Safety Evaluation and Reporting

1. Assessment of Safety Endpoints

Safety endpoints will encompass serious adverse events (SAEs), adverse events of special interest (AESI), physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters and ECG parameters. All adverse events (AEs) will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and abnormal laboratory test results, if applicable, will be graded according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Safety analyses will generally be descriptive and will be presented in tabular format with the appropriate summary statistics.

2. Adverse Event Collection and Reporting

All clinical adverse events (AEs) occurring after the subject signs the Main ICF and during hospitalization, whether observed by the investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) diagnosed or known to exist prior to informed consent will be recorded as part of the medical history.

All AEs, SAEs, and adverse events of special interest (AESI) are to be reported according to the procedures. Laboratory results, vital signs, and ECG results or findings should be evaluated by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study treatment discontinuation, require corrective treatment, or are considered an AE in the investigator's clinical judgment.

At each visit, the investigator will assess whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or elicited through questioning at each study visit. Subjects should be questioned in a general manner, without specifically inquiring about the occurrence of any particular symptoms. The investigator must evaluate all AEs to determine seriousness, severity, and causality, in accordance with the definitions provided. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature.

The investigator should always report the diagnosis as the AE or SAE term. In cases where a diagnosis is unavailable, the primary sign or symptom should be reported as the AE or SAE term, with additional details included in the narrative until a diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, they should be reported as individual entries of AE or SAE.

For events deemed serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure itself is not an AE or SAE, but the reason for the procedure may constitute an AE or SAE. Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalization for preexisting conditions that do not worsen in severity should not be reported as SAEs.

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently should not be reported as an AE/SAE. However, in cases where a subject dies from progressive disease with no other immediate causes, "disease progression" should be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period and that the investigator assesses as related to study treatment should also be reported and managed as an SAE.

3. Adverse Events of Special Interest

✧ Opioid-related adverse drug events (ORADEs)

Adverse drug events related to opioids (ORADEs) encompass a wide spectrum, ranging from respiratory depression and circulatory arrest to nausea and vomiting. The most common among these include urinary retention, pruritus, nausea, vomiting, as well as central nervous system effects such as somnolence and dizziness.

✧ Postoperative Pulmonary Complications

Postoperative pulmonary complications can be regarded as a comprehensive outcome measure. We adhere to the European Perioperative Clinical Outcome definitions for postoperative pulmonary complications.

Complication	Definition
Respiratory infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count $> 12 \times 10^9 l^{-1}$
Respiratory failure	Postoperative $PaO_2 < 8$ kPa (60 mmHg) on room air, a PaO_2:FiO_2 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

✧ Infection and Sepsis

Infection is defined as the pathological process caused by the invasion of pathogenic or potentially pathogenic microorganisms into usually sterile tissues, fluids, or body cavities. According to the Third International Consensus Definitions Task Force, sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection. Organ dysfunction can be identified by an acute change in the total SOFA score of ⩾2 points due to the infection. Septic shock, a subtype of sepsis, is characterized by circulatory and cellular/metabolic abnormalities profound enough to substantially increase mortality. Patients with septic shock can be identified through a clinical construct of sepsis, with persisting hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) ⩾65 mm Hg and a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

The qSOFA includes the following items and scoring system:

Respiratory rate ⩾22 breaths/minute;

Altered mentation;

Systolic blood pressure ⩽100 mm Hg.

✧ Procedure-Related Complications

Local anesthetic systemic toxicity (LAST)

LAST is a potentially life-threatening complication that occurs when a bolus of local anesthesia (LA) is inadvertently injected into peripheral tissue or venous or arterial circulation. The systemic distribution of the LA leads to LAST, which has devastating effects on the cardiovascular and nervous systems.

Specific complications

Specific complications of nerve block include puncture site infections, hematomas at the puncture site, nerve damage, pneumothorax, hemothorax, intrathecal injection, ipsilateral brachial plexus block, and hemidiaphragmatic paresis.

4. Adverse Event

✧ **Definition of Adverse Event**

An adverse event (AE) refers to any untoward medical occurrence in a subject administered a pharmaceutical product, which doesn't necessarily have to have a causal relationship with the treatment. This includes any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it's considered related to the product.

Serious Adverse Events (SAEs) and Adverse Events (AEs), defined according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0, overall and by system organ class and preferred term.

✧ **Serious Adverse Event**

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject 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 (ICH E2A Guideline.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

✧ **Severity Assessment**

All AEs will be graded (1 to 5; see below) according to the latest NCI-CTCAE version 5.0:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event, however, the event itself may be of relatively minor medical significance (such as severe headache). Seriousness of an event is based upon a universal and global regulatory definition for reporting SAEs to regulatory agencies. For example, Grade 4 (life-threatening

consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation that
immediately makes the event serious based upon hospitalization without regard to the investigator assessment of severity.

5. Serious Adverse Event Reporting - Investigator Procedure

All adverse events (AEs), serious adverse events (SAEs), events of special interest, and overdoses will be documented in the electronic case report form (eCRF).

Relevant information concerning adverse events of special interest will be gathered through targeted questionnaires integrated within the respective eCRFs in the clinical research database, irrespective of severity.