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The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling subjects into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all subjects at the current dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all subjects at the current dose level.

Table 6-3 Criteria for defining dose-limiting toxicities

Toxicity	DLT Criteria
Hematologic toxicities	Acute severe myelosuppression in absence of leukemic transformation: Neutropenia G4* Febrile neutropenia G ≥ 3 (ANC < 1.0 x 10^9/L + Fever ≥ 38.5C degrees C) Thrombocytopenia G4* (platelets < 25 x 10^9/L) persisting ≥ 3 days Prolonged myelosuppression in absence of leukemic transformation: Thrombocytopenia G3 (platelets < 50 x 10^9/L) persisting ≥ 21 days Thrombocytopenia G3 (platelets < 50 x 10^9/L) prior to dosing on C2D1 and C3D1 **
Non-hematologic toxicities	All toxicity ≥ Grade 3 not due to underlying MF or complications of the disease

* in two consecutive assessments within 24 hours (the second assessment will be considered valid and final)
** in case of platelets count of 40-50 x 10^9/L, the assessment has to be repeated within 24 hours. The second assessment will be considered valid and final
CTCAE version 5.0 will be used for all grading.

See Næste side for SAE rapportering

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), for 30 days after the last dose of ruxolitinib or siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy in Part 3), for 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3), and for 150 days after the last dose of MBG453 for subjects on ruxolitinib + MBG453 (or MBG453 monotherapy in Part 3) must be reported to Novartis safety within 24 hours of learning of its occurrence.

For Screen Failure subjects, SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on 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 must be reported separately as a new event.

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 study treatment, a 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 study treatment 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Progression of the underlying disease (myelofibrosis) (including fatal outcomes) based on the criteria described in Section 8.3.2.4 (ie. progressive splenomegaly, increase in peripheral blood blast content of > 10% (accelerated phase), deteriorating cytopenia, leukemic transformation) should not be reported as a SAE. As noted in Section 10.1.1, these disease progression events will be reported on specific CRF pages other than the AE CRF.

Any SAEs experienced more than 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), for 30 days after the last dose of ruxolitinib + siremadlin, for 105 days for ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3), and for 150 days after the last dose of ruxolitinib + MBG453 (or MBG453 monotherapy in Part 3) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - 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
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious 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. Such events should be considered as "medically significant." Examples of such events are 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 dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (Section 10.1.5).

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10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent must be reported to Novartis safety within 24 hours of learning of its occurrence until the end of the safety follow-up period, as follows:

- 30 days after the last dose of single-agent ruxolitinib (control/monotherapy)
- 30 days after the last dose of ruxolitinib or siremadlin for subjects on ruxolitinib + siremadlin (or siremadlin monotherapy in Part 3)
- 105 days after the last dose of crizanlizumab for subjects on ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3),
- 150 days after the last dose of MBG453 for subjects on ruxolitinib + MBG453 (or MBG453 monotherapy in Part 3).

If a subject starts post treatment anti-neoplastic medication then only SAEs suspected to be related to study treatment should be collected, up to the time frame noted above depending on the study treatment (30 days for ruxolitinib or siremadlin, 105 days for crizanlizumab or 150 days for MBG453).

For Screen Failure subjects, SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on 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 must be reported separately as a new event.

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 study treatment, a 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 study treatment 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Progression of the underlying disease (myelofibrosis) (including fatal outcomes) based on the criteria described in Section 8.3.2.4 (ie. progressive splenomegaly, increase in peripheral blood blast content of > 10% (accelerated phase), deteriorating cytopenia, leukemic transformation) should not be reported as a SAE. As noted in Section 10.1.1, these disease progression events will be reported on specific CRF pages other than the AE CRF.

Any SAEs experienced more than 30 days after the last dose of single-agent ruxolitinib (control/monotherapy), 30 days after the last dose of ruxolitinib + siremadlin, for 105 days for ruxolitinib + crizanlizumab (or crizanlizumab monotherapy in Part 3), and for 150 days after the last dose of ruxolitinib + MBG453 (or MBG453 monotherapy in Part 3) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.