select-d Trial Summary

Title:	select-d: Anticoagulation Therapy in **SELECTeD** Cancer Patients at Risk of Recurrence of Venous Thromboembolism (VTE)
Design:	Prospective, randomised, open label, multicentre pilot study comparing dalteparin vs. rivaroxaban with a second placebo-controlled randomisation comparing the duration of anticoagulation therapy (6 months vs 12 months treatment) in Residual Vein Thrombosis [RVT] positive (+ve) patients.
Inclusion criteria:	• Patients with active cancer (see definition in protocol, section 5.2) • Patients with a primary presentation of an objectively confirmed VTE - symptomatic lower extremity proximal DVT (see definition in protocol, section 5.3) or symptomatic or incidental PE • ECOG Performance Status 0-2 • Aged ≥18 • Written informed consent given • Adequate haematological function (recommended levels – haemoglobin (Hb) > 100g/l, white cell count (WCC) > $2x10^9$/l, platelets > 100 $x10^9$/l) • Adequate hepatic and renal function – liver enzymes < x3 upper limit of normal (ULN); creatinine clearance ≥30ml per minute
Exclusion criteria:	• Patients with primary oesophageal or gastro-oesophageal cancer • Patients taking any treatment dose of anticoagulants (excluding any anticoagulant for this episode of VTE) • Patients taking >75 mg aspirin per day or those taking dual antiplatelet therapy • Planned randomised treatment start time >72 hours* after starting anticoagulant for this episode of VTE (*this can be extended to 96 hours if necessary – please call the Trial Office to discuss extension) • Patients with a previous history of VTE • Clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis, or cirrhosis) or an alanine aminotransferase level that is ≥ 3 times ULN range • Bacterial endocarditis • Active bleeding or at high risk of bleeding, contraindicating anticoagulant treatment • Systolic blood pressure > 180 mm Hg or Diastolic blood pressure > 110 mm Hg. *Control of blood pressure using anti-hypertensive drugs is permitted* • Of childbearing potential (both male and female participants) without a combination of adequate contraceptive measures, e.g. oral contraceptives, IUD, barrier methods of contraception (condom or occlusive cap with spermicide) • Pregnancy or breast-feeding • Concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g. human immunodeficiency virus protease inhibitors or systemic ketoconazole) or inducers (e.g. rifampicin, carbamazepine, or phenytoin) or p-glycoprotein inhibitors/ inducers • Body weight < 40kg at time of venous thromboembolic event

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Selection criteria for second randomisation:	• Patients with DVT who are Residual Vein Thrombosis [RVT] positive (+ve) or patients presenting with a PE • ECOG performance status 0, 1 or 2 • Still receiving initial trial treatment • No recurrence of VTE • Adequate haematological function (recommended levels – haemoglobin (Hb) > 100g/l, white cell count (WCC) > $2x10^9$/l, platelets > 100 $x10^9$/l) Clinical discretion should be used when considering patients for the second randomisation.
Objectives:	Primary Objective: To assess VTE recurrence in **SELECTeD** cancer patients at risk of recurrence of VTE treated with rivaroxaban or dalteparin Secondary Objectives: • To ensure the safety of the patients with regards to major bleeding in an internal safety study • To assess acceptability and compliance to randomisation and allocated treatment • To assess 6 months and 12 months anticoagulation treatment in patients with evidence of RVT following initial therapy, in terms of VTE recurrence • To assess VTE recurrence in patients with evidence of RVT and those with no evidence of RVT
Outcome measures:	Primary Outcome: • VTE recurrence (including symptomatic VTE and incidental PE) Secondary Outcomes: • Symptomatic VTE and incidental PE recurrence • Major bleeding and clinically relevant non-major bleeding • Feasibility of conducting an economic evaluation • Tumour response • Acceptability and compliance to randomisation and treatment • Patient experience • Quality of life • Progression-free survival (adjuvant patients) and overall survival • Biomarker correlation
Treatment:	Dalteparin (Fragmin®, Pfizer), a low molecular weight heparin, the only licensed anticoagulant in the UK for the extended treatment and prevention of recurrence of VTE in cancer patients Rivaroxaban (Xarelto®, Bayer), an oral direct Factor Xa inhibitor, licensed for the treatment of DVT and the prevention of recurrence of DVT and PE in adult patients.
Sample size:	A total of 400 patients will be recruited to provide reliable estimates of the primary outcome (VTE recurrence) to within a width of the 95% confidence interval of 9% assuming the VTE recurrence rate at six months is 10%.
Stratification:	FIRST RANDOMISATION (dalteparin versus rivaroxaban) • Stage of disease at randomisation [early/locally advanced disease (solid tumour); metastatic disease (solid tumour); haematological malignancy]

	• Baseline platelet count [≤350,000/µL; >350,000/µL] • Type of VTE [symptomatic VTE; incidental PE] • Risk of clotting by tumour type [high risk; low risk] (See Appendix 5) SECOND RANDOMISATION (rivaroxaban versus placebo) • Treatment allocation at first randomisation [dalteparin; rivaroxaban] • Stage of disease at second randomisation [early/locally advanced disease (solid tumour); metastatic disease (solid tumour); haematological malignancy] • Platelet count at second randomisation [≤350,000/µL; >350,000/µL] • Type of VTE [symptomatic VTE; incidental PE] • Risk of clotting by tumour type [high risk; low risk]
Analysis:	Estimates of VTE recurrence at six and 12 months and 95% confidence intervals will be obtained from constructing Kaplan-Meier curves to take into account censoring. The number of RVT positive patients continuing to the second randomisation will be evaluated. Compliance to treatment will be assessed by frequency of withdrawals of therapy and duration of therapy. Kaplan-Meier curves will be constructed and estimates obtained for the composite safety parameter, progression-free survival and overall survival. Quality of life will be reported descriptively using appropriate longitudinal analyses. Frequencies of adverse events and antitumour efficacy will be reported. A pre-planned *safety* analysis will be conducted after the first 220 patients randomised (110 on each treatment arm) and have been on study at least 6 months (i.e. completed initial therapy and considered for the second randomisation) to assess treatment compliance, RVT results, adverse events and power calculation assumptions.