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Perioperative treatment with tranexamic acid in melanoma (PRIME): protocol for a Danish multicentre randomised controlled trial investigating the prognostic and treatment-related impact of the plasminogen–plasmin pathway

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ABSTRACT

Introduction Inflammation is a hallmark of cancer and is involved in tumour growth and dissemination. However, the hallmarks of cancer are also the hallmarks of wound healing, and modulating the wound inflammatory response and immune contexture in relation to cancer surgery may represent effective targets of therapies.

Repurposing anti-inflammatory drugs in a cancer setting has gained increasing interest in recent years. Interestingly, the known and thoroughly tested antifibrinolytic drug tranexamic acid reduces the risk of bleeding, but it is also suggested to play important roles in anti-inflammatory pathways, improving wound healing and affecting anti-carcinogenic mechanisms.

As a novel approach, we will conduct a randomised controlled trial using perioperative treatment with tranexamic acid, aiming to prevent early relapses by >10% for patients with melanoma.

Methods and analysis Design: investigator-initiated parallel, two-arm, randomised, blinded, Danish multicentre superiority trial.

Patients: ≥T2 b melanoma and eligible for sentinel lymph node biopsy (n=1204).

Project drug: tranexamic acid or placebo.

Treatment: before surgery (intravenous 15 mg/kg) and daily (peroral 1000 mg x 3) through postoperative day 4.

Primary outcome: relapse within 2 years after surgery.

Primary analysis: risk difference between the treatment arms (χ^2 test).

Secondary outcomes: postoperative complications, adverse events and survival.

Inclusion period: summer 2023 to summer 2026.

Ethics and dissemination The trial will be initiated during the summer of 2023 and is approved by the National Committee on Health Research Ethics, the Danish Medicine Agency, and registered under the Data Protection Act. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Patients included in the study will adhere to normal Danish treatment protocols and standards of care, and we expect only mild and temporary side effects. Positive and negative results will be published in peer-reviewed journals, with authorships adhering to the Vancouver rules.

Trial registration number NCT05899465; ClinicalTrials.gov Identifier.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ Large Danish multicentre randomised controlled trial.
⇒ The trial is designed to cause minimal inconvenience for the participants as the study adheres to typical Danish treatment protocols and standards of care.
⇒ Short treatment period.
⇒ The study includes Danish patients with selected stages of melanoma, which serves as a limitation and reduces the generalisability.

INTRODUCTION

Background and rationale

Tranexamic acid as an anti-cancer drug

Repurposing already approved drugs in a cancer setting has gained increasing interest in recent years. Tranexamic acid (TXA) was recently suggested as an anticancer drug, reducing tumour growth in animal models and reducing the viability of melanoma cell lines.[1]

Inflammation, melanoma surgery, and relapse

Inflammation is a hallmark of cancer and is involved in tumour growth and dissemination.[2] However, the hallmarks of cancer are also the hallmarks of wound healing and understanding the wound inflammatory response in relation to cancer surgery may represent effective targets of therapies.[3 4]

Surgery is a key element in the treatment of melanoma and is naturally linked with an

inflammatory response. Although surgery has a favourable intent, animal models show that surgery-induced inflammation may trigger the local growth of remnant cancer cells. This surgically induced systemic inflammatory response may trigger the outgrowth of otherwise CD8-restricted micrometastases.[5 6] Although evidence from cancer surgery in humans is limited, studies suggest an association between postoperative complications and an increased risk of relapse for patients with lung, breast and colon cancer, possibly due to a sustained postoperative inflammatory state.[7]

Between 30% and 50% of patients with stage II/III melanoma experience relapses within the first 5 years after surgery.[8] Although immunotherapy has improved survival for patients with melanoma, 24.6% of the patients receiving adjuvant immunotherapy experience relapse within the first 2 years after treatment initiation, with a significant proportion of metastases occurring within the first 3 months after surgery.[9] Thus, understanding the dynamics of perioperative inflammation and optimising the postoperative period by identifying drugs that are effective and safe for these patients is important.

TXA and the plasminogen pathway during inflammation, wound healing, and carcinogenesis

In addition to the known antifibrinolytic effects, the plasminogen–plasmin pathway impacts several key steps in inflammatory processes, wound healing and carcinogenesis with multifaceted roles depending on the context and the phenotypes of the attracted immune cells in the local microenvironment.[10–13] Perioperative TXA administration significantly reduced postoperative levels of pro-inflammatory biomarkers in two previous randomised controlled trials.[14 15] In addition, TXA treatment modulates the immune response both after surgery and in healthy persons not undergoing surgery in a theoretically less chronic inflammatory way.[16] In clinical studies, TXA treatment reduces wound complication rates after cardiac and breast surgery.[16 17] Furthermore, in vitro studies suggest that tissue plasminogen activator significantly drives melanoma growth and metastases.[18]

Safety of TXA in clinical studies

TXA has been widely used and has shown limited and mild adverse reactions (AR) in large meta-analyses for long-term use[19–22] and in a surgical setting.[23 24] For our proposed study, adverse events (AE) in a cancer setting are particularly interesting. A meta-analysis including 11 studies and 1177 patients found no increased risk of venous thromboembolism for patients receiving TXA compared with the control group (OR 0.58; 95% CI 0.26 to 1.28).[25] In a recent review, no increased risk of thromboembolic events has been found for patients receiving TXA after surgery for head and neck cancer, bladder cancer, brain tumours, liver tumours, colorectal cancer, uterine cancer, breast cancer and sarcoma.[26]

In conclusion, the current literature, investigating over 1 million patients, finds no association between the use of TXA and thromboembolic events, giving rise to no significant concerns initiating this proposed trial.

Objectives

The objective of the present clinical trial is to test if perioperative treatment with TXA reduces the early relapses and postoperative complications for patients with melanoma compared with placebo.

Primary aim and hypotheses

To test whether perioperative treatment with TXA is superior to placebo and reduces the early relapse rates from 37% to 26% for patients diagnosed with melanoma undergoing wide local excision (WLE) and sentinel lymph node biopsy (SLNB) surgery.

We hypothesise that:

- TXA is superior to placebo treatment.
- The risk difference of recurrence between TXA treatment and placebo is 11% (37%–26%) with a >3% margin.
- In subgroup analyses, male patients, compared with women, and patients with ulcerated melanoma, compared with patients with non-ulcerated melanoma, will benefit more from TXA treatment.
- In subgroup analyses, patients with diabetes mellitus will benefit less from TXA compared with patients without diabetes.

Secondary aims and hypotheses

a. Evaluate safety and tolerability: defined as mild (abdominal pain, diarrhoea or nausea) or severe (thromboembolic events) adverse effects

We hypothesise that:

- Patients treated with TXA will experience few and only mild adverse effects compared with patients treated with placebo.

b. Evaluate postoperative complications: bleeding, seroma formation, and infections within the first three postoperative months.

We hypothesise that:

- TXA treatment reduces the postoperative complication rates for all three pre-specified categories compared with placebo.

c. Estimate melanoma-specific survival probabilities and compare the two treatment groups.

We hypothesise that:

- Melanoma-specific survival is improved for patients treated with TXA compared with placebo.

Explorative translational studies

From blood and tissue samples, baseline and perioperative changes of factors associated with inflammation, fibrinolysis, metabolism, immune cell composition and activation status will be monitored, and factors will be associated with prognostic and treatment-related outcomes.

Trial design

The perioperative treatment with tranexamic acid in melanoma (PRIME) trial is an investigator-initiated parallel,

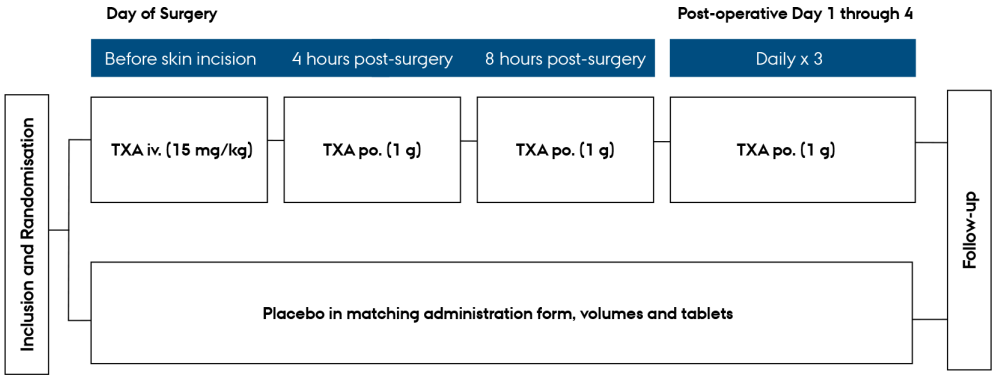

Figure 1 Treatment Regimen: treatment arm includes intravenous TXA preoperatively, and subsequently, TXA orally 4 and 8 hours postoperatively, and TXA 3 times daily through postoperative day 4. The placebo arm includes saline in matching doses. TXA, tranexamic acid.

two-arm, randomised, quadruple-blinded (participants, care provider, investigator and outcome assessor), Danish multicentre superiority trial (3% margin). Protocol version: V.6.0, 26 October 2023.

METHODS: PARTICIPANTS, INTERVENTION AND OUTCOMES

Study setting

The study is conducted at seven Danish melanoma centres: Aarhus University Hospital, Aalborg University Hospital, Vejle Hospital, Odense University Hospital, Roskilde Hospital, Herlev Hospital and Copenhagen University Hospital. The study was initiated at Aalborg University Hospital on 24th of August 2023, and Aarhus University Hospital 1st of September 2023. The remaining centres will be initiated consecutively in the winter 2023 and spring 2024. The estimated date for the last inclusion is the 1st of September 2026 or until a sample size of 1204 is reached.

Eligibility criteria

Inclusion criteria

- Diagnosed with invasive cutaneous melanoma (pathological stage/tumour grade≥T2b), defined as either:
  - Breslow thickness >1.0–2.0 mm with the presence of ulceration.
  - Breslow thickness >2.0 mm regardless of ulceration status.
- Eligible for surgery (WLE and SLNB).
- ≥18 years of age and ≤80 years of age.
- Signed informed consent form.

Exclusion criteria

- Prior history of invasive melanoma.
- Thromboembolic events within the last 3 months.
- Pregnancy.
- Actively breastfeeding.
- Known allergy or hypersensitivity to TXA
- Known and treated epilepsia or previous seizures.
- Estimated Glomerular Filtration Rate 0–50.
- Known use of TXA.

Women of childbearing potential can be included:

- With a negative pregnancy test.
- Use of contraception from the negative pregnancy test until day 5 postoperatively.

Interventions

The treatment regime is illustrated in figure 1.

- Treatment arm: a single dose of TXA (15 mg/kg) intravenously 30 min (±15 min) before skin incision, and subsequently TXA (2×500 mg) orally 4 hours and 8 hours postoperatively, and TXA (2×500 mg) three times daily through postoperative day 4.
- Placebo arm: a single dose of matching volume saline administered intravenously 30 min (±15 min) before skin incision and subsequently placebo tablets (two tablets) administered orally 4 hours and 8 hours postoperatively, and (two tablets) three times daily through postoperative day 4.

There will be no dose reduction for this trial. A sealed randomisation envelope is stored at the local investigation site in need of acute unblinding. If serious AEs occur, with evidence that TXA harms the patients, acute unblinding will decide if an individual's participation will be discontinued. The trial will then be evaluated for early discontinuation.

Apart from the treatment period, all included patients will follow normal treatment protocols and standards of care adherent to the Danish Melanoma Group (DMG) guidelines.

To improve compliance, patients will receive a recollection checklist and information, both oral and written, to return unused tablets and empty containers. Compliance will be assessed based on leftover tablets and patient reports at the outpatient visit 12 days post-surgery.

Outcomes

Primary endpoint

Histopathological confirmed relapse, defined as either local, regional (in transit or lymph node) or systemic relapses. Systemic metastases suspected on positron emission tomography (PET)/CT/MR will be used if a biopsy is not possible. Based on the primary endpoint, we will

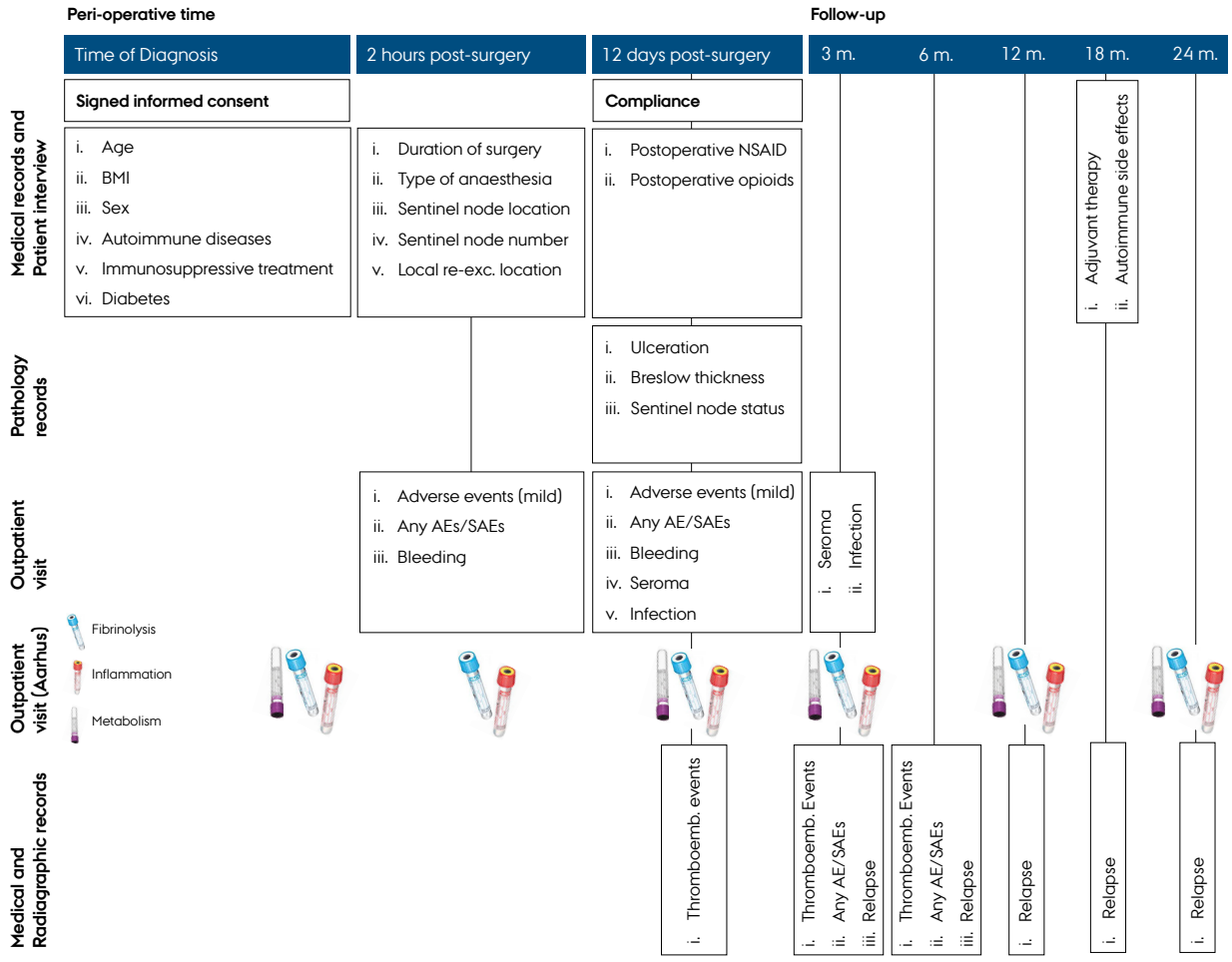

Figure 2 Participant timeline and assessments: illustration of data collection with timepoints in relation to surgery and disclosure of how data is obtained. BMI, Body Mass Index; NSAID, Non-steroidal anti-inflammatory drugs; AE, Adverse Events; SAE, Serious Adverse Events; Re-exc., Re-excision.

calculate the relapse risk proportions for each treatment arm as a binary outcome. The date of relapse or completed follow-up is noted, and the relapse-free period is defined as the date of WLE and SLNB until the date of either the first confirmed relapse or the date of completed 2-year follow-up without relapse.

Secondary endpoints

- AEs summarised according to grade:
  Mild: defined as the patient's report of abdominal pain, diarrhoea or nausea.
  Severe: thromboembolic events, verified radiologically.
- Postoperative complications, summarised according to the type and postoperative timepoint:
  Bleeding: defined as a drained or surgically removed haematoma or suggillation of blood to the skin around the operated area, occurring within the first ten days post-surgery.
  Seroma: drained seroma during the period from the end of surgery through 3 months post-surgery.
  Infection: local wound infection, treated with antibiotics or surgical intervention, from the end of surgery through 3 months post-surgery.
- Melanoma-specific survival: defined as the period from the date of surgery (WLE and SLNB) to the date of death from suspected systemic melanoma (histopathologically confirmed relapse or systemic metastases suspected on PET/CT/MR) or the date of completed 2-year- follow-up.
- Overall survival: defined as the period from the date of surgery (WLE and SLNB) to the date of death from all causes or the date of finalised 2-year follow-up.
- Relapse-free survival: defined as the period from the date of surgery (WLE and SLNB) to the date of histopathologically confirmed relapse (local, regional or systemic), death from all causes or the data or completed 2-year follow-up. Relapse-free survival: defined as the period from the date of surgery to the date of histopathologically confirmed relapse, death from all causes or completed 2-year follow-up.

Participant timeline

The participant timeline and assessments are illustrated in figure 2. Data will be obtained from medical, pathology and radiology records, patient interviews and clinical examinations.

Time of diagnosis: eligible patients will be informed about the trial, and signed informed consent will be obtained if they wish to participate and meet inclusion criteria. Health information will be obtained.

2-hour post-surgery (after surgery and before discharge): information concerning surgery, anaesthesiology, AEs and postoperative complications will be obtained.

12 days post-surgery (±2 days): outpatient visit where the patients are informed about the pathological findings, current staging and follow-up plan. Information concerning compliance, analgesic use, pathology results, postoperative complications and AEs will be obtained.

Follow-up visits 3, 6, 12, 18 and 24 months post-surgery (±14 days): information regarding relapse will be collected. AE information will be obtained at 3 and 6 months, and information on adjuvant therapy and autoimmune side effects will be collected at 18 months.

Blood and tissue samples from exploratory translational studies will be collected perioperatively at baseline, 2 hours post-surgery, 12 days, 3, 12 and 24 months or at first relapse.

Sample size

Samples of 602 patients per group are needed to show a risk difference of at least 3% (superiority margin) with a power of 85%, assuming a risk difference between the two treatment arms from 37% to 26% and an alpha of 0.05.

Background and assumptions behind the power calculation:

Recurrence was recorded in 32.8% of patients with stage II and 51% of patients with stage III melanoma, with a mean relapse rate of 42%.[8] This is in line with the DMG 2020 data. Adjuvant immunotherapy reduces relapse rates by 25% after 2 years of follow-up[9] and is offered to 50% of the included patients, equally distributed between the treatment and placebo arms. Based on these numbers, the estimated risk of relapses in the placebo group is 37%, when including the decrease in mean relapse rate due to the effects of adjuvant immunotherapy, and in the treatment group, 26%. STATA command (artbin, margin(0.03) pr(0.26 0.37) power(0.85)) and output (events needed=379 and sample size per group calculated=602). The power calculation is based on the unconditional comparison of two binomial proportions in a substantial-superiority study.

Recruitment

Patients will be continuously recruited from the screening of pathology reports, identifying newly diagnosed patients with invasive cutaneous melanoma (pathological stage/tumour grade ≥T2b). Prescreened patients are routinely informed about the diagnosis, planned surgery, and of possible participation in the PRIME trial. A physician conducts the final eligibility assessment using the inclusion and exclusion criteria if the patients wishes to participate, and hereafter, a signed informed consent is obtained.

Patients treated at Aarhus University Hospital will be invited to participate in translational studies with blood and tissue samples. The patients will be recruited and included as previously described.

Patient inclusion will continue until the aimed number of n=1204 is reached. Thirty days after the last patient has been followed up for 2 years, the study period will be closed, and the database will be cleaned, locked and prepared for unblinding and analyses of endpoints.

Patient and public involvement

A patient representative from the Danish Cancer Society evaluated this trial. In addition, a patient representative from the Patient's Union for Malignant Melanoma has contributed by critiquing patient information.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

Randomisation is computer-generated (www.sealedenvelope.com) in blocks of 25 with a 1:1 allocation ratio from the Hospital Pharmacy of the Central Denmark Region, aiming for an equal distribution of the active treatment throughout the study period and between the different centres.

Blinding (masking)

Preparation and distribution of the study drug in packed, sealed and labelled drug packages will be conducted centrally at the Hospital Pharmacy of the Central Denmark Region, blinded for sponsor-investigator, principal investigators (PIs), coinvestigators and the steering committee throughout the study period. At each local investigation site, a defined group of trained, unblinded personnel will be responsible for preparing the intravenous study drug and for delivering the drug to blinded personnel involved in the subsequent patient treatment and care.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection method

Data are collected locally, according to figure 2, and reported continuously after every visit to an electronic Case Report Form (eCRF) in REDCap. The PIs at each investigative site are responsible for data entry into the eCRF and for the validity of the data collected. Withdrawal of patients from treatment or follow-up will be noted in the eCRF, allowing the endpoints to be analysed per intention-to-treat and per protocol. No replacement of patients will be performed.

Data management

The REDCap database is a secure web-based application and database with data management procedures adherent to the Danish Data Protection Agency regulations. The eCRF is stored under the responsibility of the sponsor-investor. According to applicable laws and regulations, patient record data will be archived for 25 years.

Statistical methods

The analyses within this trial will solely be used to answer the research questions contained in the protocol in accordance with the statistical analysis plan. The risk of relapse is calculated for each group, and the risk differences between the groups are tested by χ^2, assessing a defined clinically relevant margin of>3%. The timing of events and relapse-free survival is illustrated with Aalen-Johansen estimates accounting for competing risk. Data is analysed when the estimated number of patients and power is reached and a 2-year follow-up has been completed. Subgroup analyses will be performed according to the hypotheses. For secondary outcomes, differences in binary outcome will be analysed using the χ^2 test and for continuous variables by independent t-test of the mean or Mann-Whitney test when appropriate. Melanoma-specific survival rates between the groups will be evaluated by Kaplan-Meier plots using log-rank tests and adjusted analyses by Cox regression. Baseline and treatment-related changes of the assessed inflammatory, metabolic and fibrinolytic markers will be evaluated as repeated measurements over time and t-tested as the area under the curve. Differences in the mean between the timepoints will be tested with mixed models and regression. A significance level of 0.05, mean, SD, or 95% CIs are used.

Harms

AEs will be reported according to Common Terminology Criteria for adverse effects (CTCAE, V.5, 2017) and graded as an assessment of the causal relationship to the investigational medicinal product. The PI or a delegated physician is responsible for registering and reporting AE/AR or serious AEs or serious ARs (SAE/SAR). All assessments will be documented in REDCap and registered at the follow-up visit at 2 hours, 12 days, 3 months and 6 months post-surgery. Thereafter, the safety registration and reporting will be finalised. A SAE/SAR will be reported to the sponsor-investigator no later than 24 hours after the PI becomes aware of such an event. If the PI at one of the participating sites suspects a suspected unexpected serious adverse reaction (SUSAR), they will inform the sponsor-investigator as soon as the SUSAR is suspected. The sponsor-investigator is responsible for reporting the SUSAR to the authorities and in the EudraVigilance database via the Central Region of Denmark. If the SUSAR is fatal or life threatening, the SUSAR will be reported immediately and no later than 7 days after the sponsors' knowledge of the event. Any SUSAR that is neither fatal nor life threatening is reported within 15 days of the sponsors' knowledge of such an event. In the case of a SUSAR, all participating PIs will be informed of the event, and any consequences related to the execution of the trial will be communicated.

METHODS: MONITORING

Data monitoring

The investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including providing direct access to source data and documents according to Clinical Trial Regulation (CTR) Annex I D17. All trial documents are available to the public at the European Medicines Agency website Clinical Trials Information System (CTIS) database.

If protocol deviations occur, these are reported from PIs to the sponsor-investigator as soon as possible and noted in the eCRF separately.

All known serious AEs/reactions are reported in an annual safety report and submitted through the CTIS system.

No formal interim analysis is planned because the study is powered based on complete enrolment, and a superiority of ~10% is expected. On request from an oversight body, an estimate of risk difference before complete study enrolment can be conducted when 60% of patients have been included, thereby reducing the risk of a false-positive (type I) error. An independent statistician blinded to the treatment allocation will perform the analysis on the primary endpoint. The statistician will report to the steering committee, discussing the early discontinuation of the trial. Early termination will be considered if superiority in risk difference >30% (p<0.001) is shown.

Auditing

The study will be conducted by applicable national regulatory requirements and The International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and by GCP standards, with full external monitoring completed by the GCP Units at each clinical investigative site according to risk analysis and agreement.

Roles and responsibilities

Sponsor and PI are responsible for adherence to GCP regulations, thus conducting the trial guided by international ethical and scientific quality standards for designing, conducting, recording and reporting trials involving human subjects' participation. In compliance with this standard, trial subjects' rights, safety and well-being are protected, consistent with the principles of the Declaration of Helsinki.

The PRIME steering group includes all authors, with MLB-B as sponsor-investigator. Local PIs are responsible for local screening, inclusion, data collection and AE reporting to the sponsor-investigator. Sponsor-investigator is responsible for AE reporting to the EudraVigilance database. The sponsor-investigator and steering group are responsible for trial management, operation, data management, analyses, and dissemination of the final results.

ETHICS AND DISSEMINATION

Research ethics approval

The trial has been approved by the National Committee on Health Research Ethics and the Danish Medicine Agency and registered under the Data Protection Act (under the Central Region of Denmark), complying with The General Data Protection Regulation. The protocol and approval are available in the CTIS by the European Medicines Agency with identification number 2022-502633-26-00.

Protocol amendments

Protocol amendments and modifications will be communicated to PIs, uploaded with version numbers and tracked changes in the electronic trial master files (REDCap).

Consent or assent

The informed consent process will be conducted by the EU CTR and applicable national legislation. It will take place in an undisturbed setting between the informing investigator and the potential participant. Investigators must ensure that comprehensive information is provided orally and in writing. Potential study subjects are recommended to have a third party present during the information process. Potential study subjects will be thoroughly informed about their right to deliberation time and that informed consent at any time and without reason can be withdrawn without consequences for the subsequent treatment or follow-up.

For the translational study, participants will sign a separate informed consent and be informed that they can accept or decline the translational studies without any influence on participation in the clinical study, their treatment or follow-up.

Confidentiality

Personal data identifiers, that is, name and social security number associated with the randomisation number will be encrypted in the Redcap database. Information on medical history is confidential and may only be disclosed to third parties if permitted by signature by the study subject on the informed consent form. Blood and tissue samples are labelled and stored pseudonymised.

Ancillary and post-trial care

Participants are covered by the Danish Act on Complaints and Compensation. Complications, anxiety, pain and surgery-related symptoms will be treated according to the normal standard of care. We expect AEs to be mild and temporary, occurring around the perioperative timepoints, or severe AEs that is, thromboembolic events, to occur before 6 months post-surgery. Patients with reported AEs will be followed up until all symptoms have resolved or significantly treated.

Dissemination policy

The final trial results will be communicated to participants via the website of the DMG and to the CTIS database within 1 year after the end of the trial. Positive as well as negative results will be published in peer-reviewed journals with authorships adhering to the Vancouver rules.

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Contributors MLB-B conceived the research idea and shaped the overall trial concept with substantial scientific contributions and input on design, feasibility, and how to conduct data collection, analysis and interpretation from KAK, AEK, HS and LRH. MLB-B and KAK collaborated on the initial protocol draft with critical revision from AEK, HS and LRH. The trial will be conducted under supervision from the PRIME steering group, which includes all authors. All authors have read and approved the final protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

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