the AE/SAE(s) is first reported.

11.5 Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death. This information should be recorded within 1 week of when the death is first reported.

11.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.
11.7 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE.

Adverse events (AEs) will be collected from the time the first dose of study treatment(s) is administered until 30 days following discontinuation of study treatment(s) regardless of initiation of a new cancer therapy or transfer to hospice.

Serious adverse events (SAEs) will be collected over the same time period as stated above for AEs. In addition, any SAE assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or concomitant medication(s) must be recorded from the time a subject consent to participate in the study up to and including any follow-up contact.

After discontinuation of study treatment(s), the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment(s).

11.8 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?” or “How does your child seem to feel?”
- “Have you had any (other) medical problems since your last visit/contact?” or “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?” or “Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

11.9 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the appropriate data collection tool.

It is not acceptable for the investigator to send photocopies of the subject’s medical records to the sponsor in lieu of completion of the AE/SAE data collection tool.

However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to the sponsor.
The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

Subject-completed health outcomes questionnaires and the collection of AE data are independent components of the study. Responses to each question in the health outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale’s developer. The use of single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.