Appendix 5 Adverse events: definitions and procedures for recording, evaluation, follow-up, and reporting

AE definition
• An AE is any untoward medical occurrence in a clinical trial patient that is temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • An AE can be any unfavourable and unintended sign, including an abnormal laboratory finding, symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the AE definition
• Any abnormal laboratory test results or safety assessments, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • A CLAE: a clinical abnormal laboratory finding which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality. • Abuse: Persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects (e.g. overdose with the intention to cause harm. • Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol or the terms of the marketing authorisation. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of trial product regardless of intent. • A "lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.
Events NOT meeting the AE definition
• Pre-existing conditions, anticipated day-to-day fluctuations of pre-existing conditions, including those identified during screening or other trial procedures performed before exposure to trial product. Note: pre-existing conditions should be recorded as medical history/concomitant illness. • Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial related activity after the patient has signed the informed consent.

Definition of an SAE
An SAE is an AE that fulfils at least one of the following criteria:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.
• **Requires inpatient hospitalisation or prolongation of existing hospitalisation** • Hospitalisation signifies that the patient has been detained 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils

any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
  Note:
  - Hospitalisations for administrative, trial related, and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs.
  - Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

- **Results in persistent disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experience of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following adverse events must always be reported as SAEs using the important medical event criterion, if no other seriousness criteria are applicable:
    - suspicion of transmission of infectious agents via the trial product.
    - risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x Upper Normal Limit (UNL) and total bilirubin >2 x UNL, where no alternative aetiology exists (Hy's law).

Description of AEs requiring additional data collection (via specific event form) and AESIs

AESIs

An AESI is an event, which in the evaluation of safety, has a special focus due to requirements from regulatory authorities.

In this trial, the following AEs fulfil the AESI criteria:

Thromboembolic events including but not limited to,

- disseminated intravascular coagulation (DIC) (A),
- thrombotic microangiopathy (TMA)(B)
- clinical signs or laboratory indications of arterial and venous thrombosis including myocardial infarction (C),
- pulmonary embolism (D),
- stroke (E),
- deep vein thrombosis (F),
- other clinically significant thromboembolic events (G) and peripheral artery occlusion (see below H), see definitions below

A) Definition of disseminated intravascular coagulation (DIC), as defined below:

The definition of DIC in this trial should be made according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. Thus, a DIC diagnosis may be based on clinical signs and symptoms of a bleeding tendency or thrombotic tendency, organ dysfunction and the laboratory parameters criteria as listed below:

- Platelet count (>100 × 109/L = 0, <100 × 109/L = 1, <50 × 109/L = 2)
- Elevated D-dimer (no increase = 0, moderate increase = 2, strong increase = 3)
- Prolonged PT (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
- Fibrinogen level (>1 g/L = 0, <1 g/L = 1)
- Calculate score: ≥5 compatible with overt DIC

B) Definition of thrombotic microangiopathy, as defined below:

Thrombotic microangiopathies (TMA) are a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia and microthrombi leading to ischemic tissue injury that can affect e.g. the kidneys and the central nervous system.
TMA is a clinicopathologic diagnosis. The constellation of thrombocytopenia, anemia and red blood cell fragmentation (i.e. schistocytes) on the blood film is consistent with a diagnosis of TMA. The finding of concomitant anemia and thrombocytopenia should prompt a request for a peripheral blood film to look for red blood cell fragmentation.[1]
If TMA is suspected the following laboratory assessment workup is suggested: standard hematology, hemolytic parameters (reticulocytes, hemoglobin, bilirubin, LDH, haptoglobin), Direct Anti-Globulin (DAT) test (also referred to as Coombs test), peripheral blood smear to look for schistocytes, creatinine, ADAMTS13 Antigen and ADAMTS13 Antibody[25].

C) Myocardial infarction is defined according to the "Third Universal Definition of Myocardical Infarction" [26]
Criteria for acute myocardial infarction - The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy

Criteria for prior myocardial infarction - Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathological findings of a prior MI.

Recurrent myocardial infarction - Incident MI is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, this is not counted as a new event for epidemiological purposes. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a recurrent MI.

D) Definition of pulmonary embolism:
The "Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians" on diagnosis of venous thromboembolism recommends diagnostic imaging studies for patients with intermediate or high pre-test probability of pulmonary embolism[27].

Accordingly, the definition of pulmonary embolism is the following: obstruction of a pulmonary artery or one of its branches, most frequently by detached fragments of thrombus from a leg or pelvic vein, diagnosed by at least one of the following:

- Positive findings in ventilation/perfusion scan
- Positive findings in a spiral (helical) computerised tomography (CT) or angiography
- Positive findings in a magnetic resonance imaging (MRI)
- Positive findings in a pulmonary angiography

E) Definition of stroke:
The definition of central nervous infarction is according to the American Heart Association/American Stroke Association Expert Consensus Document: "An Updated Definition of Stroke for the 21st Century"[28].

Accordingly, the term "stroke" should be broadly used to include all of the following:
Definition of central nervous system (CNS) infarction: CNS infarction is brain, spinal cord or retinal cell death attributable to ischemia, based on:
pathological, imaging or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution or
clinical evidence of cerebral, spinal cord or retinal focal ischemic injury based on symptoms persisting 24 hours or until death, and other etiologies excluded
Note: CNS infarction includes haemorrhagic infarctions, types I and II; see "Haemorrhagic Infarction"

Definition of ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction. Note: Evidence of CNS infarction is defined above.

Definition of silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.

Definition of intracerebral haemorrhage: A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. Note: Intracerebral haemorrhage includes parenchymal haemorrhages after CNS infarction, types I and II - see "Haemorrhagic Infarction").

Definition of stroke caused by intracerebral haemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Definition of silent cerebral haemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.

Definition of subarachnoid haemorrhage: Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).

Definition of stroke caused by subarachnoid haemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Definition of stroke caused by cerebral venous thrombosis: Infarction or haemorrhage in the brain, spinal cord or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or haemorrhage do not qualify as stroke.

Definition of stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥ 24 hours or until death, but without sufficient evidence to be classified as one of the above.

Definition of a Transient Ischemic Attack: The definition of Transient Ischemic Attack is according to the American Heart Association/American Stroke Association. A Transient ischemic attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction[29].

F) Definition of deep vein thrombosis:
The "Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians" on diagnosis of venous thromboembolism recommends ultrasound scanning for patients with intermediate or high pre-test probability of deep vein thrombosis (DVT) in the lower extremities[27]. Accordingly, venous thrombosis should be demonstrated by compression ultrasound, duplex ultrasound, colour Doppler imaging or venography (phlebography).

G) Definition of other clinically significant thromboembolic events:
Signs or suspicion of a clinically significant thromboembolic event (e.g. visceral arterial embolus/thrombus, extremity arterial embolus/thrombus or portal venous thrombosis). Superficial thrombophlebitis is not considered a clinically significant thromboembolic event unless evaluated as such by the investigator.

H) Definition of peripheral artery occlusion:
Clinical signs of acute arterial occlusion verified by ankle-brachial index (ABI) test, Doppler and ultrasound (Duplex) imaging, computerised tomographic angiography, Magnetic Resonance Angiography (MRA) or conventional angiography. The 2011 American College of Cardiology Foundation/American Heart Association Focused Update of the Guideline for the Management of Patients with Peripheral Artery Disease could serve as a reference for the diagnosis of lower extremity peripheral artery disease

AEs requiring additional data collection
AEs requiring additional data collection are AEs where the additional data will benefit the evaluation of the safety of the trial product.

Hypersensitivity type reactions:
In cases where clinical signs of a severe and immediate hypersensitivity reaction resembling a type I hypersensitivity reaction is present, additional blood should be sampled for central laboratory assessment of anti-drug IgE antibodies and anti-drug binding antibodies. See section 9.4.8 for further guidance on additional laboratory testing to be performed. Attention should be given to clinical signs and symptoms of hypersensitivity reactions of type II and III. Common clinical signs and symptoms characteristic for these types of reactions may include, but are not limited to: fever/malaise, cutaneous eruptions, arthralgia, lymphadenopathy, itching, headaches and myalgia. Related laboratory findings may include but are not limited to: mild proteinuria or haematuria, leukopenia or leucocytosis, decreased complement levels or increased complement split products and transient elevations of serum creatinine levels.
If according to the investigator's judgement, hypersensitivity reactions that require systemic treatment are suspected, dosing with concizumab should be stopped immediately and treatment at the discretion of the treating physician initiated.

Injection site reactions:
Any injection site reaction symptom must be reported on the AE form and the injection site reaction form, refer to section 9.4.9.

Investigation of injection site reactions will be performed locally at all visits when patients are receiving treatment with concizumab ppx based on patient feedback and by following visual inspections of injection sites for concizumab administration. The affected area should be evaluated in cm or inches using a ruler. In the event of a local reaction, assessments will be performed until resolution as judged necessary by the investigator. Assessment of injection site reactions can be performed at any time, if deemed necessary by the investigator.

Medication error:
A medication error is an unintended failure in the trial drug process that leads to, or has the potential to lead to, harm to the patient, such as:

- Administration of wrong drug or use of wrong device.
  Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.
- Wrong route of administration, such as intramuscular instead of subcutaneous.
- Accidental administration of a lower or higher dose than intended. However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial patient were likely to happen as judged by the investigator, although they did not necessarily occur.

AE and SAE recording

- The investigator will record all relevant AE/SAE information in the eCRF.
- 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 (not the individual signs/symptoms) will be documented as the AE/SAE.
- 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) related to the event.
- There may be instances when copies of source documents (e.g. medical records) for certain cases are requested by Novo Nordisk. In such cases, all patient identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to Novo Nordisk.
- For all non-serious AEs the applicable forms should be signed when the event is resolved or at the end of the trial at the latest. For sign-off of SAE related forms refer to "SAE reporting via paper CRF" later in this section.
- Novo Nordisk products used as concomitant medication if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

Assessment of severity

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: Severe is a category used for rating the intensity of an event; and both an AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least one of the outcomes described in the definition of an SAE and not when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product should be assessed as:

- Probable - Good reason and sufficient documentation to assume a causal relationship.
- Possible - A causal relationship is conceivable and cannot be dismissed.
- Unlikely - The event is most likely related to aetiology other than the trial product.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the IB for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data**.

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering/resolving:** The condition is improving, and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the patient has not improved, and the symptoms are unchanged or the outcome is not known.
- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the patient is lost to follow-up.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g. severe hypersensitivity reactions). This may include additional laboratory tests (e.g. skin prick test) or investigations, histopathological examinations, or consultation with other health care professionals.
If a patient dies during participation in the trial or during a recognised follow-up period, the investigator should provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information will be recorded in the eCRF.

SAE reporting via eCRF

- Relevant forms (AE and safety information form) must be completed in the eCRF.
- For reporting and sign-off timelines, see box below.
- If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form and if the eCRF is unavailable for more than 5 calendar days then the site will use the safety information form (see box below).

- The site will enter the SAE data into the eCRF as soon as it becomes available, see 9.3.1
- After the trial is completed at a given site, the eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after eCRF decommission, then the site can report this information on a paper AE and safety information form (see box below) or to Novo Nordisk by telephone.

SAE reporting via paper CRF

- Relevant CRF forms (AE and safety information form) must be forwarded to Novo Nordisk either by fax, e-mail or courier.
- Initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information form within the designated reporting time frames (as illustrated in Figure 3 section 9.3):
  - AE form within 24 hours.
  - Safety information form within 5 calendar days.
  - Both forms must be signed within 7 calendar days.

Contact details for SAE reporting can be found in the investigator trial master file.