Table 14-5 AE and SAE reporting

	Screening To Pre-Infusion	Treatment and Follow-up Phase (Day 1/RD1 to EOT)

Non-serious Adverse Events (AE)	Modified reporting:
	• All infections
	• All laboratory abnormalities deemed clinically significant by the investigator
	• All neutropenia grade ≥ 3
	• All clinical AEs grade ≥ 3
	• All AEs related to a study procedure
	• All AEs leading to study discontinuation
	• Any substantial change in the status of the subject that precludes the subject form proceeding to study treatment (e.g. GVHD, rapid progression of malignancy, marked decline in performance status)
		All events, including all laboratory abnormalities deemed clinically significant by the investigator.
		Reminder (events of specific interest)
		• New incidence or exacerbation of the following:
		  • A pre-existing neurologic disorder
		  • A prior rheumatologic or other autoimmune disorder
		  • Other hematologic disorder
		• Any severe AE or condition that is unexpected and/or the investigator assesses a reasonable relationship to CLT019 therapy
		• Positive RCL test result
		• Secondary malignancy, other than the primary malignancy
		• Progressive multifocal leucoencephalopathy
		• Hepatitis B reactivation

Serious Adverse Events (SAE)	Modified reporting:
	• Any AE reporting for this period that also meets criteria for serious
	• All events leading to death
	• All events related to a study procedure
	• Leukapheresis (EOI or EOC)
	  • Procedure-related AE/SAEs 24 hours post-collection
		All SAEs must be reported.
		Reminder (events of specific interest)
		• New incidence or exacerbation of the following:
		  • A pre-existing neurologic disorder
		  • A prior rheumatologic or other autoimmune disorder
		  • Other hematologic disorder
		• Any severe AE or condition that is unexpected and/or the investigator assesses a reasonable relationship to CLT019 therapy
		• Positive RCL test result
		• Secondary malignancy, other than the primary malignancy
		• Progressive multifocal leucoencephalopathy
		• Hepatitis B reactivation

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

Serious Adverse event reporting should be completed by the site (either leukapheresis or main (infusion) study site) that has identified or became aware of the SAE. Follow-up of the SAE should be completed accordingly by the same site that has identified and reported the SAE.

Any SAEs experienced during the **Screening and Pre-Infusion phases** (from the time of subject providing informed consent until the subject begins study-related treatment) should ONLY be reported to Novartis and be captured if the CRF and safety database if the event meets at least one of the following criteria:

- Any AE reportable for this study period that also meets criteria for serious
- All events leading to death
- All events related to a study procedure
  - Leukapheresis
    - Procedure-related SAEs occurring within 24 hours post-collection

To ensure subject safety, every SAE, regardless of suspected causality, that occurs during the Treatment and follow-up phase EOT and follow-up) visit must be reported to Novartis within 24 hours of learning of its occurrence. All SAEs (including events of specific interest; see Section 8.1.1 for definition of events of specific interest) should be recorded in the Adverse Events CRF.

In addition, at the specific request of a National Health Authority, the following SAEs will be reported in an expedited manner:

- Any SAE related to a study procedure
- All occurrences of CRS grade ≥ 3 (to be reported to National Health Authority on a monthly basis)
- All deaths regardless of attribution following lymphodepleting chemotherapy and/or tisagenlecleucel infusion and within 30 days of receiving tisagenlecleucel infusion
- Deaths attributed to tisagenlecleucel occurring 30 days post tisagenlecleucel infusion

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the EOT and follow-up visit should only be reported to Novartis Chief Medical Office and Patient Safety (CMO&PS) if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.