13 ADVERSE EVENTS

13.1 Adverse event definition

An AE is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology.

AZA is well studied, and the investigational product of this study is oral vitamin C supplementation, that is not classified as a medical drug, and that at a dose of 1000 mg/d as used in this study is not suspected of having any side effects. Thus, in this study we have restricted the AE reporting to the following conditions:

- Diarrhea *(patients should be directly asked)*
- Kidney stones or symptoms thereof (severe pain in the side and/or back; fluctuating pain that radiates to the lower abdomen and groin; pain on urination; pink, red, or brown urine) *(patients should be directly asked)*
- Hematological toxicity of grade ≥ 3
- Infection/Sepsis of grade ≥ 2
- Any abnormal laboratory value 1) resulting in discontinuation from the study, 2) requiring treatment, interruption of AZA or study medication, or any other therapeutic intervention, or 3) that is judged by the Investigator to be of significant clinical importance
- Any AE of grade ≥ 3

A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome, including abnormal laboratory values.

AEs will be recorded by the Investigators from start of protocol therapy = D1/C1, until the first week after the EOS, or at end of treatment (EOT) if this occurs at an earlier time point.

13.2 Serious adverse event definition

A SAE is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)

- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Events not to be reported as SAEs in this study are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur due to an accident/trauma; occur on an emergency outpatient basis and do not result in admission, or result in hospitalization < 24 hours in duration (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition. Disease progression and related signs and symptoms are not considered to constitute SAEs.

If an AE is considered serious, both the AE pages of the eCRF and the SAE Report Form along with the Concomitant Medication Form must be completed.

For each SAE, the Investigator(s) will provide information on, e.g., severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

13.3 Classification of severity

For both AEs and SAEs, the Investigator(s) must assess the severity of the event. The severity of AEs will be graded on a scale of 1 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, which can be viewed online at the following NCI website: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event

Grade	Definition
1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only: intervention not indicated
2	**Moderate**; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
3	**Severe or medically significant but not immediately life-threatening**; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
4	**Life-threatening consequences**; urgent intervention indicated
5	**Death** related to AE
*	Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**	Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

13.4 Classification of relationship/causality of adverse events (SAE/AE) to study medication

The Investigator(s) must determine the relationship between the administration of investigational product(s) (vitamin C/placebo) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the AE to administration of the investigational product(s) makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Suspected:	The temporal relationship of the AE to administration of the investigational product(s) makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event

13.5 Monitoring of adverse events

All subjects will be monitored for AEs as defined in section 13.1-13.2 during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination findings; other appropriate tests and procedures.

AEs that cause a subject to discontinue study participation must be followed until either the event resolves, stabilizes, or returns to baseline (if a baseline assessment is available).

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause), or death (due to the SAE).

13.6 Reporting of serious adverse events

The International Principal Investigator/Sponsor will inform relevant regulatory authorities and ECs:

- of all relevant information about serious unexpected AEs suspected to be related to the investigational product(s) that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such by the Investigator. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days
- of all other serious unexpected AEs suspected to be related to the investigational product(s) as soon as possible, and in any case no later than 15 days after knowledge of such by the Investigator

The International Principal Investigator/Sponsor will inform relevant regulatory authorities and ECs of AEs that are **Serious, Unlisted/Unexpected, and at least possibly associated to the drug (SUSARs),** that have not previously been reported in the Investigator's brochure. A clear description

of the suspected adverse reaction should be provided along with an assessment of whether the event is drug- or disease-related.

13.6.1 Immediate reporting by Investigator to Sponsor

The National Principal Investigator will inform the International Principal Investigator/Sponsor of any SAE defined as in section 13.2, regardless of relationship to the study medication, that 1) occurs during active treatment in the study, 2) is made known to the Investigator(s) within 28 days after a subject's last dose of investigational product(s), and 3) is made known to the Investigator(s) at any time if suspected of being related to the investigational product(s). This must be documented on an SAE form. The initial report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up SAE form.

All AE reports must include the patient study ID, age, gender, AE start and stop date, severity of reaction, relationship to study drug, action taken, outcome of AE, expected or not, and whether it constitutes a SAE. The Concomitant Medication Form must be completed and sent to the Sponsor along with the SAE form.