Serious Adverse Event (SAE)
A Serious Adverse Event is any untoward medical occurrence or effect at any dose, any undesirable or unintentional effect that:

• results in death (regardless of cause)
• is life threatening
- places the subject, in the view of the investigator, at immediate risk of death at the time of event
- It does not refer to an event that, which hypothetically might have caused death if it were more severe

• results in insubject hospitalization (overnight stay) or prolongation of existing in subjects' hospitalization, unless hospitalization is for:
- Hospitalization that does not necessitate an overnight stay.
- routine scheduled treatment or monitoring of the studied indication, not associated with any deterioration in condition
- planned prior to subject entering in the trial
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication treated in the trial and which has not worsened since the start of treatment with the medical (investigational medicinal product

• results in persistent or significant disability or incapacity of the subject
- disability is a substantial disruption of a person's ability to conduct normal life functions

• is associated with a congenital anomaly or birth defect
• is qualified as "other" important medically significant event or condition e.g. the event may jeopardize the subject or may require intervention to prevent one of the outcome listed above (e.g. intensive treatment in an emergency room or at home).

Serious Adverse (Drug) Reaction (SAR)
This is defined as an adverse drug reaction that is serious and at least possible related to IMP (see SAE criteria above). The events that are excluded from the definition of an SAE are also excluded from the definition of an SAR.

Suspected Unexpected Serious Adverse (Drug) Reaction (SUSAR)
A SUSAR is an adverse reaction, which is both serious and unexpected because the nature or severity of this event is not consistent with the applicable product information (Investigator's Brochure IMBRUVICA® (Ibrutinib), JNJ-54179060, Edition 9, 30 June 2015).

Special Reporting Situations
Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Drug Interaction
- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Suspected transmission of an infectious agent

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

13.2 Criteria to be evaluated by investigator (1st assessment)

Assessment of seriousness, causality, severity and of medical interest For each AE and SAE recorded on the applicable CRF, the investigator will make an assessment of severity, seriousness and causality.
The terms severe and serious are not synonymous. "Severe" refers to the intensity of an AE; the event itself may be of relatively minor medical significance. "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions. Seriousness serves as the guide for defining regulatory reporting obligations.

Assessment of Severity

The intensity (severity) of adverse events will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). Adverse events not explicitly included in the NCI Common Toxicity Criteria list should be described in detail and graded according to the five points system below:

Grade 1	Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Grade 2	Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
Grade 4	Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable (Please note: grade 4 does **not always** imply, that the event is serious)
Grade 5	Death - the event results in death (Please note: grade 5 does **always** imply, that the event is serious and should be reported immediately)

Assessment of Seriousness

See definition of Serious Adverse Event above (13.1). As mentioned above, the criterion "serious" serves as guide for expedited reporting obligations.
A Serious Adverse Event should be immediately reported (within 24 hours) to the sponsor after becoming aware of the event.

Assessment of Causality

Relationship of the adverse events to the investigational products should be assessed as follows:

Related	The temporal relationship between the event and study drug administration makes **causal** relationship **possible, probably or definitely**, AND other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

Not Related	The temporal relationship between the event and study drug administration makes **causal** relationship **unlikely or impossible (not related)** OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

13.4 Reporting of Serious Adverse Events

All events that meet one or more criteria of seriousness (see Section Definition for SAE Section 13.1) that occurred from the time of randomization up to 30 days after last visit with the last individual specific

examination of the subject**,** regardless the relationship to the study treatment must be carefully documented in the source documents and reported to the GLSG Pharmacovigilance Department.
For initial SAE reports, investigators should enter all data that can be gathered immediately at the latest within 24 hours after becoming aware of occurrence of the SAE in the specified Serious Adverse Event Report Electronic Form.
Relevant follow-up information should be entered immediately at the latest within 24 hours after awareness in the specified Serious Adverse Event Report Electronic Form.

Further information on reporting and documentation details are described in the study specific Safety Management Plan.
Minimum Criteria for Adverse Event Reporting
• Duration of an AE (start date and stop date)
• Grade of AE (according to CTC criteria, see Appendix 9:)
• Drug relationship of the AE to the investigational product (Causality assessment)
• Outcome of the AE
• Assessment of seriousness of the event

Due to the expected toxicity of the study treatments, only the following events must be recorded in the appropriate eCRF Adverse-Event-Form (from time of randomization up to 30 days after last visit with the last individual specific examination of the subject):

- All adverse events of any grade which are serious or of special interest must be recorded by the investigator on an eCRF AE-Form and marked as "serious" or of "special interest" within 24 hours after the investigator becomes aware of the event; only if the eCRF is not accessible, the event should be reported on the paper-based SAE-form by fax to the sponsor; the data must then be entered on an eCRF AE-Form by the investigator as soon as the eCRF becomes accessible.

- All non-hematological events of CTCAE grade 3 or 4
- All infections of CTCAE grade 2, 3 or 4
- All events with anemia, neutropenia or thrombocytopenia of CTCAE grade 2, 3 or 4

- All events of any grade, if found to be medical significant by the investigator

Clinical symptoms of progression may be reported as AE if the symptom cannot be determined as exclusively due to the progression of the underlying cancer. In case of uncertainty whether an AE is only due to the disease under study, it should be reported as an AE or SAE.
The following events should **not** be reported as AE or SAE.

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Progression of lymphoma including its clinical symptoms should not be reported as AE or SAE if it is clearly consistent with the suspected progression of the underlying lymphoma
- Hospitalization due solely to the progression of underlying MCL should not be reported as SAE; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition
- Hospitalization because of a diagnostic or elective surgical procedure for a pre-existing (= already documented in the patient's medical history!) medical condition that has not deteriorated does not require reporting as a SAE. Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.