Protocol Registration Receipt
02/06/2014

A Study to Evaluate the Efficacy and Safety of Fondaparinux for the Prevention of Venous Blood Clots in Patients With a Plaster Cast or Other Type of Immobilization for a Below-knee Injury Not Needing Surgery (FONDACAST)

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00843492

Purpose

The purpose of this study is to evaluate the efficacy and safety of fondaparinux in comparison with a heparin (nadroparin) in preventing deep vein thrombosis (blood clots in the leg veins), whether symptomatic or detected by ultrasound, and pulmonary embolism (blood clots that migrate to the lungs) in patients with leg injuries below the knee that require a cast or other type of immobilization but not surgery.

Condition	Intervention	Phase
Thrombosis, Venous	Drug: Fondaparinux sodium	Phase 3

Condition	Intervention	Phase
	Drug: Nadroparin	

Study Type: Interventional
Study Design: Prevention, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A Multicentre, Randomized, Open-label Study to Evaluate the Efficacy andSafety of Fondaparinux Versus Low Molecular Weight Heparin(Nadroparin) in Patients Requiring Rigid or Semi-rigid Immobilization for at Least 21 Days and up to 45 Days Because of Isolated Non-surgical Below-Knee Injury

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Number of Participants With Venous Thromboembolism (VTE) or Death up to the Time of Complete Mobilization [Time Frame: Day 1 to complete mobilization plus 2 days (average of 35.9 study days)] [Designated as safety issue: No]

  VTE is defined as asymptomatic deep vein thrombosis (DVT: the formation of a blood clot in a deep vein) detected by systematic compression ultrasonography, symptomatic DVT, or symptomatic fatal or non-fatal pulmonary embolism (PE). An embolism is a clot in the blood that forms and blocks a blood vessel. A pulmonary embolism is a blood clot that has travelled from elsewhere in the body through the blood stream to block the main artery of the lung or one of its branches. All venous thromboembolic events and deaths were adjudicated by the independent Central Adjudication Committee (CAC).

Secondary Outcome Measures:

- Number of Participants With Any Adjudicated Components of VTE, Asymptomatic DVT, Symptomatic DVT, Symptomatic PE, and Death [Time Frame: Day 1 to complete mobilization plus 2 days (average of 35.7 study days)] [Designated as safety issue: No]

  All components of the primary endpoint were considered separately: any VTE; symptomatic (providing no evidence of disease existence) DVT (the formation of a blood clot in a deep vein) detected by systematic compression ultrasonography; symptomatic(providing evidence of disease existence) DVT; symptomatic PE (blood clot that has travelled from elsewhere in the body through the blood stream to block the main artery of the lung of one of its branches); and death.
- Number of Participants With Confirmed VTE and Death up to the Final Visit or Contact [Time Frame: Day 1 to 5 weeks (plus or minus 1 week) after complete mobilization (average of 67.8 study days)] [Designated as safety issue: No]

  The number of participants with VTE (defined as asymptomatic deep vein thrombosis [DVT: the formation of a blood clot in a deep vein] detected by systematic compression ultrasonography, symptomatic DVT, or symptomatic fatal or non-fatal pulmonary embolism [PE]) and death was assessed. An embolism is a clot in the blood that forms and blocks a blood vessel. A PE is a blood clot that has travelled from elsewhere in the body through the blood stream to block the main artery of the lung or one of its branches.
- Number of Participants With Major Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [Time Frame: Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)] [Designated as safety issue:

No]

Major bleeding is defined as bleeding that results in a fatality, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin level of 20 grams/liter (1.24 millimoles/liter) or more compared with the pre-randomization hemoglobin level, or bleeding that leads to a transfusion of two or more units of whole blood or red blood cells. All episodes of bleeding were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.

- Number of Participants With Clinically Relevant Non-major Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [Time Frame: Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)] [Designated as safety issue: No]

  Clinically relevant non-major bleeding that does not qualify as major is defined as bleeding leading to treatment discontinuation, and/or epistaxis (bleeding through the nose) that lasts for more than 5 minutes or necessitates intervention (e.g., packing), spontaneous macroscopic haematuria (blood in urine), gastrointestinal haemorrhage, haemoptysis (coughing up blood), or subcutaneous haematoma (localized collection of blood) > 100 centimeters squared. All episodes of bleeding were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.
- Number of Participants With Minor Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [Time Frame: Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)] [Designated as safety issue: No]

  Minor bleeding is defined as clinically overt bleeding events that do not meet the criteria for major or clinically relevant non-major bleeding. All episodes of bleeding were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.
- Participants With Any Incidence of Any Bleeding Event as Adjudicated by a CAC) From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [Time Frame: Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)] [Designated as safety issue: No]

  All episodes of bleeding, except minor bruising, skin hematomas not greater than 5 centimeters in diameter, self-limited epistaxis (bleeding through the nose), and self-limited gingival (gum) bleeding, were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.

Enrollment: 1351
Study Start Date: December 2008
Study Completion Date: June 2010
Primary Completion Date: January 2010

Arms	Assigned Interventions
Active Comparator: Nadroparin After randomization (Day 1), subjects will receive subcutaneously once daily	Drug: Nadroparin After randomization (Day 1), subjects will receive subcutaneously once daily nadroparin 2850 anti-Xa IU

Arms	Assigned Interventions
nadroparin 2850 anti-Xa IU (0.3 mL) for at least 21 Days, up to complete mobilization, corresponding to cast or brace removal. The maximal duration of treatment is 45 days. Patients will then be followed up to five weeks (± one week) after the cast or brace removal.	(0.3 mL) for at least 21 Days, up to complete mobilization, corresponding to cast or brace removal. The maximal duration of treatment is 45 days.
Experimental: Fondaparinux After randomization (Day 1), subjects will receive subcutaneously, once daily, fondaparinux 2.5 mg (1.5 mg in patients with creatinine clearance between 30 and 50 mL/min) for at least 21 Days, up to complete mobilization, corresponding to cast or brace removal. The maximal duration of treatment is 45 days. Patients will then be followed up to five weeks (± one week) after the cast or brace removal.	Drug: Fondaparinux sodium After randomization (Day 1), subjects will receive subcutaneously once daily fondaparinux 2.5 mg [0.5mL] (1.5 mg [0.3mL] in patients with creatinine clearance between 30 and 50 mL/min) for at least 21 Days, up to complete mobilization, corresponding to cast or brace removal. The maximal duration of treatment is 45 days.

The study is designed to evaluate the efficacy and safety of fondaparinux sodium 2.5 mg (1.5 mg in patients with a creatinine clearance between 30 and 50 mL/min) once daily versus Low-Molecular Weight Heparin (nadroparin 2850 anti-Xa IU, 0.3 mL, once daily), with respect to the occurrence of venous thromboembolism, death and bleeding complications in patients requiring rigid or semi-rigid immobilization for at least 21 days and up to 45 days because of isolated nonsurgical below-knee injury. Treatment will be continued up to complete mobilization, e.g. plaster cast or brace removal, for a maximum of 45 days. The study will be a European, multicentre, randomized, open-label, controlled, two-parallel-group, phase III study in 1350 male and female patients 18 years of age or older, presenting with at least one additional major risk factor for VTE. After randomization (Day 1), subjects will receive subcutaneously, once daily, either fondaparinux or nadroparin up to complete mobilization. After cast or brace removal, a systematic, bilateral compression ultrasound will be done in all patients. Patients will be contacted five weeks (± one week) after complete mobilization. All suspected venous thromboembolic events, including asymptomatic deep vein thrombosis, all deaths, and all bleeding events (with the exception of certain types of minor bleeding events defined in the protocol) will be reviewed by an independent adjudication committee blind to treatment assignment.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Requiring rigid or semi-rigid immobilization (e.g. with a plaster cast or brace) for at least 21 days and up to 45 days because of isolated non-surgical below-knee injury
- With a no weight-bearing recommendation at the time of inclusion (partial weight bearing is permitted e.g. crutches, walking cast, relief shoes),
- Presenting at least one of the following risk factors for venous thromboembolism: below-knee fracture or Achilles tendon rupture, age ≥40 years, body mass index > 30 kg/m2, oestrogen-containing hormonal replacement therapy or oral contraception, active cancer (treatment ongoing or stopped for less than one year), history of VTE, congenital or acquired hypercoagulable state,
- Requiring thromboprophylaxis according to the Investigator's judgement up to complete mobilization (corresponding to cast or brace removal)
- Able and willing to provide written informed consent

Exclusion Criteria:

- Delay between injury and randomization greater than two days,
- Treatment with antithrombotic or anticoagulant therapy, including low-dose anticoagulation, for more than 2 days prior to randomization,
- Anticoagulant therapy required or likely to be required during the study period for another reason (e.g. planned surgery justifying pharmacological thromboprophylaxis, curative dose for treatment of VTE, etc.)
- Known hypersensitivity to fondaparinux or nadroparin or their excipient,
- Known history of heparin-induced thrombocytopenia,
- Women of childbearing potential not using a reliable contraceptive method throughout the study period,
- Women pregnant or breast-feeding during the study period.
- Active, clinically significant bleeding,
- Clinically significant bleeding within the past six months,
- Major surgery within the previous three months,
- Intraocular (other than cataract), spinal, and/or brain surgery within the previous twelve months,
- Haemorrhagic stroke within the previous twelve months,
- Severe head injury within the previous three months,
- Documented congenital or acquired bleeding tendency/disorder(s),
- Previous (within 12 months) or active or currently treated peptic ulcer disease,
- Uncontrolled arterial hypertension (systolic blood pressure over 180 mm Hg or diastolic blood pressure over 110 mm Hg),
- Treatment with more than one antiplatelet agents (e.g. clopidogrel and aspirin) at any dose,

- Need for chronic aspirin at doses≥ 325 mg or chronic NSAIDs,
- Bacterial endocarditis,
- Severe hepatic impairment,
- Calculated creatinine clearance < 30 mL/min,
- Thrombocytopenia (<100x10_9/L)
- Body weight < 50 kg.
- Any condition that could prevent the patient from providing written informed consent or from adhering to study treatment,
- Life expectancy under six months,
- Participation in any study using an investigational drug during the previous three months,
- Patient in whom V3 is unlikely to be feasible (e.g. patient moving house),
- In France, a subject will not be eligible for inclusion in this study if not either affiliated to or a beneficiary of a social security system. This is an additional exclusion criterion only applying to subjects enrolled in France.

Contacts and Locations

Locations

France

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Agen Cedex 9, France, 47923

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Lyon Cedex 07, France, 69365
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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	109350
Health Authority:	Spain: Agencia Española del Medicamento y Productos Sanitarios Italy: Comitato Etico della ASL Città di Milano Germany: Bundesinstitut für Arzneimittel und Medizinprodukte France: Agence Française de Sécurité Sanitaire des Produits de

Study Results

Participant Flow

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Overall Study

	Nadroparin	Fondaparinux
Started	622	621
Completed	614	607
Not Completed	8	14
Adverse Event	0	3
Lost to Follow-up	4	4
Withdrawal by Subject	0	4

	Nadroparin	Fondaparinux
Immobilization Stopped	1	0
Investigator/Orthopedic Surgeon Decision	1	1
Orthopedic Surgery	0	2
Visit Not Performed	1	0
Deep-vein Thrombosis	1	0

Baseline Characteristics

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Baseline Measures

	Nadroparin	Fondaparinux	Total
Number of Participants	622	621	1243
Age, Continuous [1] Years [units: Years] Mean (Standard Deviation)	46.5 (15.7)	46.1 (16.0)	46.3 (15.8)

	Nadroparin	Fondaparinux	Total
Gender, Male/Female [2] [units: Participants]			
Female	336	328	664
Male	286	293	579

[1] Baseline characteristic data was collected in members of the Intent-to-Treat (ITT) Population, comprised of all randomized patients (recorded in the Interactive Voice Response System [IVRS] database) with a venous thromboembolism (VTE) status or experiencing death.

[2] Baseline characteristic data was collected in members of the Intent-to-Treat (ITT) Population, comprised of all randomized patients (recorded in the Interactive Voice Response System [IVRS] database) with a venous thromboembolism (VTE) status or experiencing death.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Venous Thromboembolism (VTE) or Death up to the Time of Complete Mobilization
Measure Description	VTE is defined as asymptomatic deep vein thrombosis (DVT: the formation of a blood clot in a deep vein) detected by systematic compression ultrasonography, symptomatic DVT, or symptomatic fatal or non-fatal pulmonary embolism (PE). An embolism is a clot in the blood that forms and blocks a blood vessel. A pulmonary embolism is a blood clot that has travelled from elsewhere in the body through the blood stream to block the main artery of the lung or one of its branches. All venous thromboembolic events and deaths were adjudicated by the independent Central Adjudication Committee (CAC).
Time Frame	Day 1 to complete mobilization plus 2 days (average of 35.9 study days)

Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized participants with a VTE status or experiencing death. Participants without evaluation of the primary endpoint in the timeframe requested by the protocol were considered as missing data and therefore not included in the primary efficacy analysis.

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	586	584
Number of Participants With Venous Thromboembolism (VTE) or Death up to the Time of Complete Mobilization [units: participants]	48	15

Statistical Analysis 1 for Number of Participants With Venous Thromboembolism (VTE) or Death up to the Time of Complete Mobilization

Groups	Nadroparin, Fondaparinux
Method	Fisher Exact

P-Value	<0.001
Odds Ratio (OR)	0.30
95% Confidence Interval	0.15 to 0.54

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

2. Secondary Outcome Measure:

Measure Title	Number of Participants With Any Adjudicated Components of VTE, Asymptomatic DVT, Symptomatic DVT, Symptomatic PE, and Death
Measure Description	All components of the primary endpoint were considered separately: any VTE; symptomatic (providing no evidence of disease existence) DVT (the formation of a blood clot in a deep vein) detected by systematic compression ultrasonography; symptomatic(providing evidence of disease existence) DVT; symptomatic PE (blood clot that has travelled from elsewhere in the body through the blood stream to block the main artery of the lung of one of its branches); and death.
Time Frame	Day 1 to complete mobilization plus 2 days (average of 35.7 study days)
Safety Issue?	No

Analysis Population Description

ITT Population. Only those participants contributing data at the indicated time points were analyzed.

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	622	621
Number of Participants With Any Adjudicated Components of VTE, Asymptomatic DVT, Symptomatic DVT, Symptomatic PE, and Death [units: participants]		
Any VTE, n=586, 583	48	14
Any asymptomatic DVT, n=585, 582	42	11
Any symptomatic DVT, n=622, 621	7	2
Any symptomatic PE, n=622, 621	0	2
Death, n=622, 621	0	1

3. Secondary Outcome Measure:

Measure Title	Number of Participants With Confirmed VTE and Death up to the Final Visit or Contact
Measure Description	The number of participants with VTE (defined as asymptomatic deep vein thrombosis [DVT: the formation of a blood clot in a deep vein] detected by systematic compression ultrasonography, symptomatic DVT, or symptomatic fatal or non-fatal pulmonary embolism [PE]) and death was assessed. An embolism is a clot in the blood that forms and blocks a blood vessel. A PE is a blood clot that has travelled from elsewhere in the body through the blood stream to block the main artery of the lung or one of its branches.
Time Frame	Day 1 to 5 weeks (plus or minus 1 week) after complete mobilization (average of 67.8 study days)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	622	621
Number of Participants With Confirmed VTE and Death up to the Final Visit or Contact [units: participants]	49	15

4. Secondary Outcome Measure:

Measure Title	Number of Participants With Major Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact
Measure Description	Major bleeding is defined as bleeding that results in a fatality, symptomatic bleeding in a critical area or organ, bleeding causing a fall in hemoglobin level of 20 grams/liter (1.24 millimoles/liter) or more compared with the pre-randomization hemoglobin level, or bleeding that leads to a transfusion of two or more units of whole blood or red blood cells. All episodes of bleeding were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.
Time Frame	Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)
Safety Issue?	No

Analysis Population Description

As-Treated Population: all participants who received at least one dose of study treatment

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	670	674
Number of Participants With Major Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [units: participants]		
Up to complete mobilization plus 4 days	0	1
Up to the final visit or contact	0	1

5. Secondary Outcome Measure:

Measure Title	Number of Participants With Clinically Relevant Non-major Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact
Measure Description	Clinically relevant non-major bleeding that does not qualify as major is defined as bleeding leading to treatment discontinuation, and/or

	epistaxis (bleeding through the nose) that lasts for more than 5 minutes or necessitates intervention (e.g., packing), spontaneous macroscopic haematuria (blood in urine), gastrointestinal haemorrhage, haemoptysis (coughing up blood), or subcutaneous haematoma (localized collection of blood) > 100 centimeters squared. All episodes of bleeding were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.
Time Frame	Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)
Safety Issue?	No

Analysis Population Description

As-Treated Population

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	670	674
Number of Participants With Clinically		

	Nadroparin	Fondaparinux
Relevant Non-major Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [units: participants]		
Up to complete mobilization plus 4 days	3	1
Up to the final visit or contact	4	1

6. Secondary Outcome Measure:

Measure Title	Number of Participants With Minor Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact
Measure Description	Minor bleeding is defined as clinically overt bleeding events that do not meet the criteria for major or clinically relevant non-major bleeding. All episodes of bleeding were adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.
Time Frame	Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)
Safety Issue?	No

Analysis Population Description

As-Treated Population

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily

	Description
	subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	670	674
Number of Participants With Minor Bleeding From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [units: participants]		
Up to complete mobilization plus 4 days	3	9
Up to the final visit or contact	3	9

7. Secondary Outcome Measure:

Measure Title	Participants With Any Incidence of Any Bleeding Event as Adjudicated by a CAC) From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact
Measure Description	All episodes of bleeding, except minor bruising, skin hematomas not greater than 5 centimeters in diameter, self-limited epistaxis (bleeding through the nose), and self-limited gingival (gum) bleeding, were

	adjudicated by an independent CAC. The committee members were unaware of the participants' treatment assignment.
Time Frame	Day 1 to complete mobilization plus 4 days (average of 37.7 study days); Day 1 up to final visit or contact (average of 66.3 study days)
Safety Issue?	No

Analysis Population Description

As-Treated Population

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Measured Values

	Nadroparin	Fondaparinux
Number of Participants Analyzed	670	674
Participants With Any Incidence of Any Bleeding Event as Adjudicated by a CAC) From Day 1 to Complete Mobilization and From Day 1 up to the Final Visit or Contact [units: participants]		
Up to complete mobilization plus 4 days	6	11

	Nadroparin	Fondaparinux
Up to the final visit or contact	7	11

Reported Adverse Events

Reporting Groups

	Description
Nadroparin	2850 anti-Xa International Units (IU) nadroparin calcium (in 0.3 milliliters [ml] in disposable prefilled syringes) was injected once daily subcutaneously after randomization (Day 1) until the end of immobilization and treatment period Day 45 (Visit 3)
Fondaparinux	2.5 milligrams (mg) fondaparinux sodium (in 0.5 ml) or 1.5 mg fondaparinux (in 0.3 ml) (in participants with creatinine clearance between 30 and 50 ml per minute) was injected once daily subcutaneously from Day 1 until Day 45 (Visit 3)

Additional Description

Serious adverse events (SAEs) and non-serious AEs were collected in members of the As-Treated Population, comprised of all participants having received at least one dose of study treatment.

Serious Adverse Events

	Nadroparin	Fondaparinux
Total # participants affected/at risk	9/670 (1.34%)	6/674 (0.89%)
Cardiac disorders		
Cardiac failure		
# participants affected/at	0/670 (0%)	1/674 (0.15%)

	Nadroparin	Fondaparinux
risk		
# events		
Gastrointestinal disorders		
Abdominal wall haematoma		
# participants affected/at risk	0/670 (0%)	1/674 (0.15%)
# events		
Faecaloma		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
General disorders		
Pyrexia		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
Infections and infestations		
Appendicitis		
# participants affected/at risk	0/670 (0%)	1/674 (0.15%)
# events		

	Nadroparin	Fondaparinux
Haematoma infection		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
Subcutaneous abscess		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
Injury, poisoning and procedural complications		
Ankle fracture		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
Joint dislocation		
# participants affected/at risk	1/670 (0.15%)	1/674 (0.15%)
# events		
Musculoskeletal and connective tissue disorders		
Fracture malunion		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)

	Nadroparin	Fondaparinux
# events		
Haemarthrosis		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Prostate cancer		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		
Nervous system disorders		
Presyncope		
# participants affected/at risk	0/670 (0%)	1/674 (0.15%)
# events		
Transient ischaemic attack		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		

	Nadroparin	Fondaparinux
Skin and subcutaneous tissue disorders		
Angioedema		
# participants affected/at risk	0/670 (0%)	1/674 (0.15%)
# events		
Blister		
# participants affected/at risk	1/670 (0.15%)	0/674 (0%)
# events		

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 1%

	Nadroparin	Fondaparinux
Total # participants affected/at risk	95/670 (14.18%)	93/674 (13.8%)
Blood and lymphatic system disorders		
Lymphadenopathy		
# participants affected/at risk	13/670 (1.94%)	8/674 (1.19%)
# events		
Gastrointestinal disorders		

	Nadroparin	Fondaparinux
Nausea		
# participants affected/at risk	10/670 (1.49%)	12/674 (1.78%)
# events		
General disorders		
Injection site haematoma		
# participants affected/at risk	31/670 (4.63%)	10/674 (1.48%)
# events		
Oedema peripheral		
# participants affected/at risk	7/670 (1.04%)	11/674 (1.63%)
# events		
Musculoskeletal and connective tissue disorders		
Arthralgia		
# participants affected/at risk	8/670 (1.19%)	14/674 (2.08%)
# events		
Pain in extremity		
# participants affected/at risk	18/670 (2.69%)	21/674 (3.12%)

	Nadroparin	Fondaparinux
# events		
Nervous system disorders		
Dizziness		
# participants affected/at risk	6/670 (0.9%)	7/674 (1.04%)
# events		
Headache		
# participants affected/at risk	33/670 (4.93%)	24/674 (3.56%)
# events		
Skin and subcutaneous tissue disorders		
Pruritus		
# participants affected/at risk	8/670 (1.19%)	6/674 (0.89%)
# events		
Vascular disorders		
Haematoma		
# participants affected/at risk	1/670 (0.15%)	9/674 (1.34%)
# events		
Hypertension		

	Nadroparin	Fondaparinux
# participants affected/at risk	8/670 (1.19%)	7/674 (1.04%)
# events		

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: GSK Response Center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: