Consolidated Clinical Study Protocol

Efficacy and Safety of Long-Term (6 Months) Innohep® Treatment Versus Anticoagulation with a Vitamin K Antagonist (Warfarin) for the Treatment of Acute Venous Thromboembolism in Cancer Patients / IN 0901 INT

A Phase 3 Study of Subcutaneous Innohep® 20,000 anti-Xa IU/ml for the Treatment of Venous Thromboembolism (VTE) in Cancer Patients

Multi-National, Multi-Centre, 6-Month, Randomised, Active Controlled, Open-Label Study with Blinded Adjudication

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential information.
Summary data are included but data on individual study subjects, including data listings, are removed. This may result in page numbers not being consecutively numbered.
Access to anonymised data on individual study subject may be obtained upon approval of a research proposal by the Patient and Scientific Review Board.
Appendices to the clinical study report are omitted.
Further details and principles for anonymisation is available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA.

LEO Pharmaceutical Products Ltd. A/S  Protocol Code Number:  IN 0901 INT
(LEO Pharma A/S)  Date:  30-Jan-2012
Clinical Development  Version:  6.0
EudraCT Number:  2009-018141-20
1 CLINICAL STUDY PROTOCOL APPROVAL

1.1 APPROVAL STATEMENT
On behalf of LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S), only the Vice President, International Clinical Development, and the Head of Biostatistics, LEO Head Quarters (HQ) are authorised to approve the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

The following persons have approved this Clinical Study Protocol using electronic signatures as presented on the last page of this document:

[Signature]

[Signature], LEO HQ

[Signature]

[Signature], International Clinical Development

1.2 APPROVAL STATEMENT INVESTIGATORS
The International Co-ordinating Investigator approves the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

The following person has approved this Clinical Study Protocol by manually signing the International Co-ordinating Investigator Clinical Study Protocol Approval Form adjoined as a separate page to this document:

[Signature]

International Co-ordinating Investigator
2 PROTOCOL STATEMENTS

2.1 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This Clinical Study Protocol is designed to comply with the guideline produced by the International Conference on Harmonisation (ICH) on the topic Good Clinical Practice (GCP) and published by EMEA (European Medicines Agency) as “Note for Guidance on Good Clinical Practice” (CPMP/ICH/135/95) (Approval 17 July 1996) as well as other relevant guidelines issued by ICH, primarily the efficacy guidelines.
3 PROTOCOL SYNOPSIS

Name of finished/investigational product: Innohep® 20,000 anti-Xa IU/ml

Name of active substance: Tinzaparin sodium

Title of study/protocol code number: Efficacy and Safety of Long-Term (6 Months) Innohep® Treatment Versus Anticoagulation with a Vitamin K Antagonist (Warfarin) for the Treatment of Acute Venous Thromboembolism (VTE) in Cancer Patients / IN 0901 INT

International Co-ordinating Investigator: Dr. Vancouver

Number of study sites and distribution: It is planned to initiate approximately 230 sites in approximately 30 countries to enrol patients in one or more of the following regions: Europe, South America, North America, Asia and Africa.

Planned study period: First patient in: Quarter 2, 2010
Last patient in: Quarter 4, 2012
Last patient out (last patient last visit): Quarter 3, 2013
End of study is defined as the last patient last visit date.

Main objectives: Primary objective:
The primary objective of the study is to assess the efficacy of Innohep® in preventing the recurrence of VTE in patients with active cancer who have had an acute VTE episode.
Secondary objectives:
Secondary objectives are to:

- Assess the safety of long-term Innohep®.
- Identify clinical risk factors for recurrent VTE and major bleeding.
- Assess overall mortality at 6 months.
- Identify the possible role of coagulation parameters to predict recurrent VTE or prognosis.
- Assess incidence and severity of post-thrombotic syndrome (PTS).
- Assess health-related quality of life (QoL).
- Assess healthcare resource utilisation.

Methodology:
This is a Phase 3, multi-national, multi-centre, randomised, active controlled, open-label study with blinded adjudication, assessing the efficacy and safety of long-term (6 months) Innohep® treatment versus anticoagulation with a vitamin K antagonist (warfarin) for the treatment of VTE in cancer patients.

Patients will attend the study centre for up to 11 scheduled visits: the Screening Visit (within 72 hours prior to randomisation), the Randomisation Visit (Visit 1, Day 1, this may occur on the same day (within 24 hours) as the Screening visit), Visit 2 (Day 7), Visit 3 (Day 14), Visits 4 to 8 (Day 30 to Day 150), Visit 9 (Day 180/ End of Treatment) and Visit 10 (30 days Post-Treatment Follow-Up). For this study 1 month will equal a period of 30 calendar days. In addition, patients may be asked to return to the clinic between scheduled visits for urgent assessment of recurrent VTE, bleeding or adverse events (AEs) and serious adverse events (SAEs) (unscheduled visit).

Patients will be contacted by the Investigator or delegated
study site staff by telephone 14 days (± 3 days) after each monthly visit (Visits 4-8). Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess treatment compliance, concomitant medication(s), recurrent VTE, bleedings, AEs and serious adverse events (SAEs).

All patients will be followed up for 1 month (30 days) after termination of study treatment for safety, HIT, healthcare resource utilisation, QoL, and PTS (cf Diagram 1).

Patients who are withdrawn from study treatment prior to Day 180 for any reason other than death will be asked to stay in the study and be followed up by telephone at time of the remaining regular scheduled study visits. Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess study outcomes (cf Diagram 1). Patients off study treatment may be asked to return to the clinic between telephone contacts for urgent assessment of suspected or confirmed recurrent VTE (unscheduled visit).

At the randomisation visit, patients will be randomly assigned to receive either:

- Long-term treatment with Innohep® only, OR
- Oral treatment with warfarin in combination with overlapping initial (5 to 10 days) treatment with Innohep®.

A stratified randomisation scheme will be used that accounts for the following factors:

- Tumour (known distant metastasis, no distant metastasis, haematological malignancy).
- Geographical region (Canada + Western Europe,
or Eastern Europe, or Asia, or South America).

- Known history of previously diagnosed VTE (yes or no).

**Number of patients to be randomised:**

A total of 900 patients will be randomised, 450 in each treatment arm.

**Criteria for inclusion:**

1. Patients with a diagnosis of active cancer with a histologically or cytologically diagnosed solid tumour (evidence of early stage, regionally advanced or metastatic disease) or haematological malignancy.

   Active cancer is defined as:
   - Patients diagnosed with cancer within the past 6 months, OR
   - Patients with recurrent, regionally advanced or metastatic disease, OR
   - Patients that have received any treatment for cancer during the previous 6 months, OR
   - Patients not in complete remission of a haematological malignancy.

2. Symptomatic and objectively confirmed acute proximal lower-limb deep vein thrombosis (DVT) (anatomically including popliteal, femoral [superficial and common] and iliac [external and common]) and/or pulmonary embolism (PE) diagnosed within 72 hours prior to randomisation (the 72-hour count starts when the diagnosis is confirmed by imaging). Diagnosis of DVT/PE must be made by appropriate objective imaging (see Section 10.7.3.4).

3. ≥ 18 years of age or above the legal age of consent as per country specific regulations.

4. Patients with Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2 prior to the VTE episode.

5. Signed informed consent.
Criteria for exclusion:

1. Life expectancy < 6 months.
2. Patients with basal cell carcinoma or non-melanoma skin cancer where this is their only cancer diagnosis.
3. Creatinine clearance ≤ 20 ml/min according to the abbreviated Modification of Diet in Renal Disease (aMDRD) formula (see Appendix V).
4. Contra-indications to anticoagulation:
   a. Active or recent (≤ 1 month) clinically significant bleeding, including gastrointestinal bleeding or peptic ulcer.
   b. History of bleeding disorder or coagulopathy (congenital, acquired or unexplained repeated bleeding episodes).
   c. Increased risk of bleeding due to tumour characteristics or other condition prohibiting the use of therapeutic anticoagulation according to the Investigator’s judgment.
   d. Uncontrolled arterial hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).
   e. Recent intracranial haemorrhage (in the last 1 month prior to randomisation) which is at high risk of rebleeding and would prohibit anticoagulant therapy, according to the Investigator’s judgment.
   f. Recent (in the last 1 month prior to randomisation) brain, spinal or ophthalmic surgery.
   g. Thrombocytopenia (platelet count < 50 x 10⁹/L).
   h. Coagulopathy due to liver insufficiency as indicated by a prolonged baseline activated partial thromboplastin time (aPTT) > 1.5 x upper limit of normal (ULN) or equivalent to an aPTT ratio > 1.5 (if not receiving low...
molecular weight heparin [LMWH] / unfractionated heparin [UFH]

5. Known hypersensitivity to the investigational product (Innohep®) or the reference product (warfarin).
7. Pre-randomisation therapeutic anticoagulant treatment for the current acute VTE administered for more than 72 hours prior to randomisation.
8. Patients who had been receiving therapeutic anticoagulation at the time of the VTE event (i.e. anticoagulant failure), using any anticoagulant, such as:
   a. Parenteral anticoagulants e.g. UFH, LMWH, fondaparinux, bivalirudin or hirudin.
   b. Vitamin K antagonists (VKA).
   c. New oral anticoagulants, e.g. dabigatran, rivaroxaban.
   Note: Chronic treatment with anti-platelet agents such as low dose of aspirin (up to 325 mg/day), clopidogrel or ticlopidine is allowed).
9. Patients unlikely to comply with the protocol, e.g. inability to return for study visits or inability to receive/administer daily subcutaneous (SC) injection.
10. Participation in another interventional study with active drug treatment or an investigational device.
11. Pregnant or breast-feeding women. Pregnancy status should be checked by serum or urine pregnancy testing prior to inclusion.
12. Women of childbearing potential not protected by an effective contraceptive method (as defined for contraception in the Informed Consent Form [ICF]) for the duration of the study.
13. Sexually active fertile men if they, or their partner (being a woman of childbearing potential), is not us-
ing effective birth control.

**Investigational product:**  
Innohep® (tinzaparin sodium) 20,000 anti-Xa IU/ml, dispensed in syringes of 0.5 ml, 0.7 ml and 0.9 ml.

Dosing Innohep®: 175 anti-Xa IU/kg body weight once daily by SC injection.

Innohep® syringes are supplied by LEO (Sponsor).

**Reference product:**  
Warfarin dispensed as tablets of 1 mg, 3 mg, and 5 mg. Anticoagulation with warfarin for 6 months to maintain therapeutic international normalised ratio (INR) levels in combination with initial (5-10 days) overlapping treatment with Innohep®.

Warfarin tablets are supplied by LEO (Sponsor).

**Duration of treatment:**  
Treatment Period: 6 months (180 calendar days)  
Post-Treatment Follow-Up Period: 1 month (30 calendar days).
Assessments: Patients will be randomised equally to the two treatment groups, to receive:

- Long-term treatment with Innohep® only, OR
- Oral administration of warfarin in combination with overlapping initial (5 - 10 days) treatment with Innohep®.

During the 6-month treatment period, scheduled visits will be performed to assess efficacy and safety. Final efficacy and survival assessments will be performed up until Day 180 (including 24 hours after last dose of study drug) or death, whichever comes first, for all patients (including patients who stop study drug prior to Day 180). Final assessments for safety, HIT, healthcare resource utilisation, and PTS will be performed up to 1 month (30 days) after the last dose of study drug taken (Post-Treatment Follow-Up visit). Final assessment for QoL is at Day 180 and 1 month (30 days) after the last dose of study drug.

Patients who withdraw from study (i.e. withdraws consent to continue participating in the study) will complete final efficacy assessment at the time of withdrawal and be followed for safety outcomes up to 1 month after the last dose of study drug. No other data will be collected on these patients after withdrawing consent but every reasonable effort will be made to discourage patients from withdrawing completely from the study.

In the warfarin arm, INR results should be obtained frequently during the induction phase, until the INR value is at or above 2.0 for 2 consecutive days. When the INR level has reached therapeutic level between 2.0 and 3.0, INR results will be obtained according to local practice and the Investigator’s discretion but at least every 2
weeks. INR will be closely monitored if a patient switches warfarin product during the treatment period. INR monitoring and warfarin dosing will be managed by the local Investigator.

All efficacy endpoints (i.e. recurrent lower limb DVTs, and PEs) and major safety endpoints (i.e. bleedings, HIT events and causes of death) will be adjudicated by a blinded Independent Adjudication Committee (IAC).

**Efficacy assessments:**
Each scheduled visit (Visit 1 and onwards) and telephone-contacts will include a standardised assessment (standardized questionnaire) of the signs and symptoms of recurrent VTE.

At any time during the 6-month treatment period, if a patient experiences signs and symptoms between scheduled visits or telephone contacts, the patient will be advised to contact the Investigator or delegated site staff. If signs and symptoms are assessed by the Investigator, or delegated site staff, to be suspicious of a recurrent VTE, the patient will be advised to return to the clinic urgently for an unscheduled visit at which standard assessments will be made to enable the diagnosis of recurrent VTE to be confirmed or refuted.

If the recurrent VTE is confirmed, End of Treatment assessments will be performed and the patients will be treated per local practise and investigator’s discretion. If the recurrent VTE is not confirmed, the patient will continue study medication and return for the next scheduled visit as planned.
Symptomatic DVT(s) must be confirmed using standard diagnostic criteria e.g. by compression ultrasound (CUS), contrast venography, CT or MRI venography and be associated with signs and symptoms of DVT. CUS is the preferred diagnostic examination. Both legs must be examined. A recurrent DVT coincidentally detected during other investigations (incidental DVT), e.g., cancer staging, will be included as a primary endpoint if it involves the popliteal or more proximal veins in the legs/pelvis.

Symptomatic PEs must be confirmed using standard diagnostic criteria e.g. by ventilation/perfusion (V/Q) scintigraphy, spiral computed tomography (CT), or computed tomographic pulmonary angiography (CTPA), or pulmonary angiography and be associated with signs and symptoms consistent with PE. Additional CUS is required in case of a non-diagnostic V/Q scan. A recurrent PE coincidentally detected during other investigations (incidental PE), e.g. cancer staging, will be included as a primary endpoint if it involves segmental or more proximal pulmonary arteries.

**Safety assessments:**
Safety will be assessed via the monitoring of bleeding events, HIT events and deaths, other objectively confirmed thromboses, clinically significant abnormal laboratory data, clinically significant vital signs and all other AEs and SAEs.

Safety data will be collected for up to one month after the last dose of study treatment except for death which will be followed up to Day 180.
**Other assessments:**
Coagulation biomarkers (e.g. D-dimer and tissue factor) will be assessed at the baseline and End of Treatment visits.

Additional blood will be collected at the baseline and End of Treatment visits and stored for future (post-study) coagulation biomarker assessments for consenting patients.

VTE Risk factors (e.g. tumour type, body mass index [BMI], platelets, haemoglobin, and leucocytes) will be assessed at baseline and at the time of a VTE event.

PTS will be assessed at baseline, at each monthly visit and at the end of the 1-Month Post-Treatment Follow-Up Period, using the Villalta scale that allows the staging of PTS severity using clinical measures (see Section 10.7.3.5).

Health-related QoL will be assessed using the EQ-5D (Appendix IV) at baseline, each monthly visit and the Post-Treatment Follow-Up Visit.

Healthcare resource utilisation data will be collected for assessments at each monthly visit and the Post-Treatment Follow-Up Visit; major healthcare resources associated with the prevention of recurrent VTE and the management of VTE, HIT, and bleeding events will be recorded.

**Primary endpoint/response criterion:**
The primary efficacy endpoint is a composite endpoint represented by the time in days from randomisation to the first occurrence of any of the following 5 objectively documented components:
• Symptomatic non-fatal DVTs.
• Symptomatic non-fatal PEs.
• Fatal PE.
• Incidental proximal DVT (popliteal vein or higher).
• Incidental proximal PE (segmental arteries or larger).

Results from the central adjudication of events will be used for analysis.

**Secondary endpoint/response criterion:**

**Efficacy endpoints:**
Secondary efficacy endpoints are the time in days from randomisation to the first occurrence of:

• The 5 individual components of the composite primary efficacy endpoint.
• A composite endpoint of symptomatic DVT and/or PE, including fatal PE.

Results from the central adjudication of events will be used for analysis.

**Safety endpoints:**
Safety endpoints will consist of major bleeding and clinically non-major bleeding, overall mortality, confirmed HIT events, other thromboses, clinically significant abnormal laboratory data, clinically significant abnormal vital signs and all other AEs and SAEs.

Bleeding will be defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria.

**Other endpoints:**
Other endpoints are coagulation biomarkers (e.g. D-dimer
Statistical methods:

Sample size considerations:
Assuming that Innohep® leads to a relative risk reduction of 50% an estimated event rate of 12.6% in the control group will imply an estimated event rate of 6.3% in the Innohep® group. Using a time-to-event approach with significance level $\alpha = 0.05$, a sample size of 424 patients per group is needed to ensure a 90% power of the primary analysis. To account for dropouts 450 patients will be included in each group.

Analysis of primary endpoint:
All recurrent VTE outcomes confirmed by central adjudication occurring from the time of randomization to the end of the scheduled 6-month treatment period (including 24 hours after the last dose of study drug) will be eligible for primary efficacy analysis. In the event that the diagnoses made by the local investigator and central adjudication results are discrepant, the central adjudication results will be used in the analysis.

Statistical comparison will be based on the time to the first recurrent VTE event per patient.

The primary efficacy analysis will compare the two treatment groups using a 2-sample test devised by Gray (61, 62) for comparing Cumulative Incidence Functions (CIF). The CIF is the probability of occurrence by time for a particular type of event in the presence of other risks.

The hypothesis of interest is:

$$H_0: \text{CIF (Innohep®)} = \text{CIF (control group)}$$
H₁: CIF (Innohep®) ≠ CIF (control group)

The CIF will be estimated separately for the two treatment groups using a bivariate approach and the corresponding 95% confidence interval (CI) will be computed.

**Analysis of secondary endpoints:**
The time to first occurrence of each component of the primary endpoint will be analysed separately. In addition, the 3 symptomatic components of the primary composite endpoint will be analysed as a composite secondary endpoint. For each time to event analysis, the components not defined as the event of interest will be considered a competing risk; 95% CIs will also be calculated.

For both the primary and secondary analyses, the assessment of recurrent VTE from the blinded IAC will be used. No analysis of the Investigator assessment of recurrent VTE will be performed.

**Analysis of safety endpoints:**
The proportion of patients with a major bleeding event will be compared using Fisher’s exact test. Similarly, the proportion of patients with clinically relevant non-major bleeding will be compared between the treatment groups using Fisher’s exact test. Bleeding events occurring from first dose of study drug up to 24 hours after the last dose of study drug will be included in the analysis.

Time to death (overall mortality) will be summarised using Kaplan-Meier estimates and compared between the two treatment groups using a 2-sided Log Rank test. An estimate of the treatment effect (hazard ratio and associated CI) will be obtained via Cox Regression including all stratification factors.
All other safety endpoints will be summarised as appropriate for the safety analysis set.

Exploratory analysis will be performed to assess clinical baseline factors for their association with recurrent VTE and bleeding in patients receiving anticoagulant therapy.

**Interim analysis:**
A formal interim analysis of the primary endpoint will be performed by the Data Monitoring Committee (DMC) when 50% of the patients have either completed the treatment period, died or are lost to follow-up. The study can be stopped early for superiority or futility.

Safety data will be summarised and reviewed at the time of the interim analysis.

**Sample size re-assessment:**
A sample size re-estimation will be conducted when approximately 25% of the patients have completed the treatment period, died or are lost to follow-up. The observed incidence rate for the primary endpoint in the entire group will be summarised, together with the associated 95% CI. This data will be used to establish whether the planned sample size of 900 is reasonable.
### 3.1 SCHEDULE/CHART OF STUDY PROCEDURES

<table>
<thead>
<tr>
<th>Visit window</th>
<th>Treatment Period</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day/Week/Month</td>
<td>Visit</td>
<td>Visit 1</td>
</tr>
<tr>
<td>From -72 to 0 hours</td>
<td>-72 hours</td>
<td>Day 1</td>
</tr>
<tr>
<td>VTE diagnosis (diagnostic imaging for both DVT and PE* required)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pre-randomisation therapeutic treatment of VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient demography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check of inclusion/exclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology assessments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, haematocrit, RBC, WBC including differential count. (Central Lab)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Platelets (Central Lab)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Platelets (Local Lab)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Biochemistry assessments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP, ALT, AST, creatinine, albumin, total bilirubin (Central Lab)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Creatinine (Local Lab)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* All patients must have a second VTE diagnostic imaging performed; imaging of lungs if symptomatic event was DVT or imaging of legs if symptomatic event was PE. This second imaging may be performed up to 24 hours after randomisation.  

Table continues on next page
<table>
<thead>
<tr>
<th>Day/Week/Month</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Visit window</td>
<td>From -72 to 0 hours</td>
<td>±0 Day ±3 Days ±3 Days ±7 Days +7 Days +7 Days</td>
</tr>
</tbody>
</table>

Coagulation assessments:
- aPTT (Central Lab) X X15
- aPTT (Local Lab) X X15
- INR (Central Lab) X X15
- INR2 (Local Lab) X X15 (X2) (X2) (X2) (X2)
- D-dimer, Tissue factor (Central Lab) X
- Other coagulation biomarkers (Central Lab) X X
- Pregnancy test Y
- Medical/surgical history X
- Cancer diagnosis and status X
- Prior/current medication, including prior/current treatment for cancer X
- Concomitant medications, including treatment for cancer X X X X X X
- Height X
- Weight X X
- Vital signs Y X X X X X X
- ECOG performance status Y X

Table continues on next page
### Treatment Period

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening Visit</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4 to 8</th>
<th>Visit 9 End of Treatment Visit</th>
<th>Unscheduled Visit(s)</th>
<th>Visit 10 Post-Treatment Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day/Week/Month</td>
<td>-72 hours</td>
<td>Day 1</td>
<td>Week 1 (Day 7)</td>
<td>Week 2 (Day 14)</td>
<td>Month 1 to 5 (Day 30 to Day 150)</td>
<td>Month 6 (Day 180) / stop of study treatment</td>
<td></td>
<td>Month 7 (Day 210), or 1 Month (30 Days) after discontinuation of study treatment</td>
</tr>
<tr>
<td>Visit window</td>
<td>From -72 to 0 hours</td>
<td>±0 Day</td>
<td>±3 Days</td>
<td>±3 Days</td>
<td>±7 Days</td>
<td>+7 Days</td>
<td>+7 Days</td>
<td></td>
</tr>
</tbody>
</table>

- **Central venous catheter status**<sup>7</sup> | X | X | X | X |
- **Randomisation** | X |
- **Innohep<sup>®</sup> administration (Arm 1)**<sup>8</sup> | X<sup>4</sup> | X | X | X | X |
- **Innohep<sup>®</sup> administration (Arm 2)**<sup>9</sup> | X<sup>4</sup> | X<sup>9</sup> |
- **Oral warfarin administration (Arm 2)**<sup>10</sup> | X | X | X | X | X |
- **Assessment of recurrent VTE**<sup>11</sup> | X | X | X | X | X |
- **Instruction of self-administration** | X | X | X |
- **Patient diary distribution** | X | X |
- **Compliance (patient diary check)** | X | X | X | X | X |
- **Innohep<sup>®</sup> dispensing** | X | X |
- **Warfarin dispensing** | X | X |
- **Innohep<sup>®</sup> return by patient** | X | X |
- **Warfarin return by patient** | X | X |
- **AE recording** | X | X | X | X | X | X | X |
- **SAE recording** | X | X | X | X | X | X | X |
- **Bleeding recording and transfusion assessments** | X | X | X | X | X | X |

*Table continues on next page*
### Treatment Period Follow-Up

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening Visit</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4 to 8</th>
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<td>±0 Day</td>
<td>±3 Days</td>
<td>±3 Days</td>
<td>±7 Days</td>
<td>+7 Days</td>
<td></td>
<td>+7 Days</td>
</tr>
</tbody>
</table>

| Healthcare resource utilisation<sup>15</sup> | X | X | X | X |
| Health-related QoL<sup>16</sup> | X | X | X | X |
| PTS<sup>17</sup> | X | X | X | X |
| Overall mortality<sup>18</sup> | | | X | X |
Table footnotes:
aPTT - activated partial thromboplastin time; ALP - alkaline phosphatase; ALT - alanine aminotransferase; AST - aspartate aminotransferase; ECOG - European Co-operative Oncology Group; INR - international normalised ratio; PTS - post-thrombotic syndrome; QoL - quality of life; VTE - venous thromboembolism; RBC - red blood cells; WBC - white blood cells.

General notes:

- If the Screening Visit occurs on the same day (within 24 hours) as the Randomisation Visit (Visit 1, Day 1), local and central laboratory assessments are not required to be repeated.

- Unscheduled visit occurs if a patient experiences signs and symptoms of a recurrent VTE between scheduled visits. The patient will be advised to urgently return to the investigational site for an unscheduled visit or, in emergency situations, report to any acute hospital at which standard assessments will be made to enable the diagnosis of recurrent VTE to be confirmed or refuted. When, in an emergency, the patient is advised to attend an acute hospital not involved in the study, the investigator, or delegated staff, should advise hospital staff of the blood tests that should be taken (local analysis only). If the VTE is not confirmed, the patient will return for the next scheduled visit as planned.

- All efficacy endpoints (i.e. lower limb DVTs and PEs) and causes of death occurring up until Day 180 including 24 hours after last dose of study treatment will be adjudicated by the blinded IAC (cf Diagram 1).

- Bleeding events occurring up to 24 hours after last dose of study drug will be adjudicated by the blinded IAC.

- HIT events occurring up to 1 month after last dose of study drug will be adjudicated by the blinded IAC.

- All patients will be followed up for 1 month (30 days) following discontinuation of study treatment for safety, healthcare resource utilisation, QoL, and PTS.

- Patients who are withdrawn from study treatment, for any reason other than death prior to Day 180 will be asked to stay in the study and be followed up by telephone at time of the remaining regular scheduled monthly study visits. Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess study outcomes (cf Diagram 1).

- Patients who withdraw from study (i.e. withdraws consent to continue participating in the study) will complete final efficacy assessment at the time of withdrawal and be followed for safety outcomes up to 1 month after the last dose of study drug. No other data will be collected on these patients after withdrawing consent but every reasonable effort will be made to discourage patients from withdrawing completely from the study.

- If a patient dies during the 6-month treatment period, all reasonable efforts will be made to ascertain the cause of death including copy of autopsy report (if available) and whether the patient experienced any outcome or AEs/SAEs between the last visit or telephone contact and the time of death and when the last dose of study treatment was taken.

- The date of when the last dose of study drug taken is the date of the End of Treatment.

- The date of event is the date of performed objective diagnosis.
Notes referred to in the table:

1. All patients on treatment (in both treatment arms) will be contacted by the investigator or delegated study site staff by telephone 14 days (± 3 days) after each monthly visit. Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess treatment compliance, concomitant medications, recurrent VTE, bleedings, AEs and SAEs.

2. Warfarin arm only, INR assessment should be carried out frequently during the induction phase until the INR value is at or above 2.0 for 2 consecutive days. When the INR level has reached therapeutic level between 2.0 and 3.0, assessments will then be performed according to local practice and Investigator’s discretion but at least every 2 weeks. INR will be closely monitored if a patient switches warfarin product during the treatment period.

3. Two blood samples (one serum and one plasma) will be collected and stored for future assessment of other potential coagulation biomarkers for consenting patients.

4. Pregnancy test for women of childbearing potential only.

5. Vitals signs of pulse rate and blood pressure will be assessed.

6. ECOG performance status prior to the VTE episode.

7. The central venous catheter (CVC) status (Presence of CVC, indication, the type of CVC, location of CVC and date and time of implantation).

8. The time between the last dose of LMWH prior to randomisation and the first dose of Innohep® after randomisation should be 12 hours if the LMWH was administered twice daily or 24 hours if LMWH (or fondaparinux) was administered once daily.

9. Initial (5 to 10 days) treatment with Innohep® must continue until the patient’s INR is at or above 2.0 for 2 consecutive days. The minimum duration of LMWH treatment (pre-and post-randomisation) is 5 days. The maximum duration of initial Innohep® treatment in the warfarin group is strongly recommended not to exceed 10 days.

10. Warfarin treatment should be started on the day of randomisation, concomitantly with initial (5 to 10 days) treatment with Innohep®.

11. Recurrent VTE recording includes events detected incidentally in routine cancer scans in addition to symptomatic events recorded for the duration of the study. All symptomatic events must be diagnosed using standard diagnostic criteria.

12. Healthcare resource utilisation include: medications used for VTE prevention, laboratory tests associated with anti-coagulation therapy, unscheduled clinical visits, diagnostic tests relevant for VTE diagnosis, VTE-related hospitalisations (including length of stay), and management of patients who develop HIT or bleeding events (e.g. blood transfusions, medications, hospitalisations).

13. Health-related QoL will be assessed using the EQ-5D (Appendix IV).

14. PTS will be assessed using the Villalta scale (see Section 10.7.3.5).

15. If the Screening Visit occur on the same day (within 24 hours) as the Randomisation Visit (Visit 1, Day 1), local and central laboratory assessments are not required to be repeated.

16. To be captured only once, at the visit that occurs last.
### 3.2 FLOW DIAGRAM

#### Screening Period
- Eligibility Criteria
- Diagnosis of VTE
- Informed Consent
- Laboratory Assessments

#### Screening Visit Period
- V1: 72 hrs to 0 hr
  - ± 0 Day
- V2: Day 1
  - ± 3 Days
- V3: Week 1
  - ± 3 Days
- V4: Week 2
  - ± 7 Days
- V5*: Month 1
  - ± 7 Days
- V6*: Month 2
  - ± 7 Days
- V7*: Month 3
  - ± 7 Days
- V8*: Month 4
  - ± 7 Days
- V9*: Month 5
  - ± 7 Days
- V10: Month 6
  - + 7 Days

#### Treatment Period
- Study treatment should be initiated after randomisation
- Innohep® 175 anti-Xa IU/kg body weight (N=450)

#### Warfarin
- Initial (5 to 10 days) Innohep® (until INR in target) (N=450)

#### Follow-Up
- Patients will be contacted by telephone 14 days after each monthly visit
- Patients withdrawn from study treatment will be followed up by telephone contacts in place of scheduled monthly visits until Day 180

---

*T = Patients will be contacted by telephone 14 days after each monthly visit

*N = Patients withdrawn from study treatment will be followed up by telephone contacts in place of scheduled monthly visits until Day 180*
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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

4.1 LIST OF ABBREVIATIONS

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
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<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
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<tr>
<td>aMDRD</td>
<td>Abbreviated Modification of Diet in Renal Disease</td>
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<tr>
<td>aPTT</td>
<td>Activated Partial Thromboplastin Time</td>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>bpm</td>
<td>Beats Per Minute</td>
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<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CIF</td>
<td>Cumulative Incidence Functions</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CTAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
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<tr>
<td>CTPA</td>
<td>Computed Tomographic Pulmonary Angiography</td>
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<tr>
<td>CTS</td>
<td>Clinical Trial Supplies</td>
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<tr>
<td>CVC</td>
<td>Central Venous Catheter</td>
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<tr>
<td>CUS</td>
<td>Compression Ultrasound</td>
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<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>DRG</td>
<td>Diagnosis-related Group</td>
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<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<tr>
<td>ECOG</td>
<td>Eastern Co-operative Oncology Group</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
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<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>FAS</td>
<td>Full Analysis Set</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
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<tr>
<td>HIT</td>
<td>Heparin-Induced Thrombocytopenia</td>
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<tr>
<td>HQ</td>
<td>Head Quarters</td>
</tr>
<tr>
<td>IAC</td>
<td>Independent Adjudication Committee</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>ICTM</td>
<td>International Clinical Trial Manager</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
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<tr>
<td>IP</td>
<td>Investigational Product</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ISTH</td>
<td>International Society on Thrombosis and Haemostasis</td>
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<tr>
<td>IVC</td>
<td>Inferior Vena Cava</td>
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<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
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<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance Imaging</td>
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<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
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<tr>
<td>PP</td>
<td>Per-Protocol</td>
</tr>
<tr>
<td>PTS</td>
<td>Post-Thrombotic Syndrome</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted Life Year</td>
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</table>
4.2 DEFINITION OF TERMS

Refer to Appendix III for definitions of terms.
5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEES (IECS) OR INSTITUTIONAL REVIEW BOARDS (IRBS)

The clinical study must be approved by/receive favourable opinion from relevant Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs) prior to enrolment of patients.

Any amendments to the approved clinical study must likewise, as required, be approved by/receive favourable opinion from relevant IRBs/IECs prior to implementation.

The appropriate regulatory authority(ies) must be notified of/approve the clinical study, as required.

5.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted to conform to the principles of the World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Patients, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last revised in Seoul in October 2008 by the WMA General Assembly (see Appendix II).

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) and relevant legislation.

Patients will be asked to consent that data and blood samples are recorded, collected, processed and may be transferred (to European Union [EU] and non-EU countries), in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

All information containing personal data will be handled in accordance with the general terms of the authorisation granted by the Danish Data Protection Agency to LEO (as appended to this protocol) in accordance with the EU Data Protection Directive (95/46/EC) as well as any national data protection legislation.
5.3 ETHICAL CONSIDERATION STATEMENT

Cancer patients are known to be at higher risk of developing venous thromboembolism (VTE) compared to the general population (1, 2, 3, 4), and VTE is often cited as a leading cause of death among cancer patients (5, 4, 6). Treatment of this clinically threatening condition is essential both in terms of morbidity and mortality and is costly also in terms of resource utilisation and quality of life (QoL). With the increasing incidence and prevalence of cancer combined with more aggressive, and often thrombogenic, treatment regimens, as well as improved survival, an increasing prevalence of cancer-associated thrombosis can be expected.

There are few randomised studies to support the recommendations from the American College of Chest Physicians (ACCP) (7) that low molecular weight heparin (LMWH) should be used for 3 months for treating an acute VTE in a patient with active cancer. The current study is designed to provide definitive evidence.

Prolonged treatment with Innohep® at therapeutic dosages (175 anti-Xa IU/kg) used to prevent VTE recurrence has been shown to be effective and safe in landmark studies which included patients with active cancer (8, 9, 10, 11, 12). The risk of bleeding is evaluated to be low (11) and the subcutaneous (SC) administration of Innohep® has been shown to have an acceptable compliance (13).

Patient safety will be carefully assessed by a blinded Independent Adjudication Committee (IAC) that will adjudicate all efficacy endpoints as well as all bleeding and heparin-induced thrombocytopenia (HIT) events, and cause of deaths. Efficacy and safety will also be monitored by an independent Data Monitoring Committee (DMC).

Whilst a double blind study would provide a scientifically more robust study design, such a design would be ethically and practically very difficult as it would expose oncology patients to the additional burden of SC injections of a placebo drug in patients assigned to warfarin treatment while patients assigned to Innohep® treatment would have to receive placebo tablets and be subject to sham INR monitoring with multiple unnecessary blood draws done. The study will therefore be open, but randomised, with a control arm receiving a vitamin K-antagonist (VKA): warfarin.

Innohep® is at least partially excreted via the kidneys but other elimination pathways are also available (14, 15). Clinical studies have shown that patients with mild to severe renal
insufficiency (clearance ≥ 20 ml/min) may be treated safely with Innohep® (16, 17). The elderly population is known to have decreasing renal function and both prophylactic (4500 anti-Xa IU) and therapeutic doses (175 anti-Xa IU/kg) of Innohep® have been safely used in elderly patient populations without any dose reductions (16, 17, 18). In oncology patients, renal function may be affected by chemotherapy and also by the cancer itself. Estimation of renal function in cancer patients may be done with different formulae (19). The abbreviated Modification of Diet in Renal Disease (aMDRD) formula will be used in order to ensure appropriate estimation of low/borderline clearance levels (KDIGO guidelines; 20, 21, 22).

A pharmacokinetic study of Innohep® in healthy heavy weight subjects up to 165 kg on treatment dosages (175 IU/kg) of Innohep® and prophylactic doses (75 IU/kg) supported the recommendation that SC dosing of Innohep® to heavy weight or obese patients can be based on body weight alone. There was no evidence to suggest that the dose of Innohep® should be capped at a maximal fixed dose or that further adjustments for weight or obesity are required (23). In addition, the Hull et al 1992 study included patients weighing up to 140 kg. These patients were dosed at 175 IU/kg according to actual body weight, with no reported safety concerns (8).

5.4 PATIENT INFORMATION AND INFORMED CONSENT

All patients will receive written and verbal information concerning the study. This information will emphasise that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason, and also without stating a reason. All patients will be given opportunity to ask questions and will be given ample time to consider participation in this study before consenting.

A separate consent form including a statement on the collection and storage of blood samples for potential post-study analysis of blood coagulation parameters, above and beyond those assessed in this study, will also be provided to all patients. Patient consent for collection of post-study analysis of blood coagulation parameters is not a requirement for being included in the study.

The patient’s signed and dated informed consent to participate in the study will be obtained prior to any study related procedure being carried out.
6 STUDY ADMINISTRATIVE STRUCTURE

LEO Pharmaceutical Products Ltd. A/S (LEO Pharma A/S) is the sponsor of the study and has contracted (a Contract Research Organisation (CRO)) to perform study related services.

6.1 PROTOCOL AUTHOR(S)

International Co-ordinating Investigator: 

International Clinical Trial Manager: , LEO

Statistician: , LEO

Medical Expert: , LEO

Pharmacovigilance Scientist: , LEO

6.2 INVESTIGATORS, STUDY SITES AND CROS

6.2.1 International Co-ordinating Investigator

The International Co-ordinating Investigator, , is responsible for approval of the (Consolidated) Clinical Study Protocol and the Clinical Study Report on behalf of all study Investigators, as agreed to in the International Co-ordinating Investigator Agreement. contact details are as follows:

Dr.

Vancouver,
6.2.2 Investigators

Each participating Investigator is responsible for all aspects of the study conduct at his/her study site as agreed to in a Clinical Trial Agreement to be signed prior to study initiation.

The contact details for all participating Investigators will be provided in the National Clinical Trial Applications.

6.2.3 Contract Research Organisation(s) (CRO(s))

The designated CRO for this study is as follows:

[Redacted name and location for study supplies in the USA, US]

[Redacted name and location for Interactive Voice Response System (IVRS) in the UK]

[Redacted name and location for Central Laboratory Services in the USA]
6.2.4 Study Committees

6.2.4.1 Independent Adjudication Committee (IAC)

The blinded IAC will comprise thrombosis, oncology and bleeding experts, blinded to study medication assignment. All members will be independent of the study (i.e. they will not be participating [Sub] Investigators or employees at participating sites) and of LEO (i.e. they will not be LEO employees).

The blinded IAC will be responsible for adjudicating all efficacy endpoints (i.e. lower limb deep vein thromboses [DVTs], and pulmonary embolisms [PEs]) and causes of death occurring up until day 180 including 24 hours after the last dose of investigational product. Bleeding events occurring up to 24 hours, and HIT events occurring up to 1 month, after last dose of study treatment will also be adjudicated.

A separate adjudication charter prepared under the responsibility of the chairman of the blinded IAC in order to specify the procedures and criteria used for adjudication of these events is provided as a separate document. The adjudication results will be the basis for final analysis of the efficacy endpoint, bleedings endpoints, HITs and cases of deaths.

Further details on blinding and all aspects relating to the tasks and responsibilities of IAC are provided in the IAC charter.

6.2.4.2 Data Monitoring Committee (DMC)

The DMC will comprise clinicians and methodologists. All members will be independent of the study (i.e. they will not be participating [Sub] Investigators or employees at participating sites) and of LEO (i.e. they will not be LEO employees).

The DMC members are experienced with clinical studies and will be responsible for assessing the safety of the patients through:
• Assessing the safety of the treatment regimen during the study.
• Monitoring the overall conduct of the clinical study.
• Conducting and interpreting the interim analysis.

The DMC will review data on a regular basis. The first data review meeting will be scheduled for approximately 6 months after the 115th patient has been randomised (i.e. when we expect the first 115th patients to have all completed or withdrawn). Similarly, further meetings will be scheduled for 6 months after the 225th, 340th, 450th, 600th and 750th patients have been randomised. Additional meetings may also be called on an ad hoc basis, as requested by the DMC or LEO. Exact dates of reviews will be agreed with the DMC.

All data collected at the time of the data cut-off/scheduled meetings will be included in the summaries for the DMC, including data from patients still ongoing in the study. In addition to the specified interim analysis, the DMC will examine summaries and listings of the adjudicated events (recurrent VTEs, HIT events, bleeding events and deaths from any cause), adverse events (AEs), specific laboratory parameters and patient disposition data. Full details of the analyses to be presented to the DMC will be specified in a separate DMC statistical analysis plan.

The DMC will have an Independent Statistician who will receive study data from the CRO and will remain independent of the study management team.

The DMC is independent of the sponsor. The chairman of the DMC, in conjunction with the other members, will communicate their recommendations to the Sponsors International Clinical Trial Manager (ICTM) after each meeting. The chairman of the DMC will provide written reports to LEO after each formal review to indicate the committee’s recommendation regarding safety concerns and study continuation.

Further details on all aspects relating to the DMC are provided in the DMC charter.

6.2.4.3 Steering Committee (SCO)

The SCO will comprise clinicians and methodologists, and the SCO chairman is also the International Co-ordinating Investigator. The overall responsibilities of the SCO will be to:
1. Endorse the protocol, any amendments needed, study report etc.
2. Survey the study progress in general including patient recruitment, quality, timelines etc.
3. Advise the sponsor if any changes in study conduct are recommended based on DMC conclusions, recruitment issues etc.

Further details on all aspects relating to the SCO are provided in the SCO charter.

The following are members of the SCO:

**Chairman:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Country</th>
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<tr>
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6.3 STUDY RELATED PERSONNEL

6.3.1 Personnel

6.3.1.1 Project Manager

6.3.1.2 Medical Monitor/Safety Contact

6.3.1.3 Statistician

6.3.2 Sponsor Personnel

6.3.2.1 International Clinical Trial Manager (ICTM)
7 INSURANCE

The patients in the present clinical study are covered by the product and general liability insurance of LEO in the event of study related injury or death, in accordance with applicable law and with the CPMP Note for Guidance on GCP (CPMP/ICH/135/95) of 17 July 1996.

8 INTRODUCTION AND RATIONALE

8.1 CANCER-ASSOCIATED THROMBOEMBOLISM

Venous thromboembolism is a common clinical problem in oncology and VTE is the second most common cause of death among cancer patients (24, 25, 26, 27). Cancer patients also
experience a two fold greater PE case mortality rate than patients without cancer (24). Some cancers, such as a pancreatic adenocarcinoma and cancers with a poor prognosis, are notorious for their association with thromboembolic disorders (28); in addition venous thrombosis may be the presenting feature of a malignancy (24). The significance of VTE in cancer patients is often underestimated resulting in under diagnosis which can lead to significant patient morbidity and mortality. The early and the accurate diagnosis of VTE is crucial to avoid unacceptable outcomes (29).

The incidence of symptomatic VTE in cancer patients varies considerably and incidence rates from 2% to 30% have been reported. This wide range of incidence rates reflects not only the natural history of different tumour types (30, 31, 32, 33), but also indicates that other tumour-related factors, chemotherapy-related factors and other patient related factors also influence the rates of VTE. The prevalence of incidental or asymptomatic VTE has probably been underestimated but with increasing focus on treatment modalities, treatment outcomes, staging procedures and increased cancer survival, the significance of incidental VTE is becoming more recognised (29).

Many tumour-related factors of importance for VTE have been identified, where tumour burden and location directly induce an extrinsic vascular compression and invasion resulting in venous return obstruction and blood flow stasis, endothelial cell injury and coagulation activation (30, 34). On a molecular level, cancer cells exhibit procoagulant activity by producing tissue factor. Cancer cells can also promote tissue factor production by monocytes and endothelial cells. Some selected tumours may accentuate platelet activation and accumulation, whereas other tumour cells may support prothrombin and factor X activation (35).

The risk of VTE is considerably increased with advancing stages of cancer (32) and patients with distant metastases have a higher risk of VTE than those without distant metastases (36). It is often reported that the risk of VTE is increased during the first months after diagnosis (37).

The risk of VTE is further increased by the type of treatment, including surgery, and systemic anticancer therapy. Bevacizumab, an anti-angiogenic agent indicated in a variety of cancer types, such as colon, renal, lung and breast cancer is associated with a 33% relative increase in the risk of VTE (38).
Other patient-related factors such as advanced age, comorbidities, multiple surgeries, hospitalisations, prolonged immobilisation, central venous catheters, dehydration and thrombophilic mutations commonly increase the incidence rate of VTE (38).

8.2 CURRENT THERAPEUTIC OPTIONS

Long-term treatment of symptomatic VTE is recommended in all cancer patients as described in American and European guidelines (39, 40), and UFH as well as LMWH and VKAs have been studied for their efficacy in reducing recurrent VTE in patients with cancer-associated thrombosis where rates of recurrent VTE are higher than in non-cancer patients. The major objectives in the treatment of VTE are to diminish the acute symptoms of DVT and/or PE, to reduce recurrent thromboses, fatal and non-fatal PEs. Treatment of VTE also reduces the incidence of long-term sequelae, e.g. pulmonary hypertension and post-thrombotic syndrome. With increasing life expectancy and continual improvement of oncology treatment modalities, these therapeutic goals become more and more important in cancer patients. Reliable long-term information on QoL is also of increasing importance (41).

Several studies have reported high incidences of recurrent VTE, up to 21% in patients with cancer (11, 41, 42, 43), and only a few studies have focussed on how to treat this patient population and how to identify those at risk for recurrent VTE (44, 45).

In addition to their antithrombotic effects, UFHs and LMWHs demonstrate a wide spectrum of pharmacological properties in non-clinical studies, including direct anti tumour effects, anti-angiogenic activity, and immune modification properties. Innohep®, for example, exhibits potent anti-angiogenic activity in non-clinical models, inhibits tumour metastasis in a mouse model, and tumour growth in a chick chorioallantoic membrane model. Thus, LMWH may prove to reduce mortality in cancer patients (46).

8.3 INVESTIGATIONAL PRODUCT DESCRIPTION

Innohep® is a LMWH derived from UFH of porcine intestinal mucosa origin. Innohep® has been approved for prophylaxis and treatment of DVT and PE in various moderate-to high risk patient populations. Innohep® was first approved and marketed in 1991 and has since been marketed in more that 50 countries worldwide.
Innohep® has the highest mean molecular weight of all LMWH, and unlike other LMWHs, Innohep® is produced by cleavage of UFH using a specific enzyme and it retains more of the pharmacologic properties of UFH than LMWHs formed by chemical or physical depolymerization of UFH. These include enhanced release of tissue factor pathway inhibitor (TFPI) and a greater vascular protective effect. An in vitro thrombosis model (thromboelastography) suggests that Innohep® has superior antithrombotic properties relative to other LMWHs and to UFH, and acts synergistically with platelet GP IIb/IIIa antagonists (47, 48).

Innohep® is administered by SC injections; the bioavailability is 90% and peak anticoagulant effect is seen 4-6 hours after administration. The plasma elimination half-life (anti Xa) is 3-4 hours after SC injection (14). Elimination of Innohep® is normally predominantly via the renal route, with 80-90% of an administered dose recoverable in urine and only 1-2% in faeces. The elimination of LMWHs, including Innohep® differs from UFH in that they bind less to endothelial cells, and thus are eliminated mainly via a non-saturable renal pathway. However, in patients with impaired renal function (creatinine clearance down to 20 ml/minute) Innohep® does not accumulate (16, 17). Sixty five to eighty percent of anti-Xa activity of Innohep® is neutralised by protamine sulphate, this is the highest neutralisation of any LMWH. This is an important consideration if urgent surgical intervention with reversal of anticoagulation is required (see Innohep® summary of product characteristics (SmPC)).

8.4 INNOHEP® CLINICAL EXPERIENCE

In all clinical studies, Innohep® has been effectively administered SC on a once daily schedule.

Innohep® was evaluated for the treatment of acute symptomatic DVT with Innohep® for 90 days at a treatment dose (175 anti-Xa IU/kg) in a study (8) in which approximately one quarter of the subjects had cancer (11). Overall, Innohep® proved effective relative to VKA and in the cancer population the VTE recurrence at 12 months was 7 of 100 (7%) receiving Innohep® versus 16 of 100 (16%) in the VKA group (P=0.044; risk ratio: 0.44; absolute difference: -9.0; 95% confidence interval [CI]: -21.7 to -0.7). The use of Innohep®, relative to VKA, was also safe for the cancer subjects with no increased risk of bleeding; bleeding, largely minor, occurred in 27 patients (27%) receiving Innohep® and 24 patients (24%) receiving VKA (absolute difference: -3.0; 95% CI: -9.1 to 15.1).
Innohep® proved as effective as heparin in a study of subjects presenting with acute PE (9). It is an effective extracorporeal circulation anticoagulant when administered systemically to end stage renal disease patients undergoing haemodialysis (49).

LMWHs may also reduce mortality in cancer patients. Retrospective analyses of several clinical studies suggest that LMWH, as treatment for symptomatic VTE may reduce mortality in patients with cancer (46). The reduction in mortality has been seen for cancer patients with localized disease (50) and meta-analyses have suggested that such results are not unreasonable since notable survival benefit has been shown with LMWH over UFH in cancer patients (51).

8.5 SAFETY OF INNOHEP®

Preclinical Innohep® studies include chronic (1 year) dosing toxicology studies in rats and dogs. Bleeding related adverse experiences with Innohep® in these studies were no greater than in heparin controls. Radial cataracts were noted in rats after 52 weeks with both heparin and Innohep® at doses >2 times the maximum human therapeutic dose based on body surface area. Decreased bone density was also noted in rats at high doses of Innohep® (~2x the maximum human dose based on body surface area), as well as in heparin controls.

Bleeding complications are characteristic of UFH treatment and can limit its clinical use. Bleeding complications with Innohep® appear to be less problematic than with UFH. In a large study, the risk of bleeding complications was reduced by 91% with Innohep® relative to UFH in patients with DVT (8). Similarly, major and minor bleeding complications were less frequent with Innohep® than with UFH in patients with PE and DVT (9).

In a DVT prophylaxis study for patients undergoing orthopaedic surgery, the incidence of AEs, including bleeding complications and haematoma, was not significantly greater with Innohep®. Although postoperative blood loss was greater in the Innohep® group, total blood loss was not different between groups and was not considered clinically significant (52).

The favourable tolerability of Innohep® was highlighted by meta-analyses of LMWH studies, in which Innohep® was the only agent found to significantly reduce the incidence of bleeding complications compared with UFH (53).
As with other heparins, injection-site haematoma may occur with Innohep® and this is the side-effect most frequently encountered in clinical practice (very common). However, even in patients receiving high doses of Innohep® (175 anti-Xa IU/kg daily), major haematomas are very infrequently reported.

Similarly rare complications of Innohep® treatment are thrombocytopenia (uncommon), and transient aminotransferase elevations (rare). Other undesirable effects that have been reported with Innohep® treatment include rare allergic reactions (uncommon), priapism (not known), hypoaldosteronism (frequency unknown), and osteoporosis (frequency unknown). Most of these side-effects typically resolve after the course of treatment has finished.

References and further information on Innohep® is available in the SmPC/product Monograph and the package inserts.

8.6 STUDY RATIONALE

VTE occurs more frequently in patients with cancer compared to patients with most other diseases. As mentioned above, many risk factors for VTE in patients with malignancy are related to the cancer itself, to cancer treatment and also to patient characteristics. LMWHs have been shown to have clinical benefit in the secondary prevention of VTE in cancer patients (8, 11, 50).

Standard VTE treatment practices including the use of intravenous UFH for initial anticoagulation followed by oral warfarin/coumarin for chronic anticoagulation, and the prescription of only 3 to 6 months of total therapy may not be optimal in the setting of active cancer and ongoing anticancer therapy. It has been recommended (7) that LMWH should be used for 6 months (at least) for treating an acute VTE in a patient with active cancer. However, there is little evidence to support all the LMWHs. The main aim of this study is to perform a robust study to test if Innohep® is more efficacious than warfarin in preventing recurrent VTE in patients with cancer.

Rationale for dosage, dosage regimen(s)
Innohep® (tinzaparin sodium) 175 anti-Xa IU/kg for SC once daily injection is the standard licensed dose of Innohep® for short term (5-10 days) treatment of DVT and PE. Use of a once-daily dose allows for simpler administration with less burden on patients.

**Rationale for duration of treatment**

Guidelines on anticoagulation recommend long-term VTE treatment in cancer patients of 3 to 6 months or longer ([ASCO](#) [54], [ESMO](#) [55] and [NCCN](#) [Practice Guidelines in oncology v.1.2009]). This study will determine if 6 months of treatment with Innohep® is effective and safe.

**Rationale for choice of comparator**

Warfarin, which was approved for use as a medication in the early 1950s, has remained the standard anticoagulant for long-term treatment in patients with venous thrombotic disease. In patients with cancer, dalteparin has recently been approved for extended use to prevent recurrent VTE. However, Dalteparin is not considered standard of care in many regions. To provide greater therapeutic choice and to better study long-term outcomes of patients with cancer and thrombosis, this study will evaluate Innohep® against warfarin. The current study is designed to obtain evidence that the LMWH Innohep® is more effective than warfarin.

During the past decade, CT scans are used with greater frequency for the routine assessment of cancer staging and disease monitoring. As a consequence reporting of incidental PE has become increasingly frequent in cancer patients ([70]). Neither the prognostic impact nor the treatment of incidentally found PEs in cancer patients is completely understood, but there is generally thought that incidentally found DVT and PE should be treated ([71]).

A recent large retrospective analysis concluded that the prevalence of incidental VTE in patients with cancer in clinical practice is relatively low and most patients with PE or DVT are treated with anticoagulants ([72]). A systematic review of more than 10 thousand patients and a meta-analysis of the prevalence of incidental PE in patients with and without cancer conclude that the prevalence of incidental PE scan is clinically relevant and potentially associated with an unfavorable outcome ([73]).

Incidental VTE is included in the primary composite endpoint because of several reasons:
1) they are objectively confirmed new thrombotic events;
2) majority of these events are associated with symptoms consistent with PE or DVT;
3) there is expert consensus that these are clinically significant events with similar prognosis as symptomatic VTE;
4) treatment with therapeutic anticoagulation is recommended when incidental proximal DVT or PE are reported.

In addition, evidence in cancer patients is emerging equivalent to what is documented in orthopaedic surgery, where data show that asymptomatic VTE rates correlate directly with the symptomatic VTE rates and survival (74).

9 STUDY OBJECTIVES

9.1 PRIMARY OBJECTIVE
The primary objective of the study is to assess the efficacy of Innohep® in preventing the recurrence of VTE in patients with active cancer who have had an acute VTE episode.

9.2 SECONDARY OBJECTIVES
The secondary objectives are to:
- Assess the safety of long-term Innohep®.
- Identify clinical risk factors for recurrent VTE and major bleeding.
- Assess overall mortality at 6 months.
- Identify the possible role of coagulation parameters to predict for recurrent VTE or prognosis.
- Assess incidence and severity of post-thrombotic syndrome (PTS).
- Assess health-related QoL.
- Assess healthcare resource utilisation.

10 INVESTIGATIONAL PLAN

10.1 STUDY DESIGN
Overall Design
This is a Phase 3, multi-national, multi-centre, randomised, active controlled, open-label study with blinded adjudication, assessing the efficacy and safety of long-term (6-Month) Innohep®
therapy versus anticoagulation with warfarin for the treatment of VTE in cancer patients. The primary objective of this study is to assess the efficacy of Innohep® in preventing the recurrence of VTE in patients with active cancer who have had an acute VTE episode. Patients with active cancer with a newly diagnosed acute VTE will be considered for the study.

**Individual Phases**

Patients will attend the study centre for up to 11 scheduled visits: the Screening Visit (within 72 hours prior to randomisation), the Randomisation Visit (Visit 1, Day 1, this may occur on the same day (within 24 hours) as the Screening visit), Visit 2 (Day 7), Visit 3 (Day 14), Visits 4 to 8 (Day 30 to Day 150), Visit 9 (Day 180/End of treatment) and Visit 10 (30 days Post-Treatment Follow-Up). For this study 1 month will equal a period of 30 days; visit windows varying from ± 3 days to ± 7 days will be allowed at all scheduled visits after Visit 1. For visits 9 and 10, visits should not be scheduled prior to day 180 and 210 respectively from time of randomisation. In addition, patients may be asked to return to the clinic for an unscheduled visit for urgent assessment of recurrent VTE, bleeding or AEs/SAEs. See Figure 1 for a schematic of the study design.

All patients in both treatment arms will be contacted by the investigator or delegated study site staff by telephone 14 days (± 3 days) after each monthly visit. All patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess treatment compliance, concomitant medications, recurrent VTE, bleeding events, other outcomes, AEs and SAEs.

Patients who are withdrawn from study treatment, for any reason other than death, prior to Day 180 will be asked to stay in the study and be followed up by telephone at time of the remaining regular scheduled study visits. Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess study outcomes. Patients off study treatment may be asked to return to the clinic between telephone contacts for urgent assessment for suspected or confirmed recurrent VTE (unscheduled visit) (cf Diagram 1).

Patients who withdraw from study (i.e. withdraws consent to continue participating in the study) will complete final efficacy assessment at the time of withdrawal and be followed for safety outcomes up to 1 month after the last dose of study drug. No other new data will be
collected on these patients after withdrawing consent but every reasonable effort will be made to discourage patients from withdrawing completely from the study.

Once the acute VTE diagnosis has been confirmed during screening, patients should start LMWH or UFH or Fondaparinux treatment immediately in accordance with local practice; however, the duration of LMWH/UFH or Fondaparinux treatment should not exceed 72 hours (3 days) before randomisation (the 72 hour count starts when the first therapeutic dose of an anticoagulant is given). VKA treatment should NOT be started before randomisation.

Patients who fulfil all study eligibility criteria (as defined in Section 10.4), and provide written informed consent to participate in the study, will be randomised at Visit 1 (Day 1) to receive either:

1. Long-term treatment with Innohep® only (Arm 1),
   OR
2. Oral treatment with warfarin in combination with overlapping initial (5 to 10 days) treatment with Innohep® (Arm 2).

Those assigned to the long-term Innohep® only treatment arm will receive SC Innohep® once daily for 6 months (180 days).

Those assigned to the oral warfarin treatment arm will receive oral warfarin once daily starting on Day 1. Innohep® at a dose of 175 anti Xa IU/kg once daily will be given until their international normalised ratio (INR) is at or above 2.0 for 2 consecutive days. The minimum duration of LMWH treatment (pre-and post-randomisation) is 5 days. The maximum duration of initial Innohep® treatment in the warfarin group is strongly recommended not to exceed 10 days.

The time between the last dose of LMWH before randomisation and the first dose of Innohep® after randomisation should be 12 hours if the LMWH was administered twice daily or 24 hours if the LMWH (or Fondaparinux) was administered once daily.

The first dose of investigational product should be given on Day 1 as soon as possible after randomisation. The first injection of Innohep® will be performed at the study clinic. Subsequent Innohep® injections will be performed by the patient (self-administration), a relative, or a healthcare professional as judged by the Investigator. Patients will continue study treatment
until they complete the 6-month (180 days) treatment period unless they withdraw consent, die, or must stop study treatment due to recurrent VTE, bleeding, toxicity or other reasons outlined in Section 10.5. A Post-Treatment Follow-up Visit will be conducted 1 month (30 days) after the last dose of study drug.

Each scheduled visit (Visit 1 and onwards) will include a standardised assessment of the signs and symptoms of recurrent VTE. If a patient experiences signs and symptoms between scheduled visits, the patient will be advised to contact the Investigator or delegated staff. If signs and symptoms are assessed by the Investigator or delegated site staff to be of a recurrent VTE, the patient will be advised to return to the clinic urgently for an unscheduled visit in order to confirm or refute the suspected recurrent VTE. The patient will also be requested to return to the clinic for an unscheduled visit if a recurrent VTE is coincidentally detected during other examinations, e.g. cancer staging. The Additional investigations may be requested to confirm the diagnosis of an incidental VTE. See Section 10.7.3.4 for diagnostic criteria for incidental VTE and further details.

All efficacy endpoints (i.e. lower limb DVTs, and PEs) and major safety endpoints (i.e. bleeding events, HITs and cases of death), as defined in Section 10.8 and 10.9, will be adjudicated by the blinded IAC (Section 6.2.4.1); additionally all efficacy and safety data will be independently monitored by the DMC (Section 6.2.4.2).
Figure 1: Schematic of Study Design

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<th>Treatment Period</th>
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<td>Informed Consent</td>
<td>Warfarin + initial (5 to 10 days) Innohep® (until INR in target) (N=450)</td>
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<td>Laboratory Assessments</td>
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Screening Visit Period

-72 hrs to 0 hr

Day 1 ± 0 Day

Day 7 ± 3 Days

Day 14 ± 3 Days

Month 1 ± 7 Days

Month 2 ± 7 Days

Month 3 ± 7 Days

Month 4 ± 7 Days

Month 5 ± 7 Days

Month 6 ± 7 Days

Month 7 ± 7 Days

Day 210 ± 7 Days

V1 V2 V3 V4 V5* V6* V7* V8* V9* V10
10.2 TIME SCHEDULE
The following dates are planned for this study:

Planned date of first patient in: Quarter 2, 2010.
Planned date of last patient in: Quarter 4, 2012.
Planned date of last patient out (last patient last visit): Quarter 3, 2013.

End of study is defined as the last patient last visit date.

10.3 NUMBER OF PATIENTS/SAMPLE SIZE
It is planned that 900 patients will be randomised in this study; 450 patients in the Innohep® arm and 450 patients in the warfarin arm.

Assuming that Innohep® leads to a relative risk reduction of 50%, an estimated event rate of 12.6% in the control group will imply an estimated event rate of 6.3% in the Innohep® group. Using a time-to-event approach with a significance level of $\alpha = 0.05$ and an overall power of 90%, a sample size of 847 patients will be required to detect the above difference. Including an expected dropout rate of 5%, 900 patients should be enrolled in the trial, with 450 patients randomised to each treatment group.

A sample size re-estimation will be conducted on blinded data when approximately 25% of the patients have either completed the treatment period, died or are lost to follow-up. The observed incidence rate for the primary endpoint in the entire group will be summarised, together with the associated 95% confidence interval. This data will be used to establish whether the planned sample size of 900 is reasonable (see Section 11.4.1).

See Section 11.1 for a more detailed account of the sample size estimation.

10.4 CRITERIA FOR PATIENT SELECTION (IN- AND EXCLUSION)
Following receipt of verbal and written information about the study, the patient must provide signed and dated informed consent before any study related activity is carried out.
Any implementation of national requirements/law for the study patient’s participation in the clinical study will be ensured and will be described in submission documentation to authorities/ethics committees, as applicable.

10.4.1 Inclusion Criteria

1. Patients with a diagnosis of active cancer with a histologically or cytologically diagnosed solid tumour (evidence of early stage, regionally advanced or metastatic disease) or haematological malignancy. Active cancer is defined as:
   - Patients diagnosed with cancer within the past 6 months, OR
   - Patients with recurrent, regionally advanced or metastatic disease, OR
   - Patients that have received any treatment for cancer during the previous 6 months, OR
   - Patients not in complete remission of a haematological malignancy.

2. Symptomatic and objectively confirmed acute proximal lower-limb DVT (anatomically including popliteal, femoral [superficial and common] and iliac [external and common]) and/or PE diagnosed within 72 hours prior to randomisation (the 72 hour count starts when the diagnosis is confirmed by imaging). Diagnosis of DVT/PE must be made by appropriate objective imaging (see Section 10.7.3.4).

3. ≥ 18 years of age or above the legal age of consent as per country specific regulations.

4. Patients with Eastern Co-operative Oncology Group (ECOG) performance status of 0, 1 or 2 prior to the VTE episode.

5. Signed informed consent.

10.4.2 Exclusion Criteria

1. Life expectancy < 6 months.

2. Patients with basal cell carcinoma or non-melanoma skin cancer where this is their only cancer diagnosis.

3. Creatinine clearance ≤ 20 ml/min according to the abbreviated Modification of Diet in Renal Disease (aMDRD) formula (see Appendix V).

4. Contra-indications to anticoagulation:
   a. Active or recent (≤ 1 months) clinically significant bleeding, including gastrointestinal bleeding or peptic ulcer.
   b. History of bleeding disorder or coagulopathy (congenital, acquired or unexplained repeated bleeding episodes).
c. Increased risk of bleeding due to tumour characteristics or other condition prohibiting the use of therapeutic anticoagulation according to the Investigator’s judgment.

d. Uncontrolled arterial hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).

e. Recent intracranial haemorrhage (in the last 1 month prior to randomisation) which is at high risk of rebleeding and would prohibit anticoagulant therapy, according to the Investigator’s judgment.

f. Recent (in the last 1 month prior to randomisation) brain, spinal or ophthalmic surgery.

g. Thrombocytopenia (platelet count < 50 x 10^9/L).

h. Coagulopathy due to liver insufficiency as indicated by a prolonged baseline activated partial thromboplastin time (aPTT) > 1.5 x upper limit of normal (ULN) or equivalent to an aPTT ratio > 1.5 (if not receiving [LMWH] / unfractionated heparin [UFH]).

5. Known hypersensitivity to the investigational product (Innohep®) or reference product (warfarin).

6. History of HIT.

7. Pre-randomisation therapeutic anticoagulant treatment for the current acute VTE administered for more than 72 hours prior to randomisation.

8. Patients who had been receiving therapeutic anticoagulation at the time of the VTE event (i.e. anticoagulant failure), using any anticoagulant, such as:
   a. Parenteral anticoagulants e.g. UFH, LMWH, fondaparinux, bivalirudin or hirudin.
   b. Vitamin K antagonist (VKA).
   c. New oral anticoagulants, e.g. dabigatran, rivaroxaban.
      Note: Chronic treatment with anti-platelet agents such as low dose of aspirin (up to 325 mg/day), clopidogrel or ticlopidine is allowed.

9. Patients unlikely to comply with the protocol, e.g. inability to return for study visits or inability to receive/administer daily SC injection.

10. Participation in another interventional study with active drug treatment or an investigational device.

11. Pregnant or breast-feeding women. Pregnancy status should be checked by serum or urine pregnancy testing prior to randomisation.
12. Women of childbearing potential not protected by an effective contraceptive method of birth control (as defined for contraception in the Informed Consent Form [ICF]) for the duration of the study.

13. Sexually active fertile men if they, or their partner (being a woman of childbearing potential), is not using effective birth control.

Prior to inclusion in the study, patient eligibility details will be reviewed by the site Investigator, and if required in collaboration with medical experts from the CRO in order to confirm that patients accepted for randomisation fulfils the required criteria.

10.4.3 Patient Screening Log

A Patient Screening Log will be used in this study to document all patients who have provided written informed consent and been screened, including those who cannot be randomised due to screen failure.

10.4.4 Patient Registration

As soon as the patient provides written informed consent, that patient will be assigned the next (ascending) subject number available at the study site. The subject number is a unique patient identifier used throughout the study, in lieu of the patient’s name.

10.5 WITHDRAWAL CRITERIA (PERMANENT DISCONTINUATION OF STUDY TREATMENT)

Patients may permanently discontinue the study treatment for any of the following reasons:

1. Patient completed treatment according to the Clinical Study Protocol.
2. Patients with objectively confirmed recurrent DVT or PE occurring before the end of the 6 months treatment period.
3. The Investigator deems that patient should be taken off study treatment due to safety concerns or other medical reasons
4. Unacceptable AEs/SAEs: any AE/SAE that the Investigator or the patient considers unacceptable.
5. Pregnancy.
6. **Voluntary withdrawal**: patients will be free to withdraw from the study treatment at any time and for any reason, and without stating a reason. The patient will be encouraged to remain in the study, and to complete follow-up assessments.

7. Patient dies or wishes to withdraw from the clinical study at any time and for any reason.

8. Patients who are discovered, after enrolment/randomisation, not to have fulfilled all inclusion/exclusion criteria at the time of enrolment, should be withdrawn from the study unless the Investigator finds withdrawal inappropriate based on clinical and ethical evaluation. Such deviation(s) from the Clinical Study Protocol must be confirmed with the Medical Monitor, reported to LEO (and the IEC/IRB as appropriate) and recorded in the Clinical Study Report.

9. Other reasons: other reasons than stated above which requires the subject to discontinue study treatment must be specified in the CRF.

**10.5.1 Follow-up (Permanent Treatment Discontinuation)**

1. All patients will be followed up for 1 month (30 days) following last dose of study treatment for safety, ongoing AEs, ongoing/new SAEs, HIT, healthcare resource utilisation, and PTS. QoL will be followed up to Day 180 and 1 month after the last dose of study treatment.

2. Patients will be followed for overall mortality at 6 months (180 days) after randomisation.

3. If a patient dies during the 6-month treatment period, all reasonable efforts will be made to ascertain the cause of death including copy of autopsy report (if available) and whether the patient experienced any outcome or AEs/SAEs between the last visit or telephone contact and the time of death and when the last dose of study treatment was taken. The cause of death will be adjudicated.

4. Patients withdrawn from study treatment will be followed up by telephone contacts in place of scheduled monthly visits until Day 180 to assess recurrent VTE, survival and QoL.

Patients who are withdrawn will not be substituted.

For information on follow up and adjudication please refer to **Diagram 1**.
Diagram 1: Reporting of Outcome Events

- Patient on study treatment
- **VTE** and death up to Day 180 AND 24 h after last dose (all events will be adjudicated)
- Bleeding events (events on treatment and up to 24 h after last dose will be adjudicated)
- HIT, PTS, healthcare resource utilisation and new SAEs (on treatment and up to 1 month after last dose) and new AEs (on treatment). SAEs and other relevant AEs that are ongoing at end of treatment must be followed up as per protocol. All HIT events will be adjudicated.
- QoL up to Day 180 AND 1 month after last dose

Legend:
- X 24 h after last dose
- ◆ 1 month after last dose
### 10.6 INVESTIGATIONAL PRODUCTS

**Innohep® 0.5 ml, 0.7 ml, or 0.9 ml**

<table>
<thead>
<tr>
<th>Finished product (brand) name (if available)/name investigational product</th>
<th>Innohep®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Solution for injection, pre-filled syringe.</td>
</tr>
<tr>
<td>Active ingredient name/concentration</td>
<td>Tinzaparin sodium 20,000 anti-Xa IU/ml. Tinzaparin is a LMWH of porcine origin that acts as an anticoagulant by potentiating anti-thrombin’s inhibition of several activated coagulation factors, especially Factor Xa.</td>
</tr>
<tr>
<td>Excipients (not quantitative)</td>
<td>Sodium acetate, sodium hydroxide, sodium metabisulphite and water for injection.</td>
</tr>
<tr>
<td>Pack size(s)</td>
<td>Packages of 10 syringes and packages of 40 syringes of either 0.5 ml, or 0.7 ml, or 0.9 ml.</td>
</tr>
<tr>
<td>Manufacturer’s name of bulk medication (IP)</td>
<td>LEO Pharma A/S</td>
</tr>
<tr>
<td>Certifier’s name of bulk medication (IP)</td>
<td>LEO Pharma A/S</td>
</tr>
<tr>
<td>Supplier’s name</td>
<td>LEO Pharma A/S</td>
</tr>
<tr>
<td>Manufacturer’s name of patient treatment packages</td>
<td>[Redacted]</td>
</tr>
<tr>
<td>Certifier’s name of patient treatment packages</td>
<td>[Redacted]</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Finished product (brand) name</strong> (if available)/name investigational product</td>
<td>Warfarin</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Uncoated tablets.</td>
</tr>
<tr>
<td><strong>Active ingredient name/concentration</strong></td>
<td>Warfarin sodium 1 mg or 3 mg or 5 mg.</td>
</tr>
<tr>
<td><strong>Excipients (not quantitative)</strong></td>
<td>Lactose BP, maize starch BP, maize starch pregelatinised BP, dispersed blue 17488 ansteads, yellow iron oxide E172, red iron oxide E172, dispersed pink11150 ansteads, purified water BP, sodium starch glycollate NF, magnesium stearate BP.</td>
</tr>
<tr>
<td></td>
<td>Lactose monohydrate, maize starch, sucrose, pregelatinised starch, magnesium stearate, quinoline yellow E104, ponceau 4RE124, indigo carmine aluminium lake E132 erythrosine aluminium lake E127.</td>
</tr>
<tr>
<td></td>
<td>Lactose (anhydrous), pregelatinised maize starch, magnesium stearate, quinoline yellow E104, allura red E129, Indigotin E132, Erythrosine E127.</td>
</tr>
<tr>
<td></td>
<td>Lactose, sucrose, maize starch, magnesium stearate, pregelatinised starch, eurolake brown 260000 (containing E104, E123, E132), dispersed indigo carmine lake 15009 E132, dispersed erythrosine lake 15008 E127.</td>
</tr>
<tr>
<td><strong>Pack size(s)</strong></td>
<td>7 cartons of 28-tablet blister-packed warfarin will be provided in one, monthly warfarin kit</td>
</tr>
</tbody>
</table>
in permutations that allow variable daily dosing from 1mg to 15 mg per daily:
Either
4 x 28 tablets 1 mg
2 x 28 tablets 3 mg
1 x 28 tablets 5 mg
Or
3 x 28 tablets 1 mg
4 x 28 tablets 3 mg
Or
5 x 28 tablets 1 mg
2 x 28 tablets 5 mg

<table>
<thead>
<tr>
<th>Manufacturer’s name of bulk medication (IP)</th>
<th>Alternative suppliers to [\text{manufacturer}] will be used only if [\text{manufacturer}] is unable to provide new stocks of their warfarin product within the timelines required for the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certifier’s name of bulk medication (IP)</td>
<td>\text{supplier}</td>
</tr>
</tbody>
</table>

10.6.1 Packaging and Labelling of Investigational Products

Patients will be instructed on the administration of SC Innohep® injections at Visit 1, and will be reminded thereafter at subsequent visits.
For Innohep®, individual syringes and treatment kits containing syringes will be labelled. For warfarin, individual tablet boxes and treatment kits will be labelled. The medication labels for Innohep® and warfarin will be in accordance with GMP and any other national laws or regulations of the participating countries. Labelling will as a minimum detail the following information: Sponsor name, address and contact number, name of drug, protocol number, dosage form, lot number, package number, storage conditions, expiry date, “Keep out of reach of children” and “For clinical trial use only”.

10.6.1.1 Long-Term Innohep® Treatment (Arm 1)

Treatment kits containing sufficient Innohep® injections for 1 month (30 days), packed in 4 boxes of 10 syringes each (either 0.5 ml, 0.7 ml or 0.9 ml syringes), will be dispensed to patients by the Investigator or his/her designee at randomisation (Visit 1 (Day 1)) and at scheduled monthly visits thereafter (see Table 3: Schedule of Study Procedures).

10.6.1.2 Initial (5 to 10 days) Innohep® Treatment (Arm 2)

Treatment kits containing sufficient Innohep® injections for 10 days, packed in 1 box of 10 syringes (either 0.5 ml, 0.7 ml or 0.9 ml syringes), will be dispensed to patients by the Investigator or his/her designee at randomisation (Visit 1 (Day 1)).

10.6.1.3 Long-Term Warfarin Treatment (Arm 2)

Warfarin monthly treatment kits will be produced according to the supplies of commercial 28-tablet cartons that are available at the time of kit production.

Until February 2011 kits will be produced with cartons of 1 mg, 3 mg and 5 mg tablets (warfarin). Thereafter, kits will be produced with either 1 mg, 3 mg and 5 mg tablets, 1 mg and 3 mg tablets or 1 mg and 5 mg tablets (warfarin). Only in the case that warfarin is unavailable at the time of kit production, an alternative warfarin product of 1 mg, 3 mg and 5 mg tablet strengths will be used with variable kit packing options, as above. The alternative warfarin product will be a bioequivalent product to warfarin.
The warfarin tablet strengths provided in any configuration of cartons within a monthly kit will ensure the doses available to the patient remain unchanged and any daily dose between 1mg and 15 mg is possible. The treatment kits will contain the drug supply for 1 month.

The monthly treatment kits will be dispensed to patients by the Investigator or his/her designee at appropriate visits (see Table 3: Schedule of Study Procedures).

The unique kit number can be used to identify the warfarin product administered to a patient each month.

### 10.6.2 Storage of Investigational products

#### 10.6.2.1 Storage of Innohep®

The investigational products should be stored in a safe and secure place inaccessible to children. Do not store above 25°C. Do not freeze.

#### 10.6.2.2 Storage of Warfarin

The investigational products should be stored in a safe and secure place inaccessible to children. Do not store above 25°C and protect from light.

### 10.6.3 Administration of Investigational Products

#### 10.6.3.1 Innohep®

<table>
<thead>
<tr>
<th>Innohep®</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration:</td>
<td>SC</td>
</tr>
<tr>
<td>Dose:</td>
<td>175 anti-Xa IU/kg for injection of a anti-Xa 20,000 IU/ml solution</td>
</tr>
<tr>
<td>Dosing frequency:</td>
<td>Once daily at approximately 24 h apart (± 3 hours)</td>
</tr>
<tr>
<td>Time of day for dosing:</td>
<td>Same time daily if possible or as specified by the Investigator</td>
</tr>
</tbody>
</table>
Treatment kits will be dispensed to patients at Visit 1 (Day 1), and thereafter at monthly visits (see Table 3: Schedule of Study Procedures). For patients weighing more than 104 kg, two Innohep® dosing kits are dispensed to provide the correct dose. Each treatment kit will contain either 10 or 40 syringes (0.5, 0.7 or 0.9 mL) pre-filled with 20,000 anti-Xa IU/mL Innohep®, antiseptic wipes, a sharps container, written instructions for administration of Innohep® and a patient diary. Routine monitoring of the anticoagulant effect of Innohep® through measurement of anti-Xa is not recommended.

The investigational product (Innohep®) will be administered as soon as possible after randomisation. The first injection will be administered at the study centre on Day 1 (Visit 1) under Investigator or delegate supervision.

Subsequent injections will be performed by the patient (self-injection), a relative of the patient or a healthcare professional as judged by the Investigator. Prior to leaving the study centre at Visit 1 (Day 1), patients and patients’ relatives (if applicable) will be instructed on how to administer the investigational product and provided with a patient diary. When less than a full syringe is needed, the dose is adjusted by expelling the required volume according to the marked graduations on the syringe.
For information on dosing please refer to Table 1.

Table 1 Dosage Guide Innohep®

<table>
<thead>
<tr>
<th>Syringe size</th>
<th>Body Weight (kg)</th>
<th>International Units (IU)</th>
<th>Volume to expel from syringe prior to injection (mL)</th>
<th>Injection volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innohep® 10,000 IU in 0.5 mL</td>
<td>&lt; 34</td>
<td>6,000</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>35 – 41</td>
<td>7,000</td>
<td>0.15</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>42 – 46</td>
<td>8,000</td>
<td>0.1</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>47 – 51</td>
<td>9,000</td>
<td>0.05</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>52 -57</td>
<td>10,000</td>
<td>none</td>
<td>0.50</td>
</tr>
<tr>
<td>Innohep® 14,000 IU in 0.7 mL</td>
<td>58 – 63</td>
<td>11,000</td>
<td>0.15</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>64 – 67</td>
<td>12,000</td>
<td>0.1</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>68 – 72</td>
<td>13,000</td>
<td>0.05</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>73 – 77</td>
<td>14,000</td>
<td>none</td>
<td>0.70</td>
</tr>
<tr>
<td>Innohep® 18,000 IU in 0.9 mL</td>
<td>78 – 83</td>
<td>15,000</td>
<td>0.15</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>84 – 88</td>
<td>16,000</td>
<td>0.1</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>89 – 93</td>
<td>17,000</td>
<td>0.05</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>94 – 103</td>
<td>18,000</td>
<td>none</td>
<td>0.90</td>
</tr>
</tbody>
</table>

2 x Innohep® 10,000 IU in 0.5 mL

1 x Innohep® 10,000 IU in 0.5 mL, and 1 x Innohep® 14,000 IU in 0.7 mL

2 x Innohep® 14,000 IU in 0.7 mL

1 x Innohep® 14,000 IU in 0.7 mL, and 1 x Innohep® 18,000 IU in 0.9 mL

1 x Innohep® 18,000 IU in 0.9 mL
Patients will be instructed how to complete the patient diary, including how to record the date and time of daily Innohep® injections, and to retain used syringes in the sharps container provided. The patient will be instructed to return sharps containers (containing used syringes) to the study centre at their scheduled visits, where they will be disposed of in accordance with local health and safety regulations.

If an injection is missed, this dose should be omitted and the patient should administer only one injection on the following day in accordance with the treatment schedule. The date of any missed injections will be recorded in the patient diary.

It is essential that SC injections are administered correctly to prevent pain and bruising at the site of injection. The recommended usual site of injection is the fatty tissue of the abdomen. Injection site should be alternated between the left and the right side. When two Innohep® dosing kits are dispensed to provide the correct dose, administration sites should include the upper thigh. Firm pressure should be applied to the injection site for 1-2 minutes after the syringe is removed to minimize bruising.
10.6.3.2 Warfarin

<table>
<thead>
<tr>
<th>Warfarin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration:</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose:</td>
<td>Induction doses should be tailored to individual requirements. The use of a validated nomogram is encouraged. Maintenance doses should be adjusted to achieve a therapeutic INR level between 2.0 and 3.0. INR will be closely monitored if a patient switches warfarin product during the treatment period.</td>
</tr>
<tr>
<td>Dosing frequency:</td>
<td>Once daily at approximately 24 hours apart (± 3 hours)</td>
</tr>
<tr>
<td>Time of day for dosing:</td>
<td>Same time daily preferably in early evening</td>
</tr>
</tbody>
</table>

If the patient forgets to take the prescribed dose of warfarin at the scheduled time, the dose should be taken as soon as possible on the same day (no later than midnight). The patient should not take the missed dose the next day by doubling the daily dose. The date of any missed doses will be recorded in the patient diary.

10.6.3.3 Temporary Study Treatment Discontinuation

Reasons for permanent discontinuation of study treatment are outlined in Section 10.5. Treatment with Innohep® and warfarin may be temporarily discontinued for the following reasons:

- Thrombocytopenia (platelet count <50 x 10^9/L). Study medication (Innohep® and warfarin) administration will be resumed after the patient’s platelet count returns to >50 x 10^9/L. The treatment discontinuation duration should not exceed 3 consecutive weeks. Please refer to Section 10.7.6.
- Bleeding event. Study treatment should be restarted as soon as bleeding resolves and the Investigator deems that it is safe and reasonable for the patient to resume anticoagulant therapy.
• Any medically or surgically invasive procedure; in these cases, Innohep® or warfarin should be discontinued as clinically appropriate and resumed as soon as hemostasis is achieved. Bridging therapy with a LMWH in patients in the warfarin arm, if necessary, should follow local protocols or local guidelines.

10.6.4 Precautions/ Excessive use of Anticoagulation

Excessive anticoagulation or over dosage of anticoagulants can cause potentially serious bleeding complications.

Innohep®

In case of excessive use of anticoagulation, protamine sulphate may be given if clinically indicated. The SmPC for Protamine Sulphate (LEO) indicates that it neutralizes 81% of the anti-Xa of tinzaparin (in vitro studies). Studies in healthy volunteers indicate that 65 to 80% of the anti-Xa activity is neutralised by protamine sulphate 1 mg/100 anti-Xa IU of Innohep®, however, the largest single slow bolus dose of protamine sulphate is 50 mg. A return of Innohep® anti-Xa, anti-IIa and aPTT activities are seen 3 hours after initial reversal, probably due to continuous absorption of Innohep® from the SC depot. It may therefore be necessary to give protamine sulphate intermittently or as a continuous infusion to achieve and maintain neutralisation of SC Innohep® for at least 24 hours. Potential side-effects of protamine must be considered and patients carefully observed.

Warfarin

In case of overdose, administration of vitamin K (oral or parenteral) or a prothrombin complex concentrate (e.g., Octaplex®) may be given if clinically indicated. Excessive anticoagulation should be controlled; therefore, warfarin therapy should be discontinued temporarily and blood tests performed (haemoglobin haematocrit, RBC, WBC including a differential count, platelets, INR, liver function tests [ALT and AST] and albumin) to determine the next appropriate dose. After recovery from suspected or overt abnormal bleeding, the patient may resume warfarin at an adjusted dose.
10.6.5 Treatment Assignment

Patients who have been found to comply with all of the protocol’s inclusion and exclusion criteria will be randomised to receive treatment with either SC Innohep® OR warfarin in addition to initial (5 to 10 days) treatment with Innohep®.

Treatment assignment will be pre-planned according to a computer generated randomisation schedule in a [1:1] ratio. Patients will be assigned a unique randomisation number via an IVRS. Treatment allocation will only be issued to a local Investigator or delegate after written informed consent has been obtained.

In order to balance treatment groups, a stratified randomisation scheme will be used that accounts for the following factors:

- Tumour (known distant metastasis, no distant metastasis, haematological malignancy).
- Geographical region (Canada + Western Europe, or Eastern Europe, or Asia, or South America)
- Known history of previously diagnosed VTE (yes or no).

10.6.5.1 Randomisation List

A randomisation list i.e. a list of (sequential) numbers to each of which a treatment is allocated (assigned), will be generated in this study.

10.6.6 Blinding of the Study

This is an open-label study. However, all efficacy endpoints (i.e. lower limb DVTs, and PEs) and major safety endpoints (i.e. bleedings, HITs and causes of death) will be adjudicated by the blinded IAC (Section 6.2.4).

10.6.7 Breaking the Randomisation Code

Not applicable, this is an open-label study.
10.6.7.1 Un-blinding of Individual Patient Treatment
Not applicable.

10.6.7.2 Un-blinding of the Clinical Study
Not applicable.

10.6.8 Drug Accountability and Compliance Checks
The Investigator is fully responsible for the investigational products at the study site. Dispensing of investigational product may be delegated to, e.g. a hospital pharmacy as locally applicable.

The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transactions with them. Investigational products must be stored in a safe and secure place, and proper dispensing arrangements must be made.

10.6.8.1 Sponsor-Investigator Drug Accountability
All unused and/or expired investigational products supplied on behalf of LEO will be returned to [REDACTED] or stored at the study site until LEO requests destruction. The investigational product will be fully accounted for by the monitor with the help of the person responsible for dispensing the medication. Accountability will be documented by use of drug accountability forms.

10.6.8.2 Investigator-Patient Drug Accountability
At the monthly visits (Months 1 to 6), all unused investigational product, including (empty) boxes, dispensed to the patient must be returned by the patient. Used syringes must be returned in a sharps container to the site and they will then be disposed of in accordance with local health and safety practice.

The Investigator and/or pharmacist must maintain adequate and accurate records of investigational products. An inventory (drug accountability form) will be kept of all
investigational product given to, and returned by, each patient randomised in the study. This inventory must be available for inspection during monitoring visits and will be checked by the monitor to ensure correct dispensing of investigational product.

10.6.8.3 End of Study Drug Accountability
All investigational product supplies returned to the study centres will be reconciled with the individual Drug Accountability Forms. At the end of the study, complete investigational product reconciliation will be performed by [Medication Name].

10.6.8.4 Treatment Compliance
The study medication must be used in accordance with this protocol. The (Sub) Investigator or delegate is responsible for dispensing study medication, administering study medication (on the days the patient attends for study visits), and providing study medication administration instructions to the patient (and patient’s relative or healthcare professional if applicable). The (Sub) Investigator or delegate will record all study medication dispensed, used and returned.

Patients will be instructed to record the time and date of daily study medication administrations in their patient diaries, which will be handed out at Visit 1. At all treatment visits the patient will be asked if s/he has used the investigational product as prescribed. If this is not the case the degree and nature of non-compliance will be specified in the CRF.

10.6.9 Prior and Concomitant Treatment
Use of concomitant treatment should be recorded in the patient’s medical record and the CRF (treatment/drug name, dose, indication and dates of start and stop). Concomitant medication must be in accordance with the study inclusion and exclusion criteria (Section 10.4).

During the study, patients must not receive other investigational drugs, agents or devices. In case a patient has participated in another study prior to randomisation an appropriate wash-out period must be allowed to assure that any other investigational drug has been eliminated. Systemic anticancer therapy (chemotherapy, hormonal therapy, immunotherapy, and targeted anticancer therapy) is allowed. Chemo-radiation therapy for locally advanced disease is
allowed as is standard or curative radiation therapy. All other medication necessary for the well-being of the patient may be given at the discretion of the Investigator. Changes of doses (including starting) of drugs that, while not specifically indicated for treatment of the indication being studied, are known to have an effect (positive or negative) on the indication, are not permitted. Concomitant medications that are prohibited or discouraged during the study are presented in Table 2.

Table 2: Concomitant Medications Prohibited or Discouraged During the Study

<table>
<thead>
<tr>
<th>Prohibited</th>
<th>Discouraged and should be avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>any oral anticoagulants (e.g. vitamin K antagonists, direct thrombin inhibitors, activated factor X inhibitors)</td>
<td>non-steroidal anti-inflammatory drugs (NSAID) excluding acetylsalicylic acid ≤ 325 mg/day</td>
</tr>
<tr>
<td>thrombolytics</td>
<td>intramuscular injections should be avoided while patients are receiving study treatment</td>
</tr>
<tr>
<td>pentasaccharide (e.g. fondaparinux)</td>
<td></td>
</tr>
<tr>
<td>glycoprotein IIb/IIIa inhibitors</td>
<td></td>
</tr>
<tr>
<td>acetylsalicylic acid at doses &gt;325 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

10.7 STUDY PROCEDURES

10.7.1 Schedule of Study Procedures

The randomisation visit (Visit 1, Day 1) may occur on the same day (within 24 hours) as the screening visit. The first dose of investigational product on Day 1 should be given as soon as possible after randomisation. The time between the last dose of LMWH before randomisation and the first dose of Innohep® after randomisation should be 12 hours if the LMWH was administered twice daily or 24 hours if the LMWH was administered once daily. Enrolment criteria will be reviewed at the randomisation visit to confirm patient eligibility.
Diagnosis of VTE must be confirmed by appropriate objective imaging (see Section 10.7.3.4). Randomisation should take place within 72 hours of the objectively confirmed diagnosis. In order to detect any incidental/asymptomatic DVT or PE present at baseline (i.e. at randomisation), all patients must have diagnostic imaging performed of the legs and lungs (i.e. imaging of lungs if symptomatic event was DVT or imaging of legs if symptomatic event was PE). This additional baseline imaging may be performed up to 24 hours after randomisation.

The schedule of study procedures is presented in Table 3.
Table 3: Schedule of Study Procedures

<table>
<thead>
<tr>
<th>Visit window</th>
<th>Visit</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4 to 8</th>
<th>Visit 9</th>
<th>Unscheduled</th>
<th>Visit 10</th>
<th>Post-Treatment Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening Visit</td>
<td>Day 1</td>
<td>Week 1 (Day 7)</td>
<td>Week 2 (Day 14)</td>
<td>Month 1 to 5 (Day 30 to Day 150)</td>
<td>Month 6 (Day 180) / stop of study treatment</td>
<td>Month 7 (Day 210), or 1 Month (30 Days) after discontinuation of study treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>From -72 to 0 hours</td>
<td>±0 Day</td>
<td>±3 Days</td>
<td>±3 Days</td>
<td>±7 Days</td>
<td>+7 Days</td>
<td>+7 Days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE diagnosis (diagnostic imaging for both DVT and PE* required)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre-randomisation therapeutic treatment of VTE</td>
<td>X</td>
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<td></td>
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<td>Informed consent</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Patient demography</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check of inclusion/exclusion criteria</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology assessments:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, haematocrit, RBC, WBC including differential count. (Central Lab)</td>
<td>X</td>
<td>X$^{13}$</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (Central Lab)</td>
<td>X</td>
<td>X$^{13}$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (Local Lab)</td>
<td>X</td>
<td>X$^{13}$</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Biochemistry assessments:</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ALP, ALT, AST, creatinine, albumin, total bilirubin (Central Lab)</td>
<td>X</td>
<td>X$^{13}$</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (Local Lab)</td>
<td>X</td>
<td>X$^{13}$</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* all patients must have a second VTE diagnostic imaging performed; imaging of lungs if symptomatic event was DVT or imaging of legs if symptomatic event was PE. This second imaging may be performed up to 24 hours after randomisation.

Table continues on next page
<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening Visit</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4 to 8</th>
<th>End of Treatment Visit</th>
<th>Unscheduled Visit(s)</th>
<th>Visit 9</th>
<th>Visit 10</th>
<th>Post-Treatment Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day/Week/Month</td>
<td>-72 hours</td>
<td>Day 1</td>
<td>Week 1 (Day 7)</td>
<td>Week 2 (Day 14)</td>
<td>Month 1 to 5 (Day 30 to Day 150)(^2)</td>
<td>Month 6 (Day 180) / stop of study treatment</td>
<td></td>
<td></td>
<td>Month 7 (Day 210), or 1 Month (30 Days) after discontinuation of study treatment</td>
<td></td>
</tr>
<tr>
<td>Visit window</td>
<td>From -72 to 0 hours</td>
<td>±0 Day</td>
<td>±3 Days</td>
<td>±3 Days</td>
<td>±7 Days</td>
<td></td>
<td>+7 Days</td>
<td></td>
<td>+7 Days</td>
<td></td>
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</tbody>
</table>

Coagulation assessments:
- aPTT (Central Lab) X X\(^1\)
- aPTT (Local Lab) X X
- INR (Central Lab) X X\(^1\)
- INR\(^2\) (Local Lab) X X\(^1\) X\(^2\) X\(^2\) X\(^3\) X\(^3\) X\(^3\)
- D-dimer, Tissue factor (Central Lab) X
- Other coagulation biomarkers\(^4\) (Central Lab) X
- Pregnancy test\(^5\) X
- Medical/surgical history X
- Cancer diagnosis and status X
- Prior/current medication, including prior/current treatment for cancer X
- Concomitant medications, including treatment for cancer X X X X X X
- Height X
- Weight X
- Vital signs\(^6\) X X X X X X
- ECOG performance status\(^7\) X X

Table continues on next page
### Treatment Period

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening Visit</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4 to 8</th>
<th>Visit 9 End of Treatment Visit</th>
<th>Unscheduled Visit(s)</th>
<th>Visit 10 Post-Treatment Follow-Up</th>
</tr>
</thead>
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<tr>
<td>Day/Week/Month</td>
<td>-72 hours</td>
<td>Day 1</td>
<td>Week 1 (Day 7)</td>
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<td>Month 1 to 5 (Day 30 to Day 150)</td>
<td>Month 6 (Day 180) / stop of study treatment</td>
<td>Month 7 (Day 210), or 1 Month (30 Days) after discontinuation of study treatment</td>
<td></td>
</tr>
<tr>
<td>Visit window</td>
<td>From -72 to 0 hours</td>
<td>±0 Day</td>
<td>±3 Days</td>
<td>±3 Days</td>
<td>±7 Days</td>
<td>+7 Days</td>
<td>+7 Days</td>
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<tr>
<td>Central venous catheter status</td>
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<td>X</td>
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<td>Randomisation</td>
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<tr>
<td>Innohep® administration (Arm 1)</td>
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<td>Innohep® administration (Arm 2)</td>
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<td>Oral warfarin administration (Arm 2)</td>
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<tr>
<td>Assessment of recurrent VTE</td>
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<tr>
<td>Instruction of self-administration</td>
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<td>Patient diary distribution</td>
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<tr>
<td>Compliance (patient diary check)</td>
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<tr>
<td>Innohep® dispensing</td>
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<tr>
<td>Warfarin dispensing</td>
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<tr>
<td>Innohep® return by patient</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Warfarin return by patient</td>
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<td>AE recording</td>
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<td>SAE recording</td>
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<tr>
<td>Bleeding recording and transfusion assessments</td>
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<td>X</td>
<td>X</td>
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*Table continues on next page*
<table>
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<tr>
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</tbody>
</table>

| Healthcare resource utilisation^{15} | X | X | X |
| Health-related QoL^{15} | X | X | X |
| PTS^{4} | X | X | X |
| Overall mortality^{36} | X | X | X |
Table footnotes:
apTT - activated partial thromboplastin time; ALP - alkaline phosphatase; ALT - alanine aminotransferase; AST - aspartate aminotransferase; ECOG - European Co-operative Oncology Group; INR - international normalised ratio; PTS - post-thrombotic syndrome; QoL - quality of life; VTE - venous thromboembolism; RBC - red blood cells; WBC - white blood cells.

General notes:

• If the Screening Visit occur on the same day (within 24 hours) as the Randomisation Visit (Visit 1, Day 1), local and central laboratory assessments are not required to be repeated.

• Unscheduled visit occurs if a patient experiences signs and symptoms of a recurrent VTE between scheduled visits. The patient will be advised to urgently return to the investigational site for an unscheduled visit or, in emergency situations, report to any acute hospital at which standard assessments will be made to enable the diagnosis of recurrent VTE to be confirmed or refuted. When, in an emergency, the patient is advised to attend an acute hospital not involved in the study, the investigator, or delegated staff, should advise hospital staff of the blood tests that should be taken (local analysis only). If the VTE is not confirmed, the patient will return for the next scheduled visit as planned.

• All efficacy endpoints (i.e. lower limb DVTs and PEs) and causes of death occurring up until Day 180 including 24 hours after last dose of study treatment will be adjudicated by the blinded IAC (cf Diagram 1).

• Bleeding events occurring up to 24 hours after last dose of study drug will be adjudicated by the blinded IAC.

• HIT events occurring up to 1 month after last dose of study drug will be adjudicated by the blinded IAC.

• All patients will be followed up for 1 month (30 days) following discontinuation of study treatment for safety, healthcare resource utilisation, QoL, and PTS.

• Patients who are withdrawn from study treatment, for any reason other than death prior to Day 180 will be asked to stay in the study and be followed up by telephone at time of the remaining regular scheduled monthly study visits. Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess study outcomes (cf Diagram 1).

• Patients who withdraw from study (i.e. withdraws consent to continue participating in the study) will complete final efficacy assessment at the time of withdrawal and be followed for safety outcomes up to 1 month after the last dose of study drug. No other data will be collected on these patients after withdrawing consent but every reasonable effort will be made to discourage patients from withdrawing completely from the study.

• If a patient dies during the 6-month treatment period, all reasonable efforts will be made to ascertain the cause of death including copy of autopsy report (if available) and whether the patient experienced any outcome or AEs/SAEs between the last visit or telephone contact and the time of death and when the last dose of study treatment was taken.

• The date of when the last dose of study drug taken is the date of the End of Treatment.

• The date of event is the date of performed objective diagnosis.
Notes referred to in the table:

1. All patients on treatment (in both treatment arms) will be contacted by the investigator or delegated study site staff by telephone 14 days (± 3 days) after each monthly visit. Patients will be interviewed using a standardized questionnaire during these telephone contacts in order to assess treatment compliance, concomitant medications, recurrent VTE, bleedings, AEs and SAEs.

2. Warfarin arm only, INR assessment should be carried out frequently during the induction phase until the INR value is at or above 2.0 for 2 consecutive days. When the INR level has reached therapeutic level between 2.0 and 3.0, assessments will then be performed according to local practice and Investigator’s discretion but at least every 2 weeks. INR will be closely monitored if a patient switches warfarin product during the treatment period.

3. Two blood samples (one serum and one plasma) will be collected and stored for future assessment of other potential coagulation biomarkers for consenting patients.

4. Pregnancy test for women of childbearing potential only.

5. Vitals signs of pulse rate and blood pressure will be assessed.

6. ECOG performance status prior to the VTE episode.

7. The central venous catheter (CVC) status (Presence of CVC, indication, the type of CVC, location of CVC and date and time of implantation).

8. The time between the last dose of LMWH prior to randomisation and the first dose of Innohep® after randomisation should be 12 hours if the LMWH was administered twice daily or 24 hours if LMWH (or fondaparinux) was administered once daily.

9. Initial (5 to 10 days) treatment with Innohep® must continue until the patient’s INR is at or above 2.0 for 2 consecutive days. The minimum duration of LMWH treatment (pre-and post-randomisation) is 5 days. The maximum duration of initial Innohep® treatment in the warfarin group is strongly recommended not to exceed 10 days.

10. Warfarin treatment should be started on the day of randomisation, concomitantly with initial (5 to 10 days) treatment with Innohep®.

11. Recurrent VTE recording includes events detected incidentally in routine cancer scans in addition to symptomatic events recorded for the duration of the study. All symptomatic events must be diagnosed using standard diagnostic criteria.

12. Healthcare resource utilisation include: medications used for VTE prevention, laboratory tests associated with anti-coagulation therapy, unscheduled clinical visits, diagnostic tests relevant for VTE diagnosis, VTE-related hospitalisations (including length of stay), and management of patients who develop HIT or bleeding events (e.g. blood transfusions, medications, hospitalisations).

13. Health-related QoL will be assessed using the EQ-5D (Appendix IV).

14. PTS will be assessed using the Villalta scale (see Section 10.7.3.5).

15. If the Screening Visit occur on the same day (within 24 hours) as the Randomisation Visit (Visit 1, Day 1), local and central laboratory assessments are not required to be repeated.

16. To be captured only once, at the visit that occurs last
10.7.2 Patient Eligibility

Patient’s eligibility for the clinical study will be checked and recorded according to the inclusion and exclusion criteria at visits specified in the schedule of assessments (see Table 3: Schedule of Study Procedures).

10.7.3 Clinical Assessment

10.7.3.1 Demographic and Medical History

The following demographic data will be collected: date of birth, gender, ethnic origin, height and weight.

The patient’s medical history will be recorded and must include the following:

- Cancer diagnosis or status:
  - Primary diagnosis, histological or cytological proof of malignant disease and cancer staging.
- Prior anticancer therapy.
- Previous and current relevant diseases, signs and symptoms.
- Previous comorbidity.
- Previous treatment, other than cancer treatment, administered in the last 14 days prior to randomisation.

10.7.3.2 Vital Signs and Weight

Systolic blood pressure and diastolic blood pressure will be measured on the same arm (preferentially on the left arm) after the patient has been resting for 5 minutes. Pulse will be recorded simultaneously with blood pressure measurements. Body weight (kg) will be measured without shoes or jacket.

Clinically relevant abnormal findings will be reported as AEs.

10.7.3.3 Central Venous Catheter Status

The central venous catheter status of applicable patients will be assessed at visits specified in the schedule of assessments (see Table 3: Schedule of Study Procedures). For each patient the
following will be recorded: whether the patient has a venous catheter, the indication for implantation, the type and location of the CVC and the date of implantation.

10.7.3.4 Venous Thromboembolism Assessments - Clinical Diagnosis and Imaging

Each scheduled visit (Visit 1 onwards) and telephone contacts will include a standardised assessment of the signs and symptoms of recurrent VTE. At any time during the 6-month treatment period, if a patient experiences any signs and symptoms between scheduled visits or telephone calls, the patient will be advised to contact the Investigator or delegated site staff. If signs and symptoms are assessed by the Investigator, or delegated site staff, to be of a recurrent VTE, the patient will be advised to urgently return to the investigational site for an unscheduled visit or, in emergency situations, report to any acute hospital, at which standard assessments will be made to enable the diagnosis of recurrent VTE to be confirmed or refuted. When, in an emergency, the patient is advised to attend an acute hospital not involved in the study, the investigator, or delegated staff, should advise hospital staff of the blood tests that should be taken (local analysis only). Standard objective imaging is required for symptomatic VTE. If there are symptoms from leg(s) AND lungs, objective imaging is required for both. The date of the start of a recurrent VTE event will be the date of objective diagnosis.

At any time during the 6-month treatment period, if a recurrent VTE is coincidentally detected during other investigations, e.g. cancer staging, the patient will also be advised to return to the clinic urgently for an unscheduled visit. The Additional investigations may be requested to confirm the diagnosis of an incidental VTE. See below schedule for diagnostic criteria for incidental VTE and further details.

If the recurrent VTE is confirmed, End of Treatment assessment will be performed and the patient will be assigned alternative appropriate treatment according to investigator’s discretion. Patients will be followed up for safety with a face-to-face visit 1 month (30 days) after last dose of study treatment. Patients will also be asked to stay in the study until day 180 for assessments of recurrent VTE via telephone contacts replacing remaining scheduled monthly study visits.

If the recurrent VTE is not confirmed, the patient will continue study treatment and return for the next scheduled visit as planned. This includes any events occurring up until 24 hours following the last dose of study treatment (i.e. greater than 5 x the half life of Innohep®).
**Consistent signs or symptoms of DVT**
At least one of the following new or progressive symptoms must be present in either leg:

1. Objective swelling (greater than or equal to 2 cm increase in calf circumference at 10 cm below tibial tuberosity from baseline measurement).
2. Pain or tenderness.
3. Pitting oedema.
4. Erythema or cyanosis.
5. Collateral superficial veins

**Consistent symptoms of PE**
At least one of the following new or progressive symptoms must be present:

1. Atypical, unexplained, or pleuritic chest pain.
2. Shortness of breath or tachypnea not due to congestive heart failure (CHF) or pneumonia.
3. Cough
4. Palpitations.
5. Haemoptysis.
6. Cyanosis.
7. Syncope or presyncope
8. Light headedness

**Consistent signs of PE**
The following consistent signs of PE must be assessed, but their presence is not required:

1. Dysrhythmia, e.g. atrial fibrillation.
2. Haemoptysis.
3. Unexplained hypotension.
4. Unexplained tachycardia (> 100 bpm).
5. Unexplained tachypnoea.
6. Pleural effusion on chest X-ray without other pulmonary pathology.
7. Hypoxemia (oxygen saturation less than or equal to 90% of room air) not due to CHF or pneumonia.
8. Increased pulmonary arterial pressure
Diagnosis of symptomatic DVT/PE (at randomisation and at recurrence) must be made by appropriate objective imaging using standard diagnostic criteria:

Acceptable diagnostic examinations for exploring symptomatic DVT are CUS, contrast venography, CT or MRI venography. CUS is the preferred diagnostic examination.

Acceptable diagnostic examinations for exploring symptomatic PE are ventilation/perfusion (V/Q) scintigraphy, spiral computed tomography (CT), or computed tomographic pulmonary angiography (CTPA), or pulmonary angiography. Additional CUS is required in case of a non-diagnostic V/Q scan.

All patients must have diagnostic imaging performed of both legs as well as the lungs in order to determine the baseline (i.e. at randomisation) presence or absence of DVT or PE. This additional baseline imaging may be performed up to 24 hours after time of randomisation.

A recurrent VTE coincidentally detected during other investigations, e.g. cancer staging, will be included as a primary endpoint if it involves segmental or more pulmonary arteries or is involving the popliteal or more proximal veins in the legs. The investigator must review these investigations and request additional imaging studies if needed to confirm the diagnosis of PE or DVT. Because staging imaging does not use the same technical protocols for the detection of PE or DVT, any suspicion that these findings are not PE or DVT should be followed up with standard diagnostic imaging to confirm or refute the presence of PE or DVT. In addition, the investigator must determine whether the patient had symptoms of PE or DVT at the time of the staging test.

Symptomatic patients with suspected lower limb DVT
For symptomatic patients who present with suspected lower limb DVT, at least one of the following criteria must be met:
Criteria for Diagnosing Lower Limb DVT(s)

<table>
<thead>
<tr>
<th>Previous objective imaging normal</th>
<th>Previous objective imaging abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A non-compressible venous segment of the deep veins in the leg on ultrasonography.</td>
<td>1. Abnormal compression ultrasound (CUS) of the deep veins of the leg where compression had been normal during previous examination.</td>
</tr>
<tr>
<td>2. An intraluminal filling defect on venography, CT-scan or MR venography in the deep veins of the leg.</td>
<td>2. An extension of ≥ 5 cm of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of the right deep veins of the leg in the presence of a sudden cut-off on venography CT-scan or MR-venography.</td>
</tr>
</tbody>
</table>

Symptomatic patients with suspected PE

For symptomatic patients who present with suspected PE, at least one of the following criteria must be satisfied:
Criteria for Diagnosing PE

- A (new) intraluminal filling defect in (sub)segmental or more proximal branches on spiral CT scan.
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram,
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (VPLS),
- A non-diagnostic ventilation/perfusion lung scintigraphy (VPLS) accompanied by documentation of new deep vein thrombosis by ultrasonography or venography;
- Diagnosis of fatal PE is based on one or more of the following:
  - Objective diagnostic testing
  - Autopsy report
  - Sudden and unexplained death within the 6-month study period which cannot be attributed to a documented cause and for which PE is the most probable cause.

Criteria for diagnosing incidental VTE:

Incidental PE or DVT are defined as thrombi that were reported during imaging testing performed for other reasons and NOT for suspicion of PE or DVT. Patients may or may not have symptoms of PE or DVT at the time of the test.

An incidentally (unsuspected) PE will be categorised into:

- symptomatic, but incidental (symptoms established retrospectively)
- asymptomatic AND incidental (no symptoms).

Incidental PE is only included as an outcome if located in segmental or more proximal pulmonary arteries. If subsegmental PE is reported or suspected on a CT scan performed for staging or other reasons, an examination of the proximal deep leg veins should be performed.
If a DVT is found, the patient will be diagnosed with incidental DVT. Repeat CT scan of the chest using a PE protocol is not recommended to limit radiation and contrast exposure.

Incidental DVT is only included as an outcome if located in the popliteal or more proximal leg veins. Thrombus detected in the inferior vena cava (IVC) or iliac veins on an abdominal or pelvic CT will be considered diagnostic. Thrombus detected in the common femoral vein or lower can only be confirmed if CUS diagnostic criteria are also met.

### Incidental DVT

<table>
<thead>
<tr>
<th>Previous objective imaging normal</th>
<th>Previous objective imaging abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A non-compressible venous segment in the popliteal vein or above on ultrasonography.</td>
<td>• Abnormal compression ultrasound (CUS) where compression had been normal if non-compressible during previous examination.</td>
</tr>
<tr>
<td>• An intraluminal filling defect on CT scan or MR venography in the IVC or iliac veins of the leg.</td>
<td>• An extension of ≥ 5 cm of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of the proximal deep veins of the leg in the presence of a sudden cut-off on CT-scan or MR-venography.</td>
</tr>
</tbody>
</table>

### Incidental PE

- A (new) intraluminal filling defect in segmental or more proximal branches on CT or MR scan.
- Incidental non-fatal PE findings in segmental or more proximal branches on autopsy.

### Causes of death:

All deaths will be adjudicated and cause of death will be classified in the following way:

- Due to PE.
  - PE confirmed by autopsy
  - PE confirmed by objective testing/imaging
Sudden and unexplained death which cannot be attributed to a documented cause and for which PE is the most probable cause.

- Due to cancer progression.
- Due to bleeding
- Other.

All outcomes will be adjudicated by an IAC (blinded to treatment assignment) using standard diagnostic criteria. Analyses of outcomes will be based on the adjudicated result, not on the local physician’s decision.
**Diagnostic requirements for VTE**

<table>
<thead>
<tr>
<th></th>
<th>VTE Before Randomisation</th>
<th>Recurrent VTE After Randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic VTE</strong></td>
<td>All patients must have diagnostic imaging performed of both legs and the lungs in order to determine baseline presence or absence of DVT or PE.</td>
<td>On suspicion of recurrent VTE, an unscheduled visit must occur. In emergency situations, recurrent VTE may be confirmed or refuted by any acute hospital. Standard objective imaging is required for symptomatic VTE. If there are symptoms from both leg(s) AND lungs, objective imaging is required for both. In case of a non-high probability ventilation perfusion scan objective imaging of both legs should be performed to investigate for DVT. If imaging of the legs is positive, then DVT and PE are diagnosed. If imaging of the legs is negative for DVT, then PE cannot be diagnosed based on a non-high probability ventilation perfusion scan alone.</td>
</tr>
<tr>
<td><strong>Incidental VTE</strong></td>
<td>Not valid as inclusion criterion. Diagnosis of an incidental VTE during the required baseline imaging represents the baseline status.</td>
<td>An unscheduled visit must occur on detection of an incidental VTE (thrombi that were reported during imaging testing performed for other reasons and NOT for suspicion of PE or DVT). Incidental (unsuspected) VTE is categorised into symptomatic, but incidental (symptoms established retrospectively) or asymptomatic AND incidental (no symptoms). Repeat CT scan is not recommended but a CUS is necessary in those with incidental subsegmental PE or common femoral DVT to confirm a thrombotic event.</td>
</tr>
</tbody>
</table>

Please refer to the Outcome Reporting and Diagnostic Test Manual
10.7.3.5 Post-thrombotic Syndrome (PTS)

Post-thrombotic syndrome is a major cause of morbidity that occurs despite optimal anticoagulation therapy. The definition of this syndrome includes symptoms such as occasional leg pain or swelling; in severe cases, venous ulcers may occur. Patients who developed PTS have a detrimental QoL. The Villalta scale (56) allows the staging of PTS severity using clinical measures. Unfortunately there is no optimal treatment for PTS; most experts recommend that patients with persistent leg swelling after DVT wear compression stockings (56).
The Villalta scale is scored in accordance with the following criteria:

<table>
<thead>
<tr>
<th>Symptoms and Clinical Signs</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Cramps</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Heaviness</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Clinical Signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretibal oedema</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Skin induration</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Redness</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Venous ectasia</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Pain on calf compression</td>
<td>0 points</td>
<td>1 point</td>
<td>2 points</td>
<td>3 points</td>
</tr>
<tr>
<td>Venous ulcer</td>
<td>Absent</td>
<td>Present</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Points are summed into a total scale (range 0-33). PTS is classified as mild if the Villalta scale is 5-9, moderate if the Villalta scale is 10-14 and severe if the Villalta scale is ≥ 15 or a venous ulcer is present.

10.7.3.6 Eastern Cooperative Oncology Group Performance Status
The ECOG performance status (57) for each patient will be assessed at the Screening visit and the End of Treatment.

The ECOG performance status will be scored in accordance with the following criteria:

0  Fully active, able to carry on all pre-disease performance without restriction.

1  Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).

   Ambulatory and capable of all self-care but unable to carry out any work activities.

2  Up and about more than 50% of waking hours.

3  Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4  Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

10.7.4 Laboratory Assessments
Blood samples for routine laboratory assessments regarding the patient’s systemic anticancer therapeutic regimen are at the Investigator’s discretion.

10.7.4.1 Central Analysis
A schedule of the laboratory parameters requiring analysis at the central laboratory is presented in Table 3: Schedule of Study Procedures.
All samples will be shipped from the site to a central laboratory. Handling and shipment of the samples to the central laboratory will be described in a manual provided by the central laboratory. Management of central laboratory services will be provided by 

Note: Additional blood may be required for repeats of safety laboratory tests.

**10.7.4.2 Local Analysis**

In addition to central laboratory analysis of all blood samples, local laboratory analysis will be performed for the exclusionary laboratory parameters performed at the screening visit: platelets, aPTT, INR, and creatinine. Creatinine clearance (exclusion criteria #3) will be estimated using the (aMDRD) Study equation.

Inclusion of patients will be based on local laboratory assessments. For consistency and comparative purposes, analysis of study data will be based on central laboratory assessments only. If local laboratory assessment allows for inclusion of a patient (aPTT, platelets and creatinine clearance), the patient will not be withdrawn from the study if the central laboratory assessment is inconsistent with inclusion. Likewise, such a discrepancy will not be reported as a protocol violation.

INR assessment for patients randomised to the Warfarin Arm will be performed locally throughout the study, and according to local practice and Investigator discretion.

All women of childbearing potential must have a negative pregnancy test when entering the study and must use a birth control method. A urine or serum pregnancy test will be performed locally at the study centres at randomisation.

Note: Additional blood may be required for repeats of safety laboratory tests and for serum pregnancy tests.
10.7.5 Bleeding Assessment

Events of bleeding will be recorded throughout the study. Bleeding events will be recorded starting from the first dose of study drug and included in the analysis up to 24 hours following the last administration of investigational product (i.e. greater than 5 x the half-life of Innohep®).

Bleeding will be defined in accordance with the International Society of Thrombosis and Haemostasis (ISTH) (58). Major bleeding criteria are defined as follows:

- Bleeding with a fall in haemoglobin of > 2 g/dL
- Bleeding requiring a transfusion of > 2 units of red cells or whole blood.
- Bleeding that occurs in a critical location, i.e. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial.
- Bleeding that causes death.

All non-major bleedings (i.e. bleedings that do not meet the criteria for major bleeding above) that require any medical or surgical intervention, including unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment will be classified as “clinically relevant non-major bleeding”. Bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding will be classified as trivial bleeding. All bleedings occurring during the study will be sent to the blinded IAC for review.

10.7.6 Diagnosis of Heparin-induced Thrombocytopenia (HIT)

The diagnosis of HIT reported as AEs in this study requires both clinical and laboratory diagnostic confirmation that is consistent with standard practice including the use of the Warkentin 4T score (59). If HIT is confirmed, Innohep® and warfarin treatment will be permanently discontinued. Laboratory analyses performed for confirmation of HIT are performed locally and must be confirmed at the central laboratory. The patient will be treated according to the site practice and followed up.

All cases of HIT occurring while patient is on study treatment and up to 1 month after the last dose of study treatment will be sent to the blinded IAC for adjudication.
10.7.7 Quality of Life

Health-related QoL will be assessed using the EQ-5D (see Appendix IV) at baseline, all monthly visits, at the End of Treatment, and at the Post-Treatment Follow-Up Visit. EQ-5D is primarily designed for self-completion by the patient. However, EQ-5D self-report data can also be collected by telephone interview scripts, relevant for follow up visits performed by telephone.

The EuroQol Group’s EQ-5D is a brief questionnaire designed to measure health status. The 6-item measure generates a descriptive profile and single index value for health status. The 5-item descriptive portion addresses five health dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression) with respondents indicating one of three possible responses for each dimension. Summary data can be reported as the proportion of respondents with problems in each dimension. Additionally, the multidimensional “health state” can be converted to a single weighted health status index that reflects the valuation of various possible health states from general population samples. The second portion of the EQ-5D is a single item (0-100) visual analogue scale that is used to report overall health status. The visual analogue scale offers a simple method for obtaining a self-rating of current health status. The EQ-5D is a public domain instrument available through the EQ-5D website, www.euroqol.org.

10.7.8 Healthcare Resource Utilisation

The major healthcare resources associated with the prevention of recurrent VTEs in high risk patients and the management of VTE, HIT and bleeding events will be collected over the 7 month study period at each monthly visit. Resources will include medications used for prevention of recurrent VTE (number of dosages and strength of dosage); INR test (number of INRs); unscheduled clinical visits and unscheduled emergency department visits (number and purpose of unscheduled visits); diagnostic tests relevant for VTE diagnosis (number of diagnostic tests for VTE diagnosis); VTE-related hospitalisations (including number of hospitalisations [divided in to PE or DVT], length of stay, DRG code if relevant in the country); management of patients who develop HIT (number of HITs and resources for their management) or bleeding events (number of bleeding events [divided in to major and clinically relevant non-major events], number of blood transfusions, name, length and dosage of treatment, number of hospitalisations for bleeding and length of hospitalisation and DRG...
10.7.9 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation occurring after the patient has signed the ICF. The AE does not necessarily have a causal relationship with the study treatment or study procedures. Consequently, AEs include adverse drug reactions (ADRs), significant abnormal laboratory values and intercurrent diseases.

AEs are expected when their nature, severity or outcome are consistent with the latest version of the Investigator’s Brochure for Innohep® or equivalent latest version of [redacted], approved by the Medicines and Healthcare products Regulatory Agency in the UK, as the adverse event profiles according to the SmPCs are confirmed medically identical between the different suppliers of warfarin.

At each patient visit, from the date the patient provides written informed consent until the end of study, each patient will be asked non-leading questions regarding their well-being since the last visit using a standardized questionnaire. Any unintended and unfavourable sign (e.g. a clinically significant abnormal laboratory finding), symptom or disease described by the patient or noted by the site staff will be recorded as an AE in the source documents, reported on the CRF and followed up with more specific questions or actions as required.

If a change in the patient’s health status was noted prior to drug administration, it will be recorded in the patient’s source documents and reported in the patient’s medical, surgical or physical screening CRF pages. Only medically qualified personnel must assess AEs. For the purpose of data collection, all untoward events that occur after informed consent through 30 days after last dose of study treatment are to be recorded on the CRF by the investigational site. This requirement includes AEs recorded from unscheduled as well as scheduled visits.

10.7.9.1 Reporting of Adverse Events

All AEs, whether or not they are considered related to the drug, must be recorded in the CRF.
All AEs must be described using the appropriate medical terminology. If a sign or symptom is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. Each event is to be evaluated for duration, severity grade, relationship with the investigational product and action taken regarding investigational product.

Any AE or clinically relevant abnormal laboratory value or clinically significant abnormal physical finding which is considered by the Investigator to be study drug-related must be followed up with appropriate medical management and documented in the study records (patient’s medical records or CRF) until recovery or stabilisation within 30-day Post-Treatment Follow-Up period.

A pre-existing condition must not be reported as an AE at baseline but must be reported in the appropriate section of the CRF concerning baseline data. Medical conditions/diseases present before starting study treatment are to be considered as an AE only in cases where they worsen after starting study treatment.

All diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, occurring during the study, must be reported under “Comments” in the CRF and the medical condition for which the procedure was performed should be recorded as an AE.

The Investigator is responsible for determining the relationship between the administration of investigational product and the occurrence of an AE.

Events reported by the patient, or observed by the (Sub) Investigator or delegate, that fall into any of the above definitions must be recorded on the AE page of the CRF and should be described in the following manner:

The **nature** of the event will be described in precise, English medical terminology (i.e. not necessarily the exact words used by the patient). Whenever possible, a specific diagnosis should be stated (e.g. allergic contact dermatitis).

The study will use the latest version of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.002 to grade the severity of AEs (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). If the AE is not specified in the CTCAE the
severity will be assessed on the following scale according to the Investigator’s clinical judgment.

- **Mild**: The AE does not interfere in a significant manner with the patient’s normal functioning level and requires no medical intervention.
- **Moderate**: The AE interferes with the patient’s normal functioning level and may or may not require medical intervention.
- **Severe**: The AE produces significant impairment of the patient’s functioning or requires medical intervention.

The **duration** of the event will be reported as the start date and stop date of the event.

The **causal relation** of the event to the use of the investigational product will be described in terms of probable, possible, or not related according to the following definitions:

**Probable**
- Follows a reasonable temporal sequence from administration of the investigational product.
- Could not be reasonably explained by the patient’s clinical state, environmental or toxic factors or other therapies administered to the patient.
- Follows a known pattern of response to the investigational product.
- Disappears or decreases on cessation or reduction in dose of the investigational product.
- Reappears or worsens upon re-challenge.

**Possible**
- Follows a reasonable temporal sequence from administration of the investigational product.
- Could also be reasonably explained by the patient’s clinical state, environmental or toxic factors or other therapies administered to the patient.
- Follows a known pattern of response to the investigational product.

**Not related**
- Does not follow a reasonable temporal sequence from administration of the investigational product.
- Is better explained by other factors like the patient’s clinical state, environmental or toxic factors or other therapies administered to the patient.
- Does not follow a known pattern of response to the investigational product.
The **outcome** of the event will be classified and handled as follows:

- **Recovered/resolved**  
The event has stopped. The stop date of the event must be recorded.

- **Recovering/resolving**  
The patient is clearly recovering from an event. The event is, however, not yet completely resolved. Follow-up on the event is required until final outcome is established.

- **Not recovered/not resolved**  
Event is still ongoing.  
Follow-up on the event is required until final outcome is established.

- **Recovered with sequelae**  
The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.  
The stop date of the event must be recorded.

- **Fatal**  
The patient has died as a consequence of the event. Date of death is recorded as the stop date for the AE.

- **Unknown**  
Unknown to Investigator, e.g. patient lost to follow-up.

Once a patient has completed the study, the Investigator should follow-up for outcome on all non-SAEs classified as possibly/probably related to the investigational product for 30 days after the last dose of study drug or until final outcome is determined, whichever comes first.
10.7.9.2 Other Events to be Reported

**Pregnancy**

Pregnancy or pregnancy of partner which occurs during a clinical study with an investigational product must be reported to Drug Safety within 1 working day of first knowledge using the Pregnancy Follow-up Form supplied by Drug Safety. All pregnancies must be followed-up until delivery or termination.

Please also confer with Section 10.5, withdrawal criteria.

**Overdose**

Any overdose defined as any higher dose than prescribed for the individual patient must be reported on the AE page of the CRF. AEs originating in the overdose must be documented on a separate line.

**Aggravation of condition**

Any clinically significant aggravation/exacerbation/worsening of the initially treated condition compared to baseline, judged by an overall medical assessment, must be reported as an AE.

10.7.10 Serious Adverse Events (SAEs)

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect.

OR

- Other medically important events*.

*) Medically important events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
The Investigator and others who are responsible for patient care should institute any supplementary investigations of serious and otherwise significant AEs based on their clinical judgment of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the AE.

Events not considered to be SAEs are hospitalisations for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
- Treatment on an emergency outpatient basis not fulfilling any of the definitions of serious given above and not resulting in hospital admission.
- Events that result in hospital stays of less than 24 hours and that do not require admission, e.g., an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics.

SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalisation.

10.7.10.1 Reporting of Serious Adverse Events

Any SAE, regardless of causal relationship, must be reported to Drug Safety immediately (within 24 hours of the Investigator’s knowledge of the event) by faxing the completed SAE report form and any other pertinent SAE information to the dedicated SAE fax line indicated on the SAE report form and confirming the fax was received. All SAEs must also be recorded on the AE page of the CRF as described in Section 10.7.9.1.

For each SAE, the Investigator will provide information on severity grade, start and stop dates, relationship and action taken with the investigational product and outcome. This applies to all SAEs, regardless of the relationship to investigational product that occur during the study, those made known to the Investigator within the 30 day Post-Treatment Follow-Up period after study discontinuation or if the investigator learns of any SAEs that occurred after the post-treatment follow-up period for which there is a reasonable possibility of study drug relationship. SAEs will be reported from the date the patient provides written informed consent.
The SAE report should provide a detailed description of the SAE. Anonymized copies of hospital records and other relevant documents may be requested based on judgement of the Medical Monitor. If a patient has died and an autopsy has been performed, copies of the autopsy report are to be sent to the Medical Monitor as soon as these become available.

All SAEs that have not resolved upon discontinuation of the patient’s participation in the study must be followed until either the event resolves, stabilizes, or returns to baseline (if a baseline value is available).

The Investigator is responsible for reporting SAEs to the IEC according to local regulations.

NOTE: Symptomatic DVT of the lower limbs, non fatal PE and the related hospitalisations are components of the primary endpoint of the study; however, these events must be reported as SAEs if they meet the criteria for an SAE. These events will also be reported as efficacy endpoints in a specific page in the CRF for the duration of the study.

10.7.11 Regulatory Reporting

Drug Safety will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Drug Safety will make a preliminary determination as to whether the criteria for expedited reporting have been met which is finally approved by LEO.

SAEs which meet the criteria for expedited reporting will be submitted to the Regulatory Authorities in accordance with local regulations governing safety reporting. This includes SAEs which occur in relation to Innohep® used in protocol IN 0901 INT, whether that reaction occurs during the course of that study or another study for which the sponsor is responsible. This also includes SAEs which occur in relation to warfarin used in protocol IN 0901 INT. In accordance with national legislation of the concerned European Member States the sponsor or designee will provide the concerned Ethics Committee(s) with expedited individual reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) and/or periodic SUSAR line listings.

Reporting of SAEs by the investigator to his or her IRB or IEC will be done in accordance with current regulation and the standard operating procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.
10.7.12 Source Data

**Source data:** All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).

**Source documents:** Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patients diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).

Source Data Verification (SDV) is a key function in assuring the sponsor that clinical study information is recorded and handled in a way that allows its accurate reporting, interpretation and verification. Monitors will, during the conduct of the clinical study, perform SDV to confirm the accuracy and completeness of CRFs by verifying data recorded in the CRF against data recorded in source documents to ensure such records are consistent. To enable SDV it is essential, that what constitutes source data/documents (see definition above) for the study data to be collected in the CRF as well as where such data can be found at the study site, is established and agreed with the Investigator at each study site and documented, prior to initiation of the clinical study.

Source data cannot be entered directly into the CRF. Source data should, as a general rule, be recorded in the patient’s medical record or other defined document normally used at the study site. Source data may be entered on a worksheet only if the clinical study requires capture of data, which are normally not part of the patient’s medical record.

For this clinical study, the following parameters collected in the CRF should be verifiable from source documents available at the study site, this includes:

- Date of study visits and date leaving the clinical study.
- Relevant medical history and diagnoses at time of randomisation
- Data for evaluation of selected eligibility criteria
In addition to the above, the following should be added to the patient’s medical record, in chronological order, i.e. when these are allocated to the patient.

- Date(s) of conducting the informed consent process including date of provision of patient information
- Date of enrolment
- Subject number
- Treatment allocation
- This patient is participating in a clinical study to assess the recurrence of VTE in patients with active cancer who have had an active VTE episode. Patients are randomised to receive either 1) Innohep® for 6 months or 2) Warfarin for 6 months. LEO study ID IN 0901 INT.

10.8 EFFICACY EVALUATION

The efficacy analysis period is defined as the period from randomisation up to 180 days after randomization and at least 24 hours following the last administration of investigational product.

10.8.1 Primary Response Criterion

The primary efficacy endpoint is a composite endpoint represented by the time in days from randomisation to the first occurrence of any of the following 5 objectively documented components

- Symptomatic non-fatal DVTs.
- Symptomatic non-fatal PEs.
- Fatal PE.
- Incidental proximal DVT (popliteal vein or higher).
- Incidental proximal PE (segmental arteries or larger).

### 10.8.2 Secondary Response Criteria
Secondary efficacy endpoints are the time to first occurrence of each of the primary endpoint components from randomisation up to end of study treatment (including the 24 hours following the End of Treatment Visit). In addition, the 3 symptomatic components of the primary composite endpoint are a composite secondary endpoint.

### 10.9 SAFETY EVALUATION
The main safety analysis period is defined as the period from first dose of study drug up to 24 hours after the last dose of study drug. The baseline safety variable value for each patient is defined as the last available value prior to randomisation. The scheduling of safety parameter assessments prior to randomisation is outlined in Section 10.7.1 and in Table 3: Schedule of Study Procedures.

Safety endpoints will consist of major and clinically relevant non-major bleedings according to ISTH criteria (see Section 10.7.5), overall mortality, HIT, other objectively confirmed thromboses (including symptomatic and incidentally detected venous thromboses (e.g. subsegmental PE, portal or renal vein thrombosis) as well as arterial thromboses (e.g. myocardial infarction, stroke or systemic embolic events), clinically significant laboratory data, clinically significant vital signs and all other AEs/SAEs.

### 10.9.1 Evaluation of Adverse Events
AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) AE dictionary, which is an AE reporting system that allows for the grouping of AEs and for the classification of AEs into a system organ class and preferred term.

Each AE will be classified as a treatment-emergent AE, pre-treatment emergent AE or post-treatment emergent AE as follows:
- **Pre treatment-emergent AEs/SAEs**: any AE/SAE with onset prior to first dose of study drug.
- **Treatment-emergent AEs/SAEs**: any AE/SAE with onset or worsening of intensity after first dose of study drug and until 24 hours after stop of study treatment.
- **Post treatment-emergent AEs/SAEs**: any SAE with onset or worsening of intensity more than 24 hours after stop of study treatment. AEs with onset 24 hours after stop of study treatment are not reportable.

Bleeding events are always considered as AEs. All bleedings will be reviewed by the blinded IAC and classified as follows:
- Major bleeding.
- Clinically relevant non-major bleeding.
- Trivial bleeding

Only major and clinically relevant non-major bleeding will be considered in the statistical analysis.

**11 STATISTICAL ANALYSIS**

The statistical analyses will be performed by LEO and will be based on the pooled data from the individual study sites. Further details of the statistical analysis will be provided in the Statistical Analysis Plan, which will be finalised prior to database lock.

**11.1 NUMBER OF PATIENTS/SAMPLE SIZE**

In the available literature the incidence rate of the primary endpoint varies in the population of cancer patients. The CLOT study (50) supports an incidence rate of 15%, while a meta analysis (60) supports an incidence rate of 12.6%.

Assuming that Innohep® leads to a relative risk reduction of 50% an estimated event rate of 12.6% in the control group will imply an estimated event rate of 6.3% in the Innohep® group.

Using a time-to-event approach with a significance level of $\alpha = 0.05$ and an overall power of 90%, 80 events will be needed to detect the above difference. The competing risk is included.
in the quoted event rates of 12.6% and 6.3% in the two treatment groups, yielding a combined overall 6 months event rate of 9.45%. A sample size of 847 patients is required to reach the 80 events needed. Including an expected dropout rate of 5%, 900 patients should be enrolled in the trial, with 450 patients randomised to each treatment group.

A sample size re-estimation is planned for to assess the appropriateness of the assumptions made.

11.2 PATIENT QUALIFICATION FOR ANALYSIS

All patients recruited for the study (i.e. signed informed consent obtained and a subject number assigned) will be accounted for in the study report.

All randomised patients will be included in the full analysis set (FAS) (intention-to-treat) and will be analysed for efficacy. Patients will be analysed as per the treatment group they were randomised to, irrespective of the treatment they received.

The per-protocol (PP) analysis set will consist of the patients in the FAS who do not violate any major entry condition and do not violate the protocol between randomisation and the end of the treatment period. Major deviations from the protocol procedures include:

- Violation of inclusion/exclusion criteria.
- Disallowed concomitant medication.
- Presence of other protocol violations/deviations likely to affect the efficacy evaluation (e.g. a poor compliance with study medication, visit schedule or study procedures).

The exclusion of patients or patient data from the per protocol analysis set will be decided upon during the review of the data and discussed at the Data Review Meeting before final database lock.

The safety analysis set will comprise all randomised patients who take study medication. Patients will be analysed for safety as per the treatment the patient received.
The decisions regarding inclusion/exclusion of patients and/or patient data from the study analysis sets will be documented in the statistical analysis plan which will be finalised before database lock.

11.3 STATISTICAL METHODS

11.3.1 Reasons for Leaving the Study
The reasons for leaving the study will be presented for all randomised patients and by treatment group.

11.3.2 Demography and Baseline Characteristics
Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised patients and by treatment group and stratification stratum.

Critical demographic and baseline characteristics will be examined according to qualitative or quantitative data. Qualitative data (e.g. gender, race) will be summarised by means of contingency tables. Quantitative data will be summarised using quantitative descriptive statistics such as mean, standard deviation, minimum and maximum values.

Statistical comparisons of the treatment groups at baseline may be conducted in order to assess the performance of the randomisation.

11.3.3 Prior/Concomitant Medication
Prior medication is defined as a medication starting prior to the first dose of study treatment. Concomitant medication is defined as a medication that is taken on or after the first dose of study treatment.

For incomplete or partial concomitant medication start and/or stop dates, where it is not possible to classify the concomitant medication as before or during using available date information, it will be assumed that the concomitant medication was taken during the treatment period.
Prior and concomitant medication will be summarised by treatment group for the safety analysis set using drug class and preferred term. Patients will only be counted once within a drug class and once for a medication.

All medication, taken both prior to and during the treatment period, will be included in the supportive data listing. A flag will be added to indicate where a medication was taken prior to the first dose of study treatment.

**11.3.4 Extent of Study Treatment Exposure and Compliance**

The extent of exposure variable is defined as the duration in months elapsed from the first day of study treatment up to the last day of study treatment, ignoring temporary periods without treatment. Categorisation of the extent of exposure (months) is also defined as follows: < 1, (1-2), 3, (4-5), 6, ≥ 6.

For the Innohep® group, compliance to study treatment is determined on an individual basis corresponding to the ratio of the number of investigational product injections actually taken from the first investigational product injection to the last investigational product injection divided by the theoretical number of injections. Results will be expressed in percentages for each patient.

Duration of treatment exposure and treatment compliance will be summarised as quantitative and qualitative variables. Further details will be provided in the Statistical Analysis Plan.

**11.3.5 Analysis of Efficacy**

The statistical analysis of efficacy will be based on the defined response criteria (Section 10.8).

All efficacy criteria will be analysed for the FAS. In addition, the primary efficacy criterion will be analysed for the PP analysis set. The full analysis will be regarded as primary while the PP analysis will act as supportive.

For both the primary and secondary analyses, the assessment of recurrent VTE from the blinded IAC will be used. No analysis of the Investigator assessment of recurrent VTE will be performed.
11.3.5.1 Primary Efficacy Criterion

All recurrent VTE outcomes confirmed by central adjudication occurring from the time of randomization to Day 180 (including 24 hours after the last dose of study drug) will be eligible for primary efficacy analysis. In the event that the diagnoses made by the local investigator and central adjudication results are discrepant, the central adjudication results will be used in the analysis. The date of event will be the date of objective diagnosis.

The primary efficacy endpoint is a composite endpoint represented by the time in days from randomisation to the first occurrence of any of the following 5 objectively documented components:

- Symptomatic non-fatal DVTs.
- Symptomatic non-fatal PEs.
- Fatal PE.
- Incidental proximal DVT (popliteal vein or higher).
- Incidental proximal PE (segmental arteries or larger).

Statistical comparison will be based on the time to the first recurrent VTE event per patient. The date of the VTE event is defined as the date of the objective test that confirmed the diagnosis of VTE (not symptom onset). In order to correct for competing risks, a cumulative incidence approach will be used. The competing risks considered in this study will be deaths other than fatal PE. Patients alive at the end of the treatment period and not having experienced the primary efficacy endpoint will be censored at the date of the End of Treatment visit. The primary efficacy analysis will compare the two treatment groups using a two-sample test devised by Gray (61, 62) for comparing Cumulative Incidence Functions (CIF). The CIF is the probability of occurrence by time for a particular type of event in the presence of other risks. The hypothesis of interest is:

\[ H_0: \text{CIF (Innohep®)} = \text{CIF (control group)} \]
\[ H_1: \text{CIF (Innohep®)} \neq \text{CIF (control group)} \]

The CIF will be estimated separately for the two treatment groups using a bivariate approach and the corresponding 95% CI will be computed.
11.3.5.2 Secondary Efficacy Criteria
The six secondary efficacy endpoints are given as the time in days from randomisation to the first occurrence of:

- The 5 individual components of the composite primary efficacy endpoint.
- Any symptomatic DVT and or PE, including fatal PE.

Results from central adjudication of events will be used for analysis.

In order to examine the consistency of the results between the different components of the primary endpoint, the time to first occurrence of each of the primary endpoint components or the end of the treatment period, which ever occurs first, will be analysed separately. In addition, the composite endpoint of the 3 symptomatic components of the primary endpoint will comprise a composite secondary endpoint. All six endpoints will be analysed as described in Section 11.3.5.1. For each time to event analysis, the components not defined as the event of interest will be considered a competing risk; 95% CIs will also be calculated. The p-values will be corrected for multiplicity using the Hoechberg method.

11.3.6 Analysis of Safety
The statistical analysis of safety will be based on the defined safety endpoint criteria in Section 10.9 and will be summarised for the safety analysis set.

11.3.6.1 Overall Mortality
Time to death (overall mortality) will be summarised using Kaplan-Meier estimates and compared between the two treatment groups using a 2-sided Log Rank test. An estimate of the treatment effect (hazard ratio and associated CI) will be obtained via Cox Regression including all stratification factors.

11.3.6.2 Bleeding Data
All bleeding events reported occurring from the first dose of study drug up to 24 hours of the last dose of study drug will be centrally reviewed and classified by the blinded IAC as major or clinically relevant non-major bleeding, or trivial bleeding and will be summarised by treatment group. Major bleeding is the primary safety outcome. The proportion of patients with a major bleeding event will be compared using Fisher’s exact test. Similarly, the
proportion of patients with any non-trivial bleeding will be compared between the treatment groups using Fisher’s exact test.

Any bleeding episodes reported by the Investigator but considered by the blinded IAC as trivial bleeding will not be taken into account in the statistical analyses. Such events will be tabulated separately.

As for the primary endpoint, in order to correct for competing risks, a cumulative incidence approach will be used to analyse bleeding data. Competing risks will be deaths from all causes other than fatal bleeding.

11.3.6.3 Other Thromboses
Other objectively confirmed thromboses will be listed per patient and sorted by treatment group. The number and percentage of other objectively confirmed thromboses will be summarised for each treatment group and compared using Fisher’s exact test.

11.3.6.4 Adverse Events
Individual AEs will be listed per patient and sorted by treatment group. Number of patients with treatment-emergent AEs, AEs related to treatment, SAEs, AEs leading to withdrawal and AEs leading to death will be summarised by system organ class and preferred term for each treatment group regardless of the number of times each AE is reported by each patient. The adjudicated causes of death will be summarised separately by treatment group.

11.3.6.5 Vital Signs
Vital signs, including change from baseline data, will be summarised for each visit by treatment group.

11.3.6.6 Laboratory Data
Number and percentage of patients presenting at least one post-baseline potentially clinically significant abnormality (criteria to be documented in the Statistical Analysis Plan) will be provided by laboratory parameter. In addition, descriptive statistics will be presented for the
quantitative parameters. Changes from baseline will be summarised at each visit and shift tables will be produced for each treatment group.

The number and percentage of HIT events will be summarised for each treatment group and compared using Fisher’s exact test.

Laboratory abnormalities will be flagged and listed, as appropriate.

11.3.7 Analysis of Other Variables

11.3.7.1 Coagulation Parameters
The relationship between coagulation factors (e.g. D-dimer and tissue factor) and recurrent VTE will be investigated using linear and non-linear regression models.

11.3.7.2 Clinical Baseline Characteristics
Exploratory analysis will be performed to assess clinical baseline characteristics for their association with recurrent, symptomatic and/or incidental VTE and bleeding in patients receiving anticoagulant therapy. The characteristics are listed below.
Risk factors for Recurrent VTE:

- **Current (Present At Randomisation)**
  1. Tumour type (site and histology)
  2. Tumour stage (early or localized; locally advanced, distant metastases; partial remission; not in remission)
  3. Central venous catheterization
  4. Venous compression from mass or adenopathy
  5. Inflammatory bowel disease
  6. Age > 75 year old
  7. Obesity (BMI > 30 kg/m²)
  8. Current smoker
  9. Diabetes
  10. Postpartum period (6 weeks after delivery)

- **Present Within 3 Months Prior To Randomisation:**
  11. Chemotherapy
  12. Anti-angiogenesis agents
  13. Radiation
  14. Erythropoiesis-stimulating agents
  15. Transfusion
  16. Selective estrogen receptor modulators
  17. Major surgery - requiring more than 30 minutes of anesthesia time
  18. Major trauma - multiple fractures and/or organ injury
  19. Lower-extremity injury requiring surgical intervention
  20. Acute spinal cord injury
  21. Immobility (unable to walk unassisted; more than 50% of waking hours in bed)
  22. Acute neurological disease with paresis
  23. Hospitalisation for 3 days or longer
  24. Sepsis or severe acute infection requiring hospitalisation
  25. Nephrotic syndrome
  26. Myeloproliferative disorders
  27. Estrogen-containing oral contraceptives
  28. Hormone replacement therapy
• **History Of Objectively Confirmed Risk Factors (Lifelong)**
  29. Inherited thrombophilia
  30. Antiphospholipid syndrome
  31. Previous VTE
  32. History of ischaemic or haemorrhagic stroke
  33. History of myocardial infarction

**Risk Factors for Bleeding:**

• **Current (Present at Randomisation)**
  1. Tumour type (site and histology)
  2. Tumour stage (no clinical evidence or in remission; early or localized; locally advanced, distant metastases; partial remission; not in remission)
  3. Antiplatelet agents
  4. Thrombocytopenia (50-100 x 10^9/L)
  5. Abnormal coagulation parameters (INR > 1.3 or PTT > ULN)
  6. Liver insufficiency (direct bilirubin > 2X ULN)
  7. Renal sufficiency (GFR less than 60 mL/min)
  8. Known intracranial pathology (e.g. brain metastasis)
  9. Age > 75
  10. BMI < 18 kg/m²
  11. Alcoholism (defined by local standard criteria)

• **Present Within 3 Months Prior To Randomisation:**
  12. Chemotherapy
  13. Anti-angiogenesis agents
  14. Major surgery or trauma

• **History Of Objectively Confirmed Risk Factors (Lifelong)**
  15. History of bleeding on anticoagulants
  16. History of gastrointestinal bleed
  17. History of stroke
11.3.7.3 Post Thrombotic Syndrome
The presence and severity will be analysed using the Villalta scale, (see Section 10.7.3.5) and a comparison within and between treatment groups will be done in addition to analysing the change in severity over time. The Villalta scale classifies PTS as mild if the Villalta scale is 5-9, moderate if the Villalta scale is 10-14 and severe if the Villalta scale is $\geq$ 15 or a venous ulcer is present.

11.3.7.4 Health-related Quality of Life
Descriptive statistics will be produced for the five EQ-5D dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), visual analogue scale, and utility index at each assessment for patients in the Innohep® group and patients in the control group. The dimensional outcomes and the utility indexes of the EQ-5D will then be assessed using multivariate mixed models for a repeated measures analysis. As a secondary endpoint in the QoL analysis, “clinical stability” will be evaluated. Clinical stability will be defined as an improvement or less than a 10% drop in the utility index of the EQ-5D when measured during two consecutive monthly assessments. Patients who have a 10% drop in the utility index or do not complete the EQ-5D questionnaire on consecutive assessments (i.e. missing data) will be classified as not having achieved clinical stability and therefore would be considered to have clinically deteriorated. This approach to data analysis will remove the impact of missing data that often compromises QoL assessments in oncology studies. For this secondary evaluation, logistic regression analysis, Kaplan-Meier curves and Cox proportional hazards regression will be used to evaluate clinical stability and deterioration between patients randomized to the Innohep® and control group.

11.3.7.5 Healthcare Resource Utilisation
The major healthcare resources associated with the prevention of secondary VTEs will be collected over the 6 + 1 month study period. Only healthcare resources leading to major cost drivers will be collected and these will include resource uses for VTE preventive therapy (i.e. drug etc.), routine laboratory tests, patient INR in the case of VKA, unscheduled clinical visits, diagnostic tests relevant for VTE diagnosis, blood transfusions, the occurrence of major bleeding related events that were possibly or probably due to the study drugs and costs for the management of patients who develop recurrent VTEs (e.g. hospitalisation). The above data will be used to compare the total cost of care between groups for a reference country (e.g. the
UK) using nonparametric statistical techniques such as quantile regression analysis. In addition, the incremental cost per VTE avoided and quality-adjusted life year (QALY) gained with Innohep® will also be determined. The EQ-5D will provide the required utility data to perform the cost per QALY gained analysis.

**11.4 INTERIM ANALYSIS**

A formal interim analysis will be performed by the DMC when approximately 50% of the patients have either completed the treatment period, died or are lost to follow-up. The study can be stopped early for superiority or lack of efficacy. The decision will be primarily based on the primary efficacy criterion. However, the risk benefit of Innohep® in the population of interest will also be considered.

To maintain an overall significance level of 0.05, a Lan DeMets implementation of the O’Brien and Flemming alpha spending function (63, 64, 65) will be used to create a stopping rule for superior efficacy. With this approach, the nominal significance level of the interim test will be 0.003 and the nominated level of the final analysis will be 0.049.

In addition, if the conditional power based on the interim analysis results is less than 20%, then the study may be terminated for lack of efficacy. Conditional power will be determined via simulation and/or Bootstrapping techniques. Further details will be provided in the Statistical Analysis Plan.

Safety data will be summarised and reviewed at the time of the interim analysis. The efficacy data required for the interim analysis decision making will be 100% clean.

In the event that more than 95% patients have been randomised at the time of the interim analysis, this analysis may be cancelled. The decision will be made by LEO in cooperation with the Steering Committee.

**11.4.1 Sample Size Re-assessment**

A sample size re-estimation will be conducted when approximately 25% of the patients have either completed the treatment period, died or are lost to follow-up.
The observed incidence rate for the primary endpoint in the entire group will be summarised, together with the associated 95% confidence interval. This data will be used to establish whether the planned sample size of 900 is reasonable. The pre-specified target of a 50% relative risk reduction for Innohep® as the clinically relevant difference will not be changed during the sample size re-estimation process. No adjustment will be made to the type I error rate.

The sample size re-assessment will be done by the study statistician. The evaluation will be done by LEO in cooperation with the Steering Committee.

11.5 GENERAL PRINCIPLES

Summary tables will be provided by treatment group and stratification stratum (when relevant). The statistical analyses will be performed using SAS® Version 9.1 or later.

All tests described in this section will be performed at the 5% significance level unless otherwise stated; 95% CIs will be provided where appropriate.

Missing data will not be included in the calculations of percentages.
Missing data will not be imputed for safety parameters.

12 QUALITY ASSURANCE/AUDIT

LEO has implemented a system of quality assurance, including all elements described in this protocol. Within this system SOPs are implemented to ensure that clinical studies are conducted in compliance with regulatory requirements and GCP. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Study sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by LEO or inspection by competent authorities.

Any aspect of the study may be subject to audit by LEO and/or inspection by regulatory authorities (national or foreign) or IEC/IRB. Such audits/inspections may take place at the sponsor’s premises(s), the CRO’s premises, or at any study site including laboratories, pharmacies etc.
The monitor will, in case of audit, announce this in advance to the (Sub) Investigator and be present at the particular study site during the audit.

The site staff should assist in all aspects of audit/inspection.

12.1 STUDY MONITORING

LEO, as sponsor of this clinical study, is responsible to the regulatory authorities for assuring the proper conduct of the clinical study with regard to protocol adherence and validity of the data recorded in the CRFs. LEO has therefore assigned persons to oversee this study. Their duties are to advise the Investigator on the collection and maintenance of accurate, complete, legible, well organised, and easily retrievable data for the study. In addition, they will explain to the Investigators any aspect of the (conduct of the) study, including interpretation of the protocol, the purpose of collecting the specified data and reporting responsibilities.

In order to perform their role effectively, monitors and persons involved in quality assurance and inspections (see above) will need direct access to primary patient data, e.g. medical records, laboratory reports, appointment books, etc. As this affects the patient’s confidentiality, this fact is included on the ICF.

This study is organised and conducted by the CRO and all enquiries should be made to personnel designated in Section 6.3.

13 CASE REPORT FORM AND DATA HANDLING

13.1 CASE REPORT FORMS

An electronic CRF will be used to store and transmit patient information. The file structure and format for the CRF will be provided by the CRO and should be handled in accordance with the instructions provided.

The CRF must be reviewed and electronically approved by the Investigator.
Access to the CRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the CRF completely by the Investigator or by staff authorised by the Investigator. The CRF must be completed as soon as possible after any patient visit. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The CRFs and computers that store them must be accessible to study monitors, auditors and regulatory inspectors.

13.2 DATA HANDLING

An electronic CRF and paper patient diary/quality of life questionnaire will be used for the current study, and a data management plan will be prepared by the CRO. Previous and concomitant medications will be coded using the latest available WHO Drug Reference Dictionary. Coexistent diseases and AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities). Data review and consistency checks will be performed on an ongoing basis on all data collected on the electronic CRF and paper patient diary/quality of life questionnaire.

Personal data shall be handled and processed in accordance with any national legislation regulating privacy and data protection as well as in accordance with the terms and conditions of the authorisation granted by the Danish Data Protection Agency to LEO, as set forth in the attached Appendix I.

LEO is considered responsible for the data in all international clinical studies sponsored by LEO (see Appendix I).

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between the Sponsor and the CRO’s project team.

14 PROTOCOL AMENDMENTS

Neither the Investigator(s) nor LEO will change the Clinical Study Protocol without written agreement between LEO and the SCO. Any modification considered substantial requires approval/favourable opinion by the appropriate regulatory authority and IEC/IRB.
Protocol amendments are issued as Consolidated Clinical Study Protocols comprising all current amendments. Consolidated Clinical Study Protocols become effective when written approval has been provided by the International Co-ordinating Investigator, the Vice President, International Clinical Development, LEO and the Head of Biostatistics, LEO HQ, and approval/favourable opinion from regulatory authorities and/or IEC/IRB has been obtained, as required.

15 COMPLETION OF STUDY

15.1 STUDY COMPLETION PROCEDURES

This study is anticipated to complete in Quarter 3, 2013 (last patient last visit). Investigators will be informed when patient recruitment is to cease.

Study enrolment will be stopped at a study site when the total requested number of patients for the study has been obtained, irrespective of the specific site’s planned inclusion number. Upon completion of the study, the CRO will undertake arrangements for collection and disposal of any unused study material that the Investigator is not required to keep in his/her files.

LEO may stop the clinical study prematurely after consultation with the SCO, e.g. if the patient recruitment is so slow that the study cannot be completed within a reasonable time frame. Such premature termination/suspension of the study will be notified to regulatory authorities and IECs/IRBs, as required.

15.2 PROVISION FOR PATIENT CARE FOLLOWING STUDY COMPLETION

After the completion of the study, the patients will be treated at the Investigator’s discretion, according to standard practice.

15.3 ARCHIVING OF STUDY DOCUMENTS

The Investigator at each study site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial [ICH E6, Guideline for GCP]) including the Investigator Site File.
In addition, the Investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from regulatory authorities).

The Investigator is required to ensure the continued storage of the documents, even if the Investigator, for example, leaves the clinic/practice or retires before the end of required storage period.

At present according to ICH Guideline:

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. (ICH E6, 4.9.5).

16 USE OF INFORMATION

This protocol as well as all other information, data and results relating to this clinical study and/or to the investigational product(s) is confidential information of LEO and shall not be used by the Investigator for purposes other than this clinical study.

The Investigator agrees that LEO may use any and all information, data and results from this clinical study in connection with the development of the investigational product(s), and therefore, may disclose and/or transfer information, data and/or results to other Investigators, regulatory authorities and/or commercial partners.
17 PUBLICATION

Basic information of this clinical trial will be posted on the website: www.clinicaltrials.gov before the first patient enters into the clinical trial.
This study is a multi-centre study, and a publication by the Investigator of his/her trial results shall not be made before the first multi-centre publication is made public.

Such multi-centre publication will be prepared in collaboration between LEO and the members of a Writing Committee which shall be appointed by LEO and the SCO.

If there is no multi-centre publication within eighteen (18) months after the clinical trial has been completed or terminated at all trial sites, and all data has been received, defined as Data Base Lock of the clinical trial, the Investigator shall have the right to publish results from the clinical trial generated by the Investigator, subject to the following notice requirements.

Prior to submitting or presenting a manuscript relating to the clinical trial to a publisher, reviewer, or other outside person, the Investigator shall provide to LEO a copy of all such manuscripts, and LEO shall have rights to review and comment. Upon the request of LEO the Investigator shall remove any confidential information (other than results generated by the Investigator) prior to submitting or presenting the manuscripts. Investigator shall, upon the request of LEO, delay publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still on-going and has not been made public at the time of notification, LEO and the Writing Committee may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

In case of publications made by the Investigator after the first multi-centre publication has been published, the above mentioned requirements must be followed.

LEO also subscribes to the Joint Position of the innovative pharmaceutical industry (66) for public disclosure of clinical trial results in a free, publicly accessible database, regardless of outcome.
18 REFERENCES


72. Renée A. Douma, Maayke G.M. Kok, Lisa M. Verberne, Pieter W. Kamphuisen, Harry R. Büller Incidental venous thromboembolism in cancer patients: prevalence and


19 LIST OF APPENDICES

Appendix I: English translation of the Danish Data Protection Agency’s terms and conditions for the processing of clinical trial data by medical companies
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Appendix I

English translation of the Danish Data Protection Agency’s terms and conditions for the processing of clinical trial data by medical companies
English translation of the Danish Data Protection Agency’s terms and conditions for the processing of clinical trial data by medical companies

Listed below please find an English version of the general terms and conditions, set by the Danish Data Protection Agency, in cases involving authorisation for the processing of sensitive data by medical companies conducting continuous clinical trials of medical products. Circumstances may warrant some variation in the terms and conditions in concrete cases.

**AUTHORISATION** to process personal data

The Data Protection Agency hereby grants authorisation for processing of personal data for the purpose of the Company's continuous clinical trials, cf. section 50(1)(i) of the Danish Act on Processing of Personal Data. In this connection, the Data Protection Agency lays down the following terms:

**General terms**

**Period of validity:** The authorisation is valid until further notice.

- LEO Pharma A/S - hereinafter called the "Company" is responsible for compliance with these present terms.

- The data may be used for the sole purpose of performing clinical trials.

- The Company shall once a year to the Data Protection Agency submit an overview of new, commenced trials as well as a corresponding overview of which trials have been completed in the past year. The overview shall contain as a minimum a title of the trial and name and address of the clinically responsible investigator.

*) Source: Letter dated 07-Mar-2003 from the Danish Data Protection Agency (Datatilsynet) to the Danish Association of Pharmaceutical Industries (LIF)
• Processing of personal data must be performed only by the controller or at the instance of the controller and at his responsibility. It is the responsibility of the controller that compliance of the terms is always observed when data are processed.

• Any person processing personal data must be cognizant of these present terms.

• The terms must be complied with also where processing is made by a data processor.

• Facilities used for storage and processing of the data must be organized and fitted up in order to prevent unauthorized access.

• Data processing must be organized in such a manner that data are protected against accidental or unlawful destruction, loss or impairment. Furthermore, the necessary control should be exercised to ensure that no inaccurate or misleading data are processed. Inaccurate or misleading data or data processed in contravention of the above Act or of these terms shall be rectified or erased.

• Data must not be kept in a form that makes it possible to identify the data subject for a longer period than is necessary for the implementation of the project.

• If results from the clinical trial are published this must be done so that it is impossible to identify individual persons.

• It is a condition that compliance is made with related terms, if any, laid down in accordance with other legislation.

**Electronic data**

• Identification data must be encrypted or replaced by a code number or the like. Alternatively, all data can be stored encrypted. Encryption keys, code keys etc. must be stored securely and separate from the personal data.
• Access to project data can be obtained only through the use of a confidential password. A password must be replaced at least once a year and when conditions dictate it.

• If personal data are transferred over the Internet or other external network, the necessary security measures must be taken to ensure that the data do not come to the knowledge of any unauthorized third parties. As a minimum, the data must be encrypted during transmission. Transmission of sensitive personal data requires strong encryption. When using internal networks, it must be ensured that unauthorized persons are unable to obtain access to the data.

• Removable storage media, safety copies of data etc. must be stored securely and under lock and so that unauthorized access is prevented.

**Manual data**

• Manual clinical trial materials, including print-outs, failure lists and control lists etc., as well as other material which may directly or indirectly be linked with specific persons, must be stored securely under lock and so that unauthorized access is prevented.

**Bio-bank and biological material**

• Samples with biological material and biological material in bio-banks must be stored securely under lock so that unauthorized access is prevented and in such a manner that it is ensured that the material is not lost, impaired or accidentally or illegally destroyed.

• Biological material marked with civil registration number or name must be stored subject to special safety requirements.

• The Company shall lay down internal guidelines for storage of biological material relative to the individual trials, and guidelines for storage of biological material in bio-banks. The guidelines shall be updated at least once a year.
Information to be provided to the data subject (trial subject)

- Where the personal data are to be obtained from the trial subject (through interviews, questionnaires, clinical or para-clinical examination, treatment, observation etc.), detailed data about the project shall be distributed/forwarded to the trial subject. The trial subject must be informed of the name of the controller, the purpose of the project and of the fact that it is voluntary to participate and that consent may be withdrawn at any time. Where the data are to be disclosed to be used for other scientific or statistical purposes, the trial subject shall be advised also of the purpose of the disclosure and identity of recipients, if applicable.

- The data subject should furthermore be advised that the project is notified to the Data Protection Agency in accordance with Act on Processing of Personal Data, and that the Agency has laid down specific terms to be complied with for the project for the purpose of protecting the data subject's privacy.

Disclosure of data

- Disclosure of data identifying individuals to a third party may take place for other statistical or scientific purposes only.

- Disclosure may be made only subject to prior approval of the Data Protection Agency. The Data Protection Agency may lay down new terms for the disclosure as well as the recipient’s data processing.

- Disclosure of data may, however, take place in accordance with the below-mentioned authorisation to disclose data.

Right of access to personal data

- The subject of the trial i.e. the data subject has no right of access to the data being processed concerning himself, cf. Section 32(4) of the Act on Processing of Personal Data. This Act does not prevent the grant of access.
Processing by a data processor

- The Data Protection Agency’s conditions shall apply also to processing by a data processor.

- When data are processed by a data processor, a written agreement shall be made between the controller and the data processor. The agreement shall stipulate that the data processor acts on behalf of the controller only and that the data must not be used for the data processor’s own purposes. The controller shall furthermore request sufficient data from the data processor to ensure that the Data Protection Agency’s terms can and will be complied with.

- Where the data processor is established in another Member State it shall, furthermore, appear from the agreement that such other regulations on safety measures with regard to data processors that may be in force in the Member State in question, shall apply also to the data processor in question.

Erasure of data

- Data in the individual trials shall be erased, made anonymous or destroyed no later than at the expiry of the storage period stipulated by the GCP-rules. It must not subsequently be possible to identify individuals participating in the trial.

- Alternatively, the data may be transferred for further storage in archive in accordance with the rules of the archive legislation

- Erasure of data from electronic media shall take place in such a manner that it is impossible to recover the data.

Transfer of data to third countries

- Transfer of data to third countries, including for the purpose of processing by a data processor, requires the Data Protection Agency’s prior approval.
Transfer may take place in accordance with the below-mentioned transfer authorisation.

Transfer may, however, take place without approval of the Data Protection Agency if the data subject has given his explicit consent. The data subject can withdraw his consent.

Transfer of data shall take place by courier or registered mail. In case of electronic transmission the necessary security measures shall be taken to prevent unauthorized access. As a minimum, the data must be safely encrypted during the entire transmission. Transfer of sensitive personal data requires strong encryption.

Changes of the notified data processing

The Data Protection Agency shall prior to implementation be notified of significant changes to the data processing (in the form of a change to an existing notification). Less significant changes may be notified to the Data Protection Agency subsequently, however not later than four (4) weeks after the implementation.

Discontinuance of notified data processing

The Company shall notify the Data Protection Agency immediately if the company discontinues carrying out the notified data processing.

AUTHORISATION to disclose data

In connection with its notification the Company has applied for authorisation to disclose data.

The Company has applied for authorisation to disclose data to relevant national and international health and medicines authorities in connection with an application for marketing authorization.
Furthermore, the Company has applied for authorisation to disclose data concerning adverse events to national and international health and medicines authorities according to national and international law on reporting of adverse events in clinical trials.

The Data Protection Agency hereby grants authorisation to the disclosure, cf. Section 10(3) of Act on Processing of Personal Data.

The authorisation in granted on the following terms:

**Period of validity**: The authorisation is valid until further notice.

- The relevant data may be disclosed to national and international health and medicines authorities in connection with an application for marketing authorization; to national and international health and medicines authorities according to national and international law on reporting of adverse events in clinical trials.

- Only data required in the specific situation concerned may be disclosed.

- The data may be disclosed to the recipient only in a form that does not identify individual persons. It must thus not be possible for the recipient on the basis of the received data alone to identify the persons related to the data.

- The Company shall at any time be able to verify to the Data Protection Agency which transfers of data have been made.

**AUTHORISATION** to transfer personal data to third countries

In connection with its notification the Company has applied for authorisation to transfer personal data to third countries. The company wishes to transfer data for the purpose of data processing to be carried out by named data processors in third countries.
Furthermore, the Company wishes to transfer data to health and medicines authorities in third countries to comply with these countries’ law on reporting of adverse events in clinical trials and in connection with applications for a marketing authorization.

According to Section 50(2) of Act on Processing of Personal Data, transfer of sensitive data to third countries can take place with the authorisation of the Data Protection Agency. According to section 50 (5), the Data Protection Agency may lay down more detailed conditions for the carrying out of the processing operations for reasons of protection of the privacy of the data subject in question.

**The Data Protection Agency hereby grants authorisation to transfer data to third countries, cf. Section 50(2) of Act on Processing of Personal Data.**

The authorisation is granted on the following terms:

**Period of validity:** The grant is valid until further notice.

- Data may be transferred for processing by data processors with whom the Company has an agreement on data processing, and to health and medicines authorities in third countries in order to comply with the law of these countries on reporting of adverse events in clinical trials and in connection with an application for marketing authorization.

- When data are transferred to and from third countries the necessary safety measures must be taken to ensure that the data are not abused and to prevent unauthorized access. The data shall be delivered personally or sent by courier or registered post. Electronic transmission of data may take place only if the data are securely encrypted during the entire transmission. Transfer of sensitive personal data requires strong encryption.

- Transfer of data to third countries takes place at the responsibility of the Company. The Company must therefore in each individual case assess whether the relevant transfer can take place, especially in consideration of the recipient's data safety. If it is as-
agreed that the level of protection at the recipient's place is not adequate, transfer is not allowed.

- The Company shall be able at any time to verify to the Data Protection Agency to which third countries data have been transferred and the purpose of this.

**The following terms furthermore apply to transfer to data processors in third countries.**

- Processing of the data must take place only at the instance of the Company and at the Company's responsibility.

- The Company shall always be in a position to notify the Data Protection Agency of the data processor’s name and address.

- Prior to any transfer of data a written agreement shall be made with the recipient to the effect that the Data Protection Agency’s conditions for processing of the data in Denmark shall be complied with when the data processor processes the data.

- As responsible for the processing, the Company shall obtain information sufficient to ensure that the terms of the Data Protection Agency are complied with.

- When the data are no longer to be processed by the data processor they must be erased or returned to the Company.

The terms of the Data Protection Agency are valid until further notice. The Data Protection Agency reserves the right to take up the terms for revisions at a later date, if required.
Appendix II

Declaration of Helsinki
A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when
providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to
participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental
condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious
or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008
Appendix III

Definition of Terms
Assessment
A (cluster of) characteristic(s) measured and/or recorded for a patient.

Certified Copy
A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original (Food and Drug Administration [FDA] Guidance for Industry, Computerized Systems Used in Clinical Investigations, May 2007).

Clinical Trial Agreement
A contract between the designated CRO and an Investigator specifying the conditions for cooperation in the clinical study and the Investigators’ responsibilities.

Concomitant Medication
Any medication taken by a patient during the clinical study apart from the investigational product.

Fraud
Fabrication of data, selective and undisclosed rejection of undesired results, substitution with fictitious data, deliberately incorrect use of statistical methods for the purposes of reaching other conclusions than those warranted by the data, misinterpretation of results and conclusions, plagiarism of results or entire articles from other researchers, misrepresentation of other researchers’ results, unwarranted authorship, and misleading application for positions or funds.

International Clinical Trial Manager (ICTM)
The person appointed by LEO to be the main international representative responsible for all aspects of a clinical study as outlined in Clinical Development standard operating procedures (SOPs).
Investigator Staff Signature Form
A form used:
1. for the Investigator to delegate study related tasks/duties.
2. for study site staff to sign and date to accept delegation.
3. for study site staff to document signature and initials.
4. for the Investigator to authorise tasks/duties delegated.

Investigator Site File
The collection of study documents required by the CRO SOPs, International Conference on Harmonisation (ICH) Guidelines and/or regulatory requirements to be on file at the study site.

LEO
LEO (no suffix): Refers to the corporate organisation of LEO Pharma A/S.

Monitor
A person appointed by the designated CRO to carry out monitoring of a clinical study.

Month
For this study 1 month will equal a period of 30 calendar days.

Randomisation List
A list of (sequential) numbers to each of which a treatment is allocated (assigned). Treatment may be revealed as a code letter (e.g. A, B, …) or by directly revealing the specific treatment (investigational product).

Response Criterion
An assessment or a transformation of the assessment(s) described on a patient level, for which a statistical analysis is performed, i.e. a p-value or a confidence interval (CI) is stated, or for which a tabulation serves as important supportive evidence of efficacy/safety.

Subject Number
A unique number that is assigned for each patient screened.
Patient Study Card
A card given to a patient by the study site at the time the investigational product is first dispensed to a patient, to identify that the patient is having treatment with an investigational product.

Patient Screening Log
A document kept by the Investigator which identifies patients who entered pre-study screening.

Screened Patient
A patient for whom informed consent has been obtained and a subject number has been assigned. Study activities will be performed to confirm patient eligibility.

Screen Failure
A patient who has been screened but has not been randomised regardless of the reason.

Screening Period
Indicates the period from the time the consent is signed by the patient until randomisation occurs.

Systemic Anticancer Therapy
Systemic anticancer therapy is defined as the treatment of cancer through the systemic delivery of agents that have anti-tumour effects. These agents are delivered via enteral, subcutaneous (SC) and/or intravenous routes. Systemic anticancer agents include chemotherapy, hormonal therapy, targeted therapy and immunotherapy.

Unscheduled Visit
A visit performed at the patient’s or the investigators request outside the scheduled study visits.
Appendix IV

EQ-5D Health Questionnaire
By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
Appendix V

Abbreviated Modification of Diet in Renal Disease (aMDRD) Study Equation
Abbreviated Modification of Diet in Renal Disease Study Equation

In adults the best equation for estimating glomerular filtration rate (GFR) from serum creatinine is the Modification of Diet in Renal Disease (aMDRD) Study equation (67, 68, 69). The equation is listed in two different versions, taking into consideration that creatinine can be analysed with creatinine methods that either are, or are not, traceable to IDMS. In addition, creatinine values may also be reported in different units (μmol/L or mg/dL) (cf. http://www.nkdep.nih.gov/professionals/gfr_calculators/).

**Original aMDRD Study Equation GFR Calculator**

\[
\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American}) \quad \text{(conventional units)}
\]

\[
\text{GFR (mL/min/1.73 m}^2\text{)} = 186 \times (S_{cr}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American}) \quad \text{(SI units)}
\]

**IDMS-traceable aMDRD Study Equation GFR Calculator (75)**

\[
\text{GFR (mL/min/1.73 m}^2\text{)} = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \quad \text{(conventional units)}
\]

\[
\text{GFR (mL/min/1.73 m}^2\text{)} = 175 \times (S_{cr}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \quad \text{(SI units)}
\]

**Source:**


**ELECTRONIC SIGNATURES**

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